Toronto Notes 2014

Comprehensive medical reference and review for the Medical Council of Canada Qualifying Exam Part 1 and the United States Medical Licensing Exam Step 2

30th Edition

Editors-in-Chief:
Miliana Vojvodic and Ann Young

Wherever the art of medicine is loved, there is also a love of humanity.

– Hippocrates
Thirtieth Edition

Copyright © 2014 – Toronto Notes for Medical Students, Inc.
Toronto, Ontario, Canada.
Typeset and production by Type & Graphics Inc.

All rights reserved. Printed in Toronto, Ontario, Canada. Toronto Notes 2014 is provided for the sole use of the purchaser. It is made available on the condition that the information contained herein will not be sold or photocopied. No part of this publication may be used or reproduced in any form or by any means without prior written permission from the publisher. Every effort has been made to obtain permission for all copyrighted material contained herein. Previous editions copyright © 1985 to 2014.

Cover design: Karyn Ho and Catherine Kang
Illustrations: Biomedical Communications, University of Toronto

Notice:
THIS PUBLICATION HAS NOT BEEN AUTHORED, REVIEWED OR OTHERWISE SUPPORTED BY THE MEDICAL COUNCIL OF CANADA NOR DOES IT RECEIVE ENDORSEMENT BY THE MEDICAL COUNCIL AS REVIEW MATERIAL FOR THE MCCQE. THIS PUBLICATION HAS NOT BEEN AUTHORED, REVIEWED OR OTHERWISE SUPPORTED BY THE NATIONAL BOARD OF MEDICAL EXAMINERS U.S.A. NOR DOES IT RECEIVE ENDORSEMENT BY THE NATIONAL BOARD AS REVIEW MATERIAL FOR THE USMLE.

The editors of this edition have taken every effort to ensure that the information contained herein is accurate and conforms to the standards accepted at the time of publication. However, due to the constantly changing nature of the medical sciences and the possibility of human error, the reader is encouraged to exercise individual clinical judgement and consult with other sources of information that may become available with continuing research. The authors, editors, and publisher are not responsible for errors or omissions or for any consequences from application of the information in this textbook, atlas, or software and make no warranty, expressed or implied, with respect to the currency, completeness, or accuracy of the contents of the publication. In particular, the reader is advised to check the manufacturer's insert of all pharmacologic products before administration.

FEEDBACK AND ERRATA
We are constantly trying to improve the Toronto Notes and welcome your feedback. If you have found an error in this edition please do not hesitate to contact us. As well, we look forward to receiving any comments regarding any component of the Toronto Notes package and website.

Please send your feedback to: feedback@torontonotes.ca

Alternatively, send mail to: Toronto Notes for Medical Students
Editors-in-chief
C/o The Medical Society
1 King's College Circle, Room 2171A
Toronto, Ontario M5S 1A8
Canada
Email: chiefeditors@torontonotes.ca
Tel: 1-416-946-3047 Fax: 1-416-978-8730

Library of Congress Cataloging-in-Publication Data is available upon request
Dedicated to all  
past and present contributors  
and  
supporters of Toronto Notes  
who have made the production of the 30th Anniversary Edition possible!

The Toronto Notes is dedicated to helping fund many charitable endeavours and medical student initiatives at the University of Toronto's Faculty of Medicine. Programs that have received Toronto Notes funding include:

**Community Affairs Projects**
- Saturday Program for Inner City High School and Grade 8 students
- St. Felix Mentorship Program for Inner City children
- Parkdale Mentorship Program for Grade 10-12 students
- WoodGreen Community Centre
- Let's Talk Science
- Growing Up Healthy

**Medical School Clubs**
- Books with Wings
- Women in Medicine
- University of Toronto International Health Program
- Complementary and Alternative Medicine
- Peer Support for Students
- History of Medicine Society
- Faculty of Medicine Yearbook

**Annual Faculty Showcase Events**
- Bruce Tovee Lecture Series
- Daffydil, in support of the Canadian Cancer Society
- Earthtones Benefit Concert
- Convocation and Ceremonies
- Clerkship Luncheon

**Scholarships and Bursaries**
- Nishant Fozdar Memorial Award
- Graduating Medical Class Scholarships and Bursaries

**NOTE:**
Many of you have wondered about the *Toronto Notes* logo, which is based on the rod of Asclepius, the Greek god of medicine. The rod of Asclepius consists of a single serpent entwined around a staff. This icon symbolizes both rebirth, by way of a snake shedding its skin, and also authority, by way of the staff.

In ancient Greek mythology, Asclepius was the son of Apollo and a skilled practitioner of medicine who learned the medical arts from the centaur Chiron. Asclepius' healing abilities were so great that he was said to be able to bring back people from the dead. These powers displeased the gods, who punished Asclepius by placing him in the sky as the constellation Orphiuchus.

The rod of Asclepius is at times confused with the caduceus, or wand, of Hermes, a staff entwined with two serpents and often depicted with wings. The caduceus is often used as a symbol of medicine or medical professionals, but there is little historical basis for this symbolism.

As you may have guessed, our logo uses the rod of Asclepius that is modified to also resemble the CN Tower – our way of recognizing the university and community in which we have been privileged to learn the art and science of medicine.

Thomas O’Brien, MD  
Class of 2009  
M.D. Program, University of Toronto
Dear Readers,

As Editors-In-Chief of Toronto Notes 2014, we are proud to celebrate the 30th Anniversary Edition of the present text.

First produced in 1983 from a set of study notes drafted by medical students at the University of Toronto, Toronto Notes has grown to be one of the premier study resources for generations of medical graduates in Canada and abroad. This rich history is rooted in our commitment to publish a student-edited, comprehensive study resource to serve students across clinical rotations and in preparation for the Canadian Medical Licensing Examination (Step 1) and the United States Medical Licensing Examination (Step 2).

Over the past 29 years, our vision has not wavered. We continuously build on the feedback of our readers to enhance the features of the text, handbook and accompanying online resources. The focus of Toronto Notes 2014 is to make medical knowledge accessible and retainable by distilling information into high-quality figures, charts and helpful mnemonics. This edition features a new easy-to-view layout across all 29 chapters, with updated text-referencing icons and illustrations. In keeping with rapid advances in medical research, the text also features newly updated best practice guidelines, including recent high-impact trials for clinical practice. The accompanying Toronto Notes Handbook also offers new algorithms, flow-charts and new reference cards to serve as a high-yield and portable resource across clinical rotations. This year we are also excited to announce the launch of the first colour edition of the Toronto Notes eBook to offer our readers an enhanced mobile learning experience.

Toronto Notes 2014 is produced by Toronto Notes for Medical Students Inc., a non-for profit organization supporting various medical student initiatives including community outreach programs, medical school clubs, local charity endeavors, and student bursaries. This year we are especially proud to support the Nishant Fozdar Memorial Award. Nishant was an exceptional medical student, colleague and dear friend in the University of Toronto medical class of 2014. This annual award was established in his memory, and will be awarded to University of Toronto students who demonstrate Nishant’s many qualities, including his dedication to education and community involvement.

Throughout the production of this edition, we have benefited from the gracious help of our student colleagues as well as numerous faculty and administrators at the University of Toronto Faculty of Medicine. Our dedicated team of over 150 students, artists and faculty editors remain the cornerstone of Toronto Notes and continue to enhance the text in its’ content and clarity each year. We are grateful for our lead editors Andy Tyrell, Vicki Wang, Maria Jogova, Howard Meng, Grace Lam, Hamed Nazzari, Jieun Kim, Daniel Soong, Melini Gupta, Jeffrey Martin and Gautam Goel as well as our 2014 production managers Sheron Perera and Bailey Dyck for their tireless work and dedication to this project. We would also like to acknowledge our partners at Type & Graphics, particularly Enrica Aguilera, for their continued guidance in the production of this text. We also thank our immensely talented cover artists Karyn Ho and Catherine Kang for their innovative vision and immaculate execution of the featured mosaic cover illustration.

Finally we would like to express our deepest gratitude to all previous Editors-In-Chief of Toronto Notes. Each editorial team left their unique mark on the text and helped Toronto Notes grow into one of the most recognizable student publications in Canada. Much like the pieces in a mosaic, the product of these countless contributions have formed the 30th Anniversary Edition before us today.

On behalf of the 2014 editorial team, we wish you the best in your studies and hope that you will find Toronto Notes 2014 to be an asset to your success.

Sincerely,

Miliana Vojvodic, MSc and Ann Young, PhD
Editors-In-Chief, Toronto Notes 2014
MD Program, University of Toronto
Acknowledgements

We would like to acknowledge the exceptional work of all previous Toronto Notes (formerly MCCQE Notes) Editors-in-Chief and their editorial teams. The 30th edition of this text was made possible with their contributions.

2013 (29th ed.): Curtis Woodford and Christopher Yao
2012 (28th ed.): Jesse M. Klostranec and David L. Kolin
2011 (27th ed.): Yingming Amy Chen and Christopher Tran
2010 (26th ed.): Simon Baxter and Gordon McSheffrey
2009 (25th ed.): Sagar Dugani and Danica Lam
2008 (24th ed.): Rebecca Colman and Ron Somogyi
2007 (23rd ed.): Marilyn Heng and Joseph Ari Greenwald
2006 (22nd ed.): Carolyn Jane Shiau and Andrew Jonathan Toren
2005 (21st ed.): Blair John Normand Leonard and Jonathan Chi-Wai Yeung
2004 (20th ed.): Andrea Molckovsky and Kashif S. Pirzada
2003 (19th ed.): Prateek Lala and Andrea Waddell
2002 (18th ed.): Neety Panu and Sunny Wong
2001 (17th ed.): Jason Yue and Gagan Ahuja
2000 (16th ed.): Marcus Law and Brian Rotenberg
1999 (15th ed.): Sofia Ahmed and Matthew Cheung
1998 (14th ed.): Marilyn Abraham and M Appleby
1997 (13th ed.): William Harris and Paul Kurdyak
1996 (12th ed.): Michael B. Chang and Laura J. Macnow
1995 (11th ed.): Ann L. Mai and Brian J. Murray
1994 (10th ed.): Kenneth Pace and Peter Ferguson
1993 (9th ed.): Joan Cheng and Russell Goldman
1992 (8th ed.): Gideon Cohen-Nehemia and Shanthi Vasudevan

All former Chief Editors from 1991 (7th ed.) to 1985 (1st ed.)
# Student Contributors

<table>
<thead>
<tr>
<th>Editors-in-Chief</th>
<th>Production Managers</th>
<th>Clinical Handbook Editors</th>
<th>Atlas Editors and Medical Imaging</th>
<th>Online Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miliana Vojvodic</td>
<td>Bailey Dyck</td>
<td>Andrew Tyrrell</td>
<td>Hussein Jaffar</td>
<td>Nicholas Tassone</td>
</tr>
<tr>
<td>Ann Young</td>
<td>Sheron Perera</td>
<td>Vicki Wang</td>
<td>Anish Kapadia</td>
<td></td>
</tr>
</tbody>
</table>

| Copy Editors            | Kaitlin Graham    | Farhaad Virjee           | Shinta Wijeyakulasingam         |                  |
|                        | Cassandra Greenberg | Sherry Jin               | Wen Yan Xie                     |                  |
|                        | Olga Malinowska    | Stacy Yeh                | Andrew Zasowski                 |                  |
|                        | Elizabeth Mui      |                          |                                 |                  |
|                        | Ankeeta Tadkase    |                          |                                 |                  |
|                        | Kevin Venus        |                          |                                 |                  |

| Production Managers     | Bailey Dyck        | Farhaad Virjee           | Shinta Wijeyakulasingam         |                  |
|                        | Sheron Perera      | Sherry Jin               | Wen Yan Xie                     |                  |
|                        |                    | Stacy Yeh                | Andrew Zasowski                 |                  |
|                        |                    |                          |                                 |                  |
|                        |                    |                          |                                 |                  |

<table>
<thead>
<tr>
<th>MEDICINE</th>
<th>EBM Editor</th>
<th>EBM Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associate Editors</td>
<td>Melini Gupta</td>
<td>Gautam Goel</td>
</tr>
<tr>
<td>Maria Jogova</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Howard Meng</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jieun Kim</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daniel Soong</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PRIMARY AND OTHER SPECIALTIES</th>
<th>EBM Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associate Editors</td>
<td>Melini Gupta</td>
</tr>
<tr>
<td>Maria Jogova</td>
<td></td>
</tr>
<tr>
<td>Howard Meng</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter Editors</th>
<th>Chapter Editors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethics, Legal</td>
<td>Cardiology and</td>
</tr>
<tr>
<td>and Organizational Medicine</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Molly Dingwall</td>
<td>Surgery</td>
</tr>
<tr>
<td>Jesse Kancir</td>
<td>Sangjuinne Laurence</td>
</tr>
<tr>
<td></td>
<td>Lee</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>Bryan Ross</td>
</tr>
<tr>
<td>Gavin Hamilton</td>
<td></td>
</tr>
<tr>
<td>Ashwin Sankar</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endocrinology</td>
</tr>
<tr>
<td></td>
<td>Yaii Huang</td>
</tr>
<tr>
<td></td>
<td>Angela Liu</td>
</tr>
<tr>
<td></td>
<td>Anna Liu</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>Gastroenterology</td>
</tr>
<tr>
<td>Rick Chen</td>
<td>Ian Brass</td>
</tr>
<tr>
<td>Erica Merman</td>
<td></td>
</tr>
<tr>
<td>Monique Moller</td>
<td>Ahmad Zaheen</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatology</td>
<td>Geriatric Medicine</td>
</tr>
<tr>
<td>Amanda Carleton</td>
<td>Evelyn Cheung</td>
</tr>
<tr>
<td>Thanh-Cat Ho</td>
<td>Christopher Yarnell</td>
</tr>
<tr>
<td>Anjali Papneja</td>
<td></td>
</tr>
<tr>
<td>Yuliya Velykoredko</td>
<td></td>
</tr>
<tr>
<td>Emergency Medicine</td>
<td>Hematology</td>
</tr>
<tr>
<td>Neil D. Dattani</td>
<td>Lawson Eng</td>
</tr>
<tr>
<td>Anandita Gokhale</td>
<td>Anthony La Delfa</td>
</tr>
<tr>
<td>Mackenzie Howatt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infectious Disease</td>
</tr>
<tr>
<td></td>
<td>Alice Gray</td>
</tr>
<tr>
<td></td>
<td>Alissa Visram</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMC Production Editors</th>
<th>BMC Production Editors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yi-Min Chun</td>
<td>Yi-Min Chun</td>
</tr>
<tr>
<td>Man-San Ma</td>
<td>Man-San Ma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMC ILLUSTRATORS</th>
<th>BMC ILLUSTRATORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yi-Min Chun</td>
<td>Erin Kezie</td>
</tr>
<tr>
<td>Nicole Clough</td>
<td>Joshua Lai</td>
</tr>
<tr>
<td>Jerusha Ellis</td>
<td>Jean Yi-Chun Lin</td>
</tr>
<tr>
<td>Laura Greenlee</td>
<td>Man-San Ma</td>
</tr>
<tr>
<td>Karyn Ho</td>
<td></td>
</tr>
<tr>
<td>Amanda Montanez</td>
<td></td>
</tr>
<tr>
<td>Andrew Q. Tran</td>
<td></td>
</tr>
<tr>
<td>Marissa Webber</td>
<td></td>
</tr>
<tr>
<td>Alice Zheng</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Research and Development</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Jieun Cha</td>
<td></td>
</tr>
<tr>
<td>Meah Gao</td>
<td></td>
</tr>
<tr>
<td>Howard Meng</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SURGERY</th>
<th>SURGERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Surgery</td>
<td>Plastic Surgery</td>
</tr>
<tr>
<td>Nicolas Bowers</td>
<td>Stephanie Dreckmann</td>
</tr>
<tr>
<td>Nada Gawad</td>
<td>Sangita Sequeira</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecology</td>
<td>Urology</td>
</tr>
<tr>
<td>Emily Brander</td>
<td>Alexandra L. Millman</td>
</tr>
<tr>
<td>Jena Hall</td>
<td>Andrew Stewart</td>
</tr>
<tr>
<td>Katherine McLean</td>
<td>Clare Toguri</td>
</tr>
<tr>
<td>Marina Vinder</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurosurgery</td>
<td></td>
</tr>
<tr>
<td>Farshad Nassiri</td>
<td></td>
</tr>
<tr>
<td>Johnny Nguyen</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetrics</td>
<td></td>
</tr>
<tr>
<td>Rebecca Ronsley</td>
<td></td>
</tr>
<tr>
<td>Jamie Saperia</td>
<td></td>
</tr>
<tr>
<td>Alia Sunderji</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmology</td>
<td></td>
</tr>
<tr>
<td>Harleen Bedi</td>
<td></td>
</tr>
<tr>
<td>Yao Wang</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopedics</td>
<td></td>
</tr>
<tr>
<td>Jonny Elsefari</td>
<td></td>
</tr>
<tr>
<td>Michael Neufeld</td>
<td></td>
</tr>
<tr>
<td>Kajeandra</td>
<td></td>
</tr>
<tr>
<td>Ravichandiran</td>
<td></td>
</tr>
<tr>
<td>David Stockton</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Otolaryngology</td>
<td></td>
</tr>
<tr>
<td>Peter Dixon</td>
<td></td>
</tr>
<tr>
<td>Ryan Jude Figueroa</td>
<td></td>
</tr>
</tbody>
</table>
All contributing professors have been appointed at the University of Toronto.

David Adam, MD, FRCPC  
Division of Dermatology  
Department of Medicine  
St. Michael's Hospital

Anne M. R. Agur, BSc, MSc, PhD  
Division of Anatomy  
Department of Surgery  
University of Toronto

Lori Albert, MD, FRCPC  
Division of Rheumatology  
Department of Medicine  
University Health Network - Toronto Western Hospital

Ruby Alvi, MD, CCFP, MHSc  
Department of Family and Community Medicine  
University of Toronto

Meyer Balter, MD, FRCPC  
Division of Respiratory Medicine  
Department of Medicine  
Mount Sinai Hospital

Nirit Bernhard, MSc, MD, FRCPC  
Department of Pediatrics  
Hospital for Sick Children

Andrea Boggild, MSc, MD, FRCPC  
Tropical Disease Unit and Division of Infectious Diseases  
University Health Network - Toronto General Hospital

Esther Bui, MD, FRCPC  
Division of Neurology and Division of Obstetrical Medicine  
Department of Medicine  
Sunnybrook Health Sciences Centre

Sohail Cheema, MD, FRCPC  
Department of Pediatrics  
St. Michael's Hospital

Chi-Ming Chow, MDCM, MSc, FRCPC  
Division of Cardiology  
Department of Medicine  
St. Michael's Hospital

Tae-Bong Chung, MD, FRCPC  
Department of Medical Imaging  
Mount Sinai Hospital

Isabella Devito, MD, FRCPC  
Department of Anesthesia and Pain Management  
University Health Network and Mount Sinai Hospital

Mark Freedman, MD, FRCPC  
Department of Emergency Medicine  
Sunnybrook Health Sciences Centre

Sarah Fergusson, MD, FRCSC  
Division of Gynecologic Oncology  
Department of Obstetrics and Gynaecology  
University Health Network - Princess Margaret Hospital

Barry J. Goldlist, MD, FRCPC  
Division of Geriatric Medicine  
Department of Medicine  
University Health Network

Philip C. Hébert, MA, PhD, MD, FCFPC  
Department of Family and Community Medicine  
Joint Centre for Bioethics  
Sunnybrook Health Sciences Centre

Sender Herschorn, MDCM, FRCSC  
Department of Urology  
Sunnybrook Health Sciences Centre and Women's College Hospital

Jonathan C. Irish, MD, MSc, FRCSC  
Department of Otolaryngology - Head and Neck Surgery  
University Health Network

Nasir Jaffer, MD, FRCPC  
Division of Abdominal Imaging  
Department of Medical Imaging  
Joint Department of Medical Imaging  
University of Toronto

David Juurlink, BPhm, MD, PhD, FRCPC  
Division of Clinical Pharmacology and Toxicology  
Departments of Medicine and Pediatrics  
Sunnybrook Health Sciences Centre

Gabor Kandel, MD, FRCPC  
Division of Gastroenterology, Department of Medicine  
St. Michael's Hospital

Sari L. Kives, MD, FRCSC  
Department of Obstetrics and Gynaecology  
St. Michael's Hospital and The Hospital for Sick Children

Paul Kuzyk, MASC, MD, FRCSC  
Division of Orthopedic Surgery  
Department of Surgery  
Mount Sinai Hospital

Wai-Ching Lam, MD, FRCSC  
Department of Ophthalmology and Vision Science  
University Health Network - Toronto Western Hospital

Chloe Leon, MD, FRCPC  
Division of Brain and Therapeutics  
Department of Psychiatry  
Centre for Addiction and Mental Health

Armando Lorenzo, MD, FRCSC  
Division of Urology  
Department of Surgery  
The Hospital for Sick Children

Julia Lowe, MBChB, MMedSci, FRCPC  
Division of Endocrinology and Metabolism  
Department of Medicine  
Sunnybrook Health Sciences Center

Todd Mainprize, MD, FRCSC  
Department of Neurosurgery  
Sunnybrook Health Sciences Centre

Eric Massicotte, MD, MSc, FRCSC  
Department of Neurosurgery  
University Health Network - Toronto Western Hospital

Michael McDonald, MD, FRCPC  
Division of Cardiology and The Multi-Organ Transplant Program  
Department of Medicine  
University Health Network - Toronto General Hospital

Heather McDonald-Blumer, MD, MSc, FRCPC  
Division of Rheumatology  
Department of Medicine  
Mount Sinai Hospital

Filomena Meffe, MD, MSc, FRCSC  
Department of Obstetrics and Gynaecology  
St. Michael's Hospital

Yvette Miller-Monthrope, MD, FRCPC  
Division of Dermatology  
Department of Medicine  
Women's College Hospital

Azadeh Moaveni, MD, CCFP  
Department of Family and Community Medicine  
University Health Network - Toronto Western Hospital

Eva Mocarski, MD, FRCSC  
Department of Obstetrics and Gynaecology  
St. Michael's Hospital

Andrew Morris, MD, SM, FRCPC  
Division of Infectious Diseases  
Department of Medicine  
Mount Sinai Hospital
Faculty Contributors, University of Toronto

Steven Moss, MD, FRCPC
Division of Paediatric Emergency Medicine
Department of Paediatrics
University of Toronto

Brian J. Murray, MD, FRCPC, D,ABSM
Division of Neurology and Sleep Medicine
Department of Medicine
Sunnybrook Health Sciences Centre

Melinda Musgrave, MD, PhD, FRCSC
Division of Plastic and Reconstructive Surgery
Department of Surgery
St. Michael's Hospital

Sharon Naymark, MD, FRCPC
Department of Pediatrics
St. Joseph's Health Centre - Toronto

Markku T. Nousiainen, MD, MSc, MEd, FRCSC
Division of Orthopedic Surgery
Department of Surgery
Sunnybrook Health Sciences Centre
Holland Orthopedic & Arthritic Centre

Melissa Nutik, MD, CCFP, FCFP
Department of Family and Community Medicine
Mount Sinai Hospital

George Oreopoulos, MD, MSc, FRCSC
Division of Vascular Surgery
Department of Surgery
University Health Network

Andrea V. Page, MD, FRCPC
Division of Infectious Diseases
Department of Medicine
University Health Network

Susan Poutanen, MD, MPH, FRCPC
Department of Microbiology
University Health Network and Mount Sinai Hospital

Ramesh Prasad, MBBS, MSc, FRCPC
Division of Nephrology
Department of Medicine
St. Michael's Hospital

Evan Propst, MD, MSc, FRCSC
Division of Head and Neck Surgery
Department of Otolaryngology
The Hospital for Sick Children

Angela Punnett, MD, FRCPC
Department of Pediatrics
The Hospital for Sick Children

Fran E. Scott, MD, CCFP, FRCP, MSc
Division of Epidemiology
Dalla Lana School of Public Health

Phillip Segal, MD, FRCPC
Division of Endocrinology and Metabolism
Department of Medicine
University Health Network - Toronto General Hospital

Amanda Selk, MD, FRCSC
Department of Obstetrics and Gynaecology
Mount Sinai Hospital

Marisa Sit, MD, FRCSC
Department of Ophthalmology and Vision Science
University Health Network - Toronto Western Hospital

Peter Stotland, MSc, MD, FRCSC
Division of General Surgery
Department of Surgery
Sunnybrook Health Sciences Centre

Diana Tamir, MD, FRCPC
Department of Anesthesia and Pain Management
University Health Network

Darrell Tan, MD, PhD, FRCPc
Division of Infectious Diseases
St. Michael's Hospital

David Tang-Wai, MDCM, FRCPc
Division of Neurology and Geriatric Medicine
Department of Medicine
University Health Network

Piero Tartaro, MD, FRCPC
Division of Gastroenterology
Department of Medicine
University of Toronto

Fernando Teixeira, MD, FRCPC
Department of Emergency Medicine
St. Michael's Hospital

Margaret Thompson, MD, FRCPC, FACMT
Department of Emergency Medicine
St. Michael's Hospital and The Hospital for Sick Children

Martina Trinkaus, MD, FRCPC
Division of Hematology
Department of Medicine
St. Michael's Hospital

Herbert P. von Schroeder, MD, MSc, FRCSC
Divisions of Orthopedic Surgery and Plastic Surgery
Department of Surgery
University Health Network

Oshrit Wanono, MD, FRCPC
Division of Child and Adolescent Psychiatry
Department of Psychiatry
Centre for Addiction and Mental Health

Richard Ward, MBBS, MRCP, FRCPath
Division of Hematology
Department of Medicine
University Health Network

Fay Weisberg, MD, FRCSC
Division of Reproductive Endocrinology and Infertility
Department of Obstetrics and Gynaecology
University of Toronto

Alice Wei, MD CM, MSc, FRCSC
Division of General Surgery
Department of Surgery
University Health Network

Michael Wiley, BSc, MSc, PhD
Division of Anatomy
Department of Surgery
University of Toronto

Anna Woo, MD CM, SM, DABIM, FRCPC
Division of Cardiology
Department of Medicine
University Health Network - Toronto General Hospital

Jensen Yeung, MD, FRCPC
Division of Dermatology
Department of Medicine
Women's College Hospital

Elaine Yong, MD, FRCPC
Division of Gastroenterology
Department of Medicine
Sunnybrook Health Sciences Centre

Eugene Yu, MD, FRCPC
Division of Neuroradiology
Department of Medical Imaging
University Health Network

Alireza Zahiri, MD, FRCPC
Division of Nephrology
Department of Medicine
Sunnybrook Health Sciences Centre
# Table of Contents

1. Common Unit Conversions
2. Commonly Measured Laboratory Values
3. Ethical, Legal and Organizational Aspects of Medicine .......................... ELOAM
4. Anesthesia and Perioperative Medicine ............................................. A
5. Cardiology and Cardiovascular Surgery ............................................. C
6. Clinical Pharmacology ....................................................................... CP
7. Dermatology ...................................................................................... D
8. Emergency Medicine ......................................................................... ER
9. Endocrinology .................................................................................... E
10. Family Medicine ................................................................................ FM
11. Gastroenterology ............................................................................... G
12. General Surgery ................................................................................ GS
13. Geriatric Medicine ............................................................................ GM
14. Gynecology ........................................................................................ GY
15. Hematology ........................................................................................ H
16. Infectious Diseases ........................................................................... ID
17. Medical Imaging ................................................................................ MI
18. Nephrology ........................................................................................ NP
19. Neurology .......................................................................................... N
20. Neurosurgery ...................................................................................... NS
21. Obstetrics ............................................................................................ OB
22. Ophthalmology ................................................................................... OP
23. Orthopedics ....................................................................................... OR
24. Otolaryngology .................................................................................. OT
25. Pediatrics ............................................................................................. P
26. Plastic Surgery ..................................................................................... PL
27. Population Health and Epidemiology ............................................... PH
28. Psychiatry ............................................................................................ PS
29. Respirology ........................................................................................ R
30. Rheumatology ...................................................................................... RH
31. Urology ................................................................................................. U
32. Index
How to Use This Book

This book has been designed to remain as one book or to be taken apart into smaller booklets. Identify the beginning and end of a particular section, then carefully bend the pages along the perforated line next to the spine of the book. Then tear the pages out along the perforation.

The layout of Toronto Notes 2014 allows easy identification of important information. These items are indicated by icons interspersed throughout the text:

<table>
<thead>
<tr>
<th>Icon</th>
<th>Icon Name</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Icon]</td>
<td>Key Objectives</td>
<td>This icon is found next to headings in the text. It identifies key objectives and conditions as determined by the Medical Council of Canada or the National Board of Medical Examiners in the USA. If it appears beside a dark title bar, all subsequent subheadings should be considered key topics.</td>
</tr>
<tr>
<td>![Icon]</td>
<td>Clinical Pearl</td>
<td>This icon is found in sidebars of the text. It identifies concise, important information which will aid in the diagnosis or management of conditions discussed in the accompanying text.</td>
</tr>
<tr>
<td>![Icon]</td>
<td>Memory Aid</td>
<td>This icon is found in sidebars of the text. It identifies helpful mnemonic devices and other memory aids.</td>
</tr>
<tr>
<td>![Icon]</td>
<td>Clinical Flag</td>
<td>This icon is found in sidebars of the text. It indicates information or findings that require urgent management or specialist referral.</td>
</tr>
<tr>
<td>![Icon]</td>
<td>Cross-Reference</td>
<td>This icon is found in sidebars of the text. It indicates a cross-reference for information that is discussed in a separate chapter.</td>
</tr>
<tr>
<td>![Icon]</td>
<td>Evidence Based Medicine</td>
<td>This icon is found in sidebars of the text. It identifies key research studies for evidence-based clinical decision making related to topics discussed in the accompanying text.</td>
</tr>
<tr>
<td>![Icon]</td>
<td>Colour Photo Atlas</td>
<td>This icon is found next to headings in the text. It indicates topics that correspond with images found in the Colour Photo Atlas available online. (<a href="http://www.torontonotes.ca">www.torontonotes.ca</a>).</td>
</tr>
<tr>
<td>![Icon]</td>
<td>Radiology Atlas</td>
<td>This icon is found next to headings in the text. Indicates topics that correspond to images found in the Radiology Atlas available online. (<a href="http://www.torontonotes.ca">www.torontonotes.ca</a>)</td>
</tr>
<tr>
<td>![Icon]</td>
<td>Online Resources</td>
<td>This icon is found next to headings in the text. It indicates topics that correspond with electronic resources such as Functional Neuroanatomy or ECGs Made Simple, available online. (<a href="http://www.torontonotes.ca">www.torontonotes.ca</a>)</td>
</tr>
</tbody>
</table>

Chapter Divisions

To aid in studying and finding relevant material quickly, each chapter is organized in the following general framework:

Basic Anatomy/Physiology Review
- features the high-yield, salient background information students are often assumed to have remembered from their early medical school education

Common Differential Diagnoses
- aims to outline a clinically useful framework to tackle the common presentations and problems faced in the area of expertise

Diagnoses
- the bulk of the book
- etiology, epidemiology, pathophysiology, clinical features, investigations, management, complications, and prognosis

Common Medications
- a quick reference section for review of medications commonly prescribed
## Common Unit Conversions

To convert from the conventional unit to the SI unit, **multiply** by conversion factor
To convert from the SI unit to the conventional unit, **divide** by conversion factor

<table>
<thead>
<tr>
<th>Conventional Unit</th>
<th>Conversion Factor</th>
<th>SI Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH pg/mL</td>
<td>0.22</td>
<td>pmol/L</td>
</tr>
<tr>
<td>Albumin g/dL</td>
<td>10</td>
<td>g/L</td>
</tr>
<tr>
<td>Bilirubin mg/dL</td>
<td>17.1</td>
<td>µmol/L</td>
</tr>
<tr>
<td>Calcium mg/dL</td>
<td>0.25</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Cholesterol mg/dL</td>
<td>0.0259</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Cortisol µg/dL</td>
<td>27.59</td>
<td>nmol/L</td>
</tr>
<tr>
<td>Creatinine mg/dL</td>
<td>88.4</td>
<td>µmol/L</td>
</tr>
<tr>
<td>Creatinine clearance mL/min</td>
<td>0.0167</td>
<td>mL/s</td>
</tr>
<tr>
<td>Ethanol mg/dL</td>
<td>0.217</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Ferritin ng/mL</td>
<td>2.247</td>
<td>pmol/L</td>
</tr>
<tr>
<td>Glucose mg/dL</td>
<td>0.0555</td>
<td>mmol/L</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>0.01</td>
<td>proportion of 1.0</td>
</tr>
<tr>
<td>Hemaglobin g/dL</td>
<td>10</td>
<td>g/L</td>
</tr>
<tr>
<td>HDL cholesterol mg/dL</td>
<td>0.0259</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Iron, total µg/dL</td>
<td>0.179</td>
<td>µmol/L</td>
</tr>
<tr>
<td>Lactate (lactic acid) mg/dL</td>
<td>0.111</td>
<td>mmol/L</td>
</tr>
<tr>
<td>LDL cholesterol mg/dL</td>
<td>0.0259</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Leukocytes x 10^3 cells/mm^3</td>
<td>1</td>
<td>x 10^6 cells/L</td>
</tr>
<tr>
<td>Magnesium mg/dL</td>
<td>0.411</td>
<td>mmol/L</td>
</tr>
<tr>
<td>MCV µm^3</td>
<td>1</td>
<td>fl</td>
</tr>
<tr>
<td>Platelets x 10^3 cells/mm^3</td>
<td>1</td>
<td>x 10^6 cells/L</td>
</tr>
<tr>
<td>Reticulocytes % of RBCs</td>
<td>0.01</td>
<td>proportion of 1.0</td>
</tr>
<tr>
<td>Salicylate mg/L</td>
<td>0.00724</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Testosterone ng/dL</td>
<td>0.0347</td>
<td>nmol/L</td>
</tr>
<tr>
<td>Thyroxine (T₄) ng/dL</td>
<td>12.87</td>
<td>pmol/L</td>
</tr>
<tr>
<td>Total Iron Binding Capacity µg/dL</td>
<td>0.179</td>
<td>µmol/L</td>
</tr>
<tr>
<td>Triiodothyronine (T₃) pg/dL</td>
<td>0.0154</td>
<td>pmol/L</td>
</tr>
<tr>
<td>Triglycerides mg/dL</td>
<td>0.0113</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Urea nitrogen mg/dL</td>
<td>0.357</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Uric acid mg/dL</td>
<td>59.48</td>
<td>µmol/L</td>
</tr>
</tbody>
</table>

**Celsius → Fahrenheit**
\[ F = (C \times 1.8) + 32 \]

**Fahrenheit → Celsius**
\[ C = (F – 32) \times 0.5555 \]

**Kilograms → Pounds**
1 kg = 2.2 lbs

**Pounds → Ounces**
1 lb = 16 oz

**Ounces → Grams**
1 oz = 28.3 g

**Inches → Centimetres**
1 in = 2.54 cm
### Commonly Measured Laboratory Values

<table>
<thead>
<tr>
<th>Test</th>
<th>Conventional Units</th>
<th>SI Units</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arterial Blood Gases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.35-7.45</td>
<td>7.35-7.45</td>
</tr>
<tr>
<td>PCO₂</td>
<td>35-45 mmHg</td>
<td>4.7-6.0 kPa</td>
</tr>
<tr>
<td>PO₂</td>
<td>80-105 mmHg</td>
<td>10.6-14 kPa</td>
</tr>
<tr>
<td><strong>Serum Electrolytes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>22-28 mEq/L</td>
<td>22-28 mmol/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.4-10.2 mg/dL</td>
<td>2.1-2.5 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>95-106 mEq/L</td>
<td>95-106 mmol/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.3-2.1 mEq/L</td>
<td>0.65-1.05 mmol/L</td>
</tr>
<tr>
<td>Phosphate</td>
<td>2.7-4.5 mg/dL</td>
<td>0.87-1.45 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5-5.0 mEq/L</td>
<td>3.5-5.0 mmol/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>136-145 mEq/L</td>
<td>136-145 mmol/L</td>
</tr>
<tr>
<td><strong>Serum Nonelectrolytes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5-5.0 g/dL</td>
<td>35-50 g/L</td>
</tr>
<tr>
<td>ALP</td>
<td>35-100 U/L</td>
<td>35-100 U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>8-20 U/L</td>
<td>8-20 U/L</td>
</tr>
<tr>
<td>Amylase</td>
<td>25-125 U/L</td>
<td>25-125 U/L</td>
</tr>
<tr>
<td>AST</td>
<td>8-20 U/L</td>
<td>8-20 U/L</td>
</tr>
<tr>
<td>Bilirubin (direct)</td>
<td>0-0.3 mg/dL</td>
<td>0.5 µmol/L</td>
</tr>
<tr>
<td>Bilirubin (total)</td>
<td>0.1-1.0 mg/dL</td>
<td>2.17 µmol/L</td>
</tr>
<tr>
<td>BUN</td>
<td>7-18 mg/dL</td>
<td>1.2-3.0 mmol/L</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt;200 mg/dL</td>
<td>&lt;5.2 mmol/L</td>
</tr>
<tr>
<td>Creatinine (female)</td>
<td>10-70 U/L</td>
<td>10-70 U/L</td>
</tr>
<tr>
<td>Creatinine (male)</td>
<td>25-90 U/L</td>
<td>25-90 U/L</td>
</tr>
<tr>
<td>Creatine Kinase – MB fraction</td>
<td>0-12 U/L</td>
<td>0-12 U/L</td>
</tr>
<tr>
<td>Ferritin (female)</td>
<td>12-150 µg/L</td>
<td>12-150 µg/L</td>
</tr>
<tr>
<td>Ferritin (male)</td>
<td>15-200 µg/L</td>
<td>15-200 µg/L</td>
</tr>
<tr>
<td>Glucose (fasting)</td>
<td>70-110 mg/dL</td>
<td>3.8-6.1 mmol/L</td>
</tr>
<tr>
<td>HbA1c</td>
<td>&lt;6%</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>LDH</td>
<td>100-250 U/L</td>
<td>100-250 U/L</td>
</tr>
<tr>
<td>Osmolality</td>
<td>275-300 mOsm/kg</td>
<td>275-300 mOsm/kg</td>
</tr>
<tr>
<td><strong>Serum Hormones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH (0800h)</td>
<td>&lt;60 pg/mL</td>
<td>&lt;13.2 pmol/L</td>
</tr>
<tr>
<td>Cortisol (0800h)</td>
<td>5-23 µg/dL</td>
<td>138-635 nmol/L</td>
</tr>
<tr>
<td>Prolactin</td>
<td>&lt;20 ng/mL</td>
<td>&lt;20 ng/mL</td>
</tr>
<tr>
<td>Testosterone (male,free)</td>
<td>9-30 ng/dL</td>
<td>0.31-1 pmol/L</td>
</tr>
<tr>
<td>Thyroxine (T₄)</td>
<td>5-12 ng/dL</td>
<td>64-155 nmol/L</td>
</tr>
<tr>
<td>Triiodothyronine (T₃)</td>
<td>115-190 ng/dL</td>
<td>1.8-2.9 nmol/L</td>
</tr>
<tr>
<td>TSH</td>
<td>0.5-5 µU/mL</td>
<td>0.5-5 µU/mL</td>
</tr>
<tr>
<td><strong>Hematologic Values</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR (female)</td>
<td>0-20 mm/h</td>
<td>0-20 mm/h</td>
</tr>
<tr>
<td>ESR (male)</td>
<td>0-15 mm/h</td>
<td>0-15 mm/h</td>
</tr>
<tr>
<td>Hemoglobin (female)</td>
<td>12.3-15.7 g/dL</td>
<td>123-157 g/L</td>
</tr>
<tr>
<td>Hemoglobin (male)</td>
<td>13.5-17.5 g/dL</td>
<td>140-174 g/L</td>
</tr>
<tr>
<td>Hematocrit (female)</td>
<td>36-46%</td>
<td>36-46%</td>
</tr>
<tr>
<td>Hematocrit (male)</td>
<td>41-53%</td>
<td>41-53%</td>
</tr>
<tr>
<td>INR</td>
<td>1.0-1.1</td>
<td>1.0-1.1</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>4.5-11 x 10⁹ cells/mm³</td>
<td>4.5-11 x 10⁹ cells/L</td>
</tr>
<tr>
<td>MCV</td>
<td>88-100 µm³</td>
<td>88-100 fL</td>
</tr>
<tr>
<td>Platelets</td>
<td>150-400 x 10³/mm³</td>
<td>150-400 x 10³/L</td>
</tr>
<tr>
<td>PTT</td>
<td>25-35 s</td>
<td>25-35 s</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>0.5-1.5% of RBC</td>
<td>20-84 x 10⁹/L</td>
</tr>
</tbody>
</table>
Ethical, Legal and Organizational Aspects of Medicine

Molly Dingwall and Jesse Kancir, chapter editors
Maria Jogova, associate editor
Melini Gupta, EBM editor
Dr. Philip C. Hébert, staff editor

Legal Framework ............................................... 2
Sources of Law

Ethical Framework ........................................... 2
Principles of Ethics
Code of Ethics

Specific Issues in Private Health
Law and Ethics .................................................. 4
Doctor-Patient Relationship
Consent and Capacity
Consent
Capacity
Confidentiality and Reporting Requirements
Privacy of Medical Records
Physician Competence and Professional Conduct
Truth Telling
Research Ethics
Physician-Industry Relations
Physician Responsibilities Regarding Death
Role of the Coroner
Palliative and End-of-Life Care
Reproductive and Sexual Health Law and Ethics

Organization of Health Care in Canada ............. 15
Legal Foundation
History
Key Principles of the Canada Health Act
Health Care Expenditure and Delivery in Canada
Ethical Considerations in Resource Allocation
and Physicians’ Role
Role of the Provincial Licensing Authorities
Licensure and Certification
Role of Professional Associations

The US Health Care System ......................... 19
History
Health Care Expenditure and Delivery in the US
Access to Health Services
Health Care Reform

References ......................................................... 22

Further information on these topics can be found in the Objectives of the Considerations of the Legal, Ethical and Organizational Aspects of the Practice of Medicine (CLEO) – which can be downloaded free of charge from the Medical Council of Canada website at http://mcc.ca/wp-content/uploads/CLEO.pdf

Canadian law applicable to medical practice varies between jurisdictions and changes over time. Criminal law is nationwide, but non-criminal (civil) law varies between provinces. This section is meant to serve only as a guide. Students and physicians should ensure that their practices conform to local and current laws.

Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>AMA</td>
<td>American Medical Association</td>
</tr>
<tr>
<td>ART</td>
<td>advanced reproductive technologies</td>
</tr>
<tr>
<td>CCB</td>
<td>Consent and Capacity Board</td>
</tr>
<tr>
<td>CMA</td>
<td>Canadian Medical Association</td>
</tr>
<tr>
<td>CMPA</td>
<td>Canadian Medical Protective Association</td>
</tr>
<tr>
<td>CPSD</td>
<td>College of Physicians and Surgeons of Ontario</td>
</tr>
<tr>
<td>HCCA</td>
<td>Health Care Consent Act</td>
</tr>
<tr>
<td>LACC</td>
<td>Licensee of the Medical Council of Canada</td>
</tr>
<tr>
<td>MCC</td>
<td>Medical Council of Canada</td>
</tr>
<tr>
<td>OECD</td>
<td>Organization for Economic Co-operation and Development</td>
</tr>
<tr>
<td>PIPEDA</td>
<td>Personal Information Protection and Electronic Documents Act</td>
</tr>
<tr>
<td>POA</td>
<td>power of attorney</td>
</tr>
<tr>
<td>SDM</td>
<td>substitute decision maker</td>
</tr>
</tbody>
</table>
Legal Framework

Sources of Law

<table>
<thead>
<tr>
<th>Source of Law</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Law</td>
<td>Legal rules and principles that define private rights and obligations</td>
<td>Tort Law: defines breaches of civil duty owed to someone else. Contract Law: define mutually agreed upon rights and obligations that may result in award of damages if breached.</td>
</tr>
<tr>
<td>Constitution</td>
<td>Supreme law of Canada. All other laws must be consistent with constitution.</td>
<td>Canadian Charter of Rights and Freedoms is part of the constitution and guarantees the rights of life, liberty, security of the person, and equality under the law.</td>
</tr>
</tbody>
</table>

Ethical Framework

Principles of Ethics

- ethics addresses:
  1) the principles and values that help define what is morally right and wrong
  2) the rights, duties and obligations of individuals and groups
- the practice of medicine assumes there is one code of professional ethics for all doctors and that they will be held accountable by that code and its implications

Table 1. The Four Principles Approach to Medical Ethics

<table>
<thead>
<tr>
<th>Principle</th>
<th>Definition</th>
<th>In Practice Do's</th>
<th>In Practice Don't's</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomy</td>
<td>• Recognizes an individual’s right and ability to decide for themselves according to his/her beliefs and values. • Not applicable to newborns, young children, or in situations where informed consent and choice are not possible or may not be appropriate.</td>
<td>• Respect and promote an individual patient’s values and preferences in decision making to empower him or her. • Understand, appreciate, and respect a patient’s decision even if it may differ from the recommendation of the physician. • Show fidelity to incapable patient’s prior capable views if known, and treat them with worth and dignity.</td>
<td>• Doctors are not obliged, and indeed ought not, to comply with patients wishes that are illegal or might be considered to be ‘conduct unbecoming a doctor’ (unprofessional conduct, falling below the standard of care). • A patient’s autonomy may be compromised by illness; the principle of autonomy is not a trump card and must be balanced by the rest of the listed principles. • Patients are not expected to act in ways considered ‘reasonable’ or rational by others as long as they do not harm others.</td>
</tr>
</tbody>
</table>

Autonomy vs. Competence

**Autonomy:** the right that patients have to make decisions according to their beliefs and preferences.

**Competence:** the ability or capacity to make a specific decision for oneself.
Table 1. The Four Principles Approach to Medical Ethics (continued)

<table>
<thead>
<tr>
<th>Principle</th>
<th>Definition</th>
<th>In Practice Do’s</th>
<th>In Practice Don’ts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beneficence</td>
<td>• The patient-based ‘best interests’ standard that combines doing good, avoiding harm, taking into account the patient’s values, beliefs, and preferences, so far as these are known</td>
<td>• Try to ensure that a treatment’s benefits outweigh its burdens</td>
<td>• Do not make a decision without a patient’s input (direct or indirect)</td>
</tr>
<tr>
<td></td>
<td>• Autonomy should be integrated with the physician’s conception of a patient’s medically-defined best interests</td>
<td>• Recommend treatment based on evidence and professional experience to patients and help them weigh the risks and benefits of various options</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The aim is to minimize harmful outcomes and maximize beneficial ones</td>
<td>• Where a patient’s capacity is compromised, physicians have more authority to act purely in the patient’s best interests as defined by the therapeutic relationship but they still ought to do so in ways informed by the patient’s known wishes and with the involvement, where possible, of the patient’s substitute decision-maker</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Paramount in situations where consent/choice is not possible or may not be appropriate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Maleficence</td>
<td>• Obligation to avoid causing harm; primum non nocere (“First, do no harm”)</td>
<td>• Efforts should be made to reduce error and adverse events and ensure patient safety</td>
<td>• Do not recommend a treatment because it will have some harm associated with it</td>
</tr>
<tr>
<td></td>
<td>• A limit condition of the Beneficence principle</td>
<td>• A key guide for all management plans</td>
<td></td>
</tr>
<tr>
<td>Justice</td>
<td>• Fair distribution of benefits and harms within a community, regardless of geography or privilege</td>
<td>• Scarce resources are distributed based on the needs of patients and the benefit they would receive from obtaining a specific resource e.g. organs for transplantation are fairly distributed if they go to those who are the most unwell, who are the most likely to survive the longest with the transplant, and who have waited the longest to receive a transplant</td>
<td>• Physicians ought to be ‘door openers’, not ‘gate-closers’, for their patients</td>
</tr>
<tr>
<td></td>
<td>• Concept of fairness: Is the patient receiving what he/she deserves – his/her fair share? Is he/she treated the same as equally situated patients? How do one set of treatment decisions impact on others?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Respect rules of fair play and basic human rights, such as freedom from persecution and the right to have one’s interests considered and respected</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Code of Ethics

- CMA developed a Code of Ethics that acts as a common ethical framework for Canadian physicians
  - prepared by physicians for physicians and applies to physicians, residents, and medical students
  - based on the fundamental ethical principles of medicine
  - sources include the Hippocratic Oath, developments in human rights, recent bioethical discussion
  - statements are general in nature
  - CMA policy statements address specific ethical issues not mentioned by the code (e.g. abortion, transplantation, and euthanasia)
- the American Medical Association (AMA) has a Code of Medical Ethics
  - articulates the values of medicine as a profession and defines medicine’s integrity
  - source of the profession’s authority to self-regulate
  - evolving document that changes as new questions arise; AMA policy positions (“AMA Policy”) address current health care issues, the health care system, internal organizational structure, decision-making processes, and medical science and technology

The Canadian Adverse Events Study: The Incidence of Adverse Events among Hospital Patients in Canada

**Studies:** Hospital charts randomly selected and reviewed in four randomly selected Canadian hospitals for the fiscal year 2000. Patients: 6,174 patient charts sampled, 3,745 eligible charts (>18 yr of age; nonpsychiatric, nondiabetic, minimum 24 h admission). Results: AE rate was 7.5% per 100 hospital admissions (95% CI 5.7-9.3). Highly preventable AEs occurred in 36.9% of patients with AEs (95% CI 32.0-41.3%) and death occurred in 20.0% (95% CI 17.3%-23.8%). An estimated 1521 additional hospital days were associated with AEs. Patients with AEs were significantly older than those without (mean age and standard deviation) 64.9 [16.3] v. 62.0 [18.4] yr; p = 0.016. Men and women experienced equal rates of AEs.

Conclusions: The overall incidence rate of AEs of 7.5% suggests that, of the almost 2.5 million annual hospital admissions in Canada similar to the type studied, about 185,000 are associated with an AE and close to 70,000 of these are potentially preventable.

Adverse Event (AE)

An unintended injury or complication from health care management resulting in disability, death or prolonged hospital stay.

The CMA Code of Ethics is a quasi-legal standard for physicians. If the law sets a minimal moral standard for doctors, the Code ratchets up these standards.
Doctor-Patient Relationship

**Ethical Basis**

- A partnership based on the physician providing expert opinion, information, options, and interventions that allows the patient to make informed choices about his/her health care
- Within this relationship, the doctor and patient share the goals of positive health outcomes, good communication, honesty, flexibility, sensitivity, informed consent, and respect
- This relationship has the potential to be unequal due to a power difference
  - Patients are ill and lack medical expertise
  - Physicians possess specialized medical knowledge and skills
  - Physicians are in a fiduciary relationship with their patients
- Due to the nature of the doctor-patient relationship, the physician will:
  - Place the best interests of the patient first
  - Establish a relationship of trust with the patient
  - Follow through on undertakings made to the patient in good faith
- The physician will accept or refuse patients requesting care:
  - Without consideration of race, gender, age, sexual orientation, financial means, religion or nationality
  - Without arbitrary exclusion of any particular group of patients, such as those known to be difficult or affiliated with serious disease
  - Except in emergency situations, in which case care must be rendered
- Once having accepted a patient into care, the physician may terminate the relationship provided:
  - It is not an emergency
  - After a reasonable period of time (usually a month) for the patient to find alternate care
  - Adequate notice (usually an explanatory letter by registered mail) has been given to the patient
  - There are other options to find ‘medically necessary care’ (in other words, in smaller communities with fewer options for care, there may need to be some flexibility in cessation of care)
- The reason for termination ought to be ‘failure of trust’
- The physician will not exploit the doctor-patient relationship for personal advantage – for sexual, financial, academic or other purposes
- The physician will disclose limitations to the patient where personal beliefs or inclinations limit the treatment the physician is able to offer
- The physician will maintain and respect professional boundaries at all times
  - Including physical, emotional, and sexual boundaries
  - Regarding treatment of themselves, their families, and friends

**Legal Basis**

- Duties and rights defined partly by:
  - Tort law that allows patients to recover damages for wrongful acts committed against them; the most important are:
    - A. Negligence: breach of a legal duty of care (in tort) which results in damage
    - Legal finding, not a medical one
    - Physicians may be found negligent when the following four conditions are met:
      1. The physician owed a duty of care to the patient (the existence of a doctor-patient relationship generally suffices)
      2. The duty of care was breached (e.g. by failure to provide the standard of care)
      - The standard of care is one that would reasonably be expected under similar circumstances of an ordinary, prudent physician of the same training, experience, and specialization
      3. The patient was injured or harmed
      4. The harm or injury was caused by the breach of the duty of care
    - Errors of judgment are not necessarily negligent
    - Making the wrong diagnosis is not negligent if a reasonable doctor might have made the same mistake in the same circumstances
    - Failure to reconsider the diagnosis if the patient does not respond to treatment may be negligent
    - Physicians can be held liable for the negligent actions of their employees or other individuals they are supervising
  - B. Battery: the application of force to a person’s body without their consent
  - Contractual rights and obligations that if breached may result in the award of damages
  - Fiduciary duty of physicians to their patients (i.e. to act in their best interest)

In situations in which it would be more difficult for a patient to find alternate “medically necessary care”, the physician may need to exhibit some flexibility in cessation of care.

"Failure of trust" situations include “double-doctoring” on the part of the patient and patient threats of violence.

CPSO Policy: Treating Self and Family Members
Physicians will not diagnose or treat themselves or family members except for minor conditions or in emergencies and then only if no other physician is readily available.

CPSO Policy: Ending the Physician-Patient Relationship
Discontinuing services that are needed is an act of professional misconduct unless done by patient request, alternative services are arranged, or adequate notice has been given.

Dealing with Controversial and Ethical Issues in Practice
- Discuss in a non-judgmental manner
- Ensure patients have full access to relevant and necessary information
- Identify if certain options lie outside of your moral boundaries and refer to another physician if appropriate
- Consult with appropriate ethics committees or boards
- Protect freedom of moral choice for students or trainees

Source: MCC CLEO Objectives 1998
Consent and Capacity

- the autonomous authorization of a medical intervention by a patient
- applies to acceptance and refusal of treatment

Ethical Principles Underlying Consent and Capacity
- usually the principle of respect for patient autonomy overrides the principle of beneficence
- where a patient cannot make an autonomous decision (i.e. incapable), it is the duty of the SDM (or the physician in an emergency) to act on the patient's known prior wishes or, failing that, to act in the patient's best interests
- there is a duty to discover, if possible, what the patient would have wanted when capable
- central to determining best interests is understanding the patient's values, beliefs, and cultural or religious background
- more recently expressed wishes take priority over remote ones
- patient wishes may be verbal or written
- patients found incapable to make a specific decision should still be involved in that decision as much as possible
- agreement or disagreement with medical advice does not determine findings of capacity/ incapacity
- however, patients opting for care that puts them at risk of serious harm that most people would want to avoid should have their capacity carefully assessed

Consent

Obtaining Legal Consent
- consent of the patient must be obtained before any medical intervention is provided; consent can be:
  - verbal or written, although written is usually preferred
  - a signed consent form is only evidence of consent – it does not replace the process for obtaining valid consent (see Figure 1)
  - what matters is what the patient understands and appreciates, not what the signed consent form states
  - implied (e.g. a patient holding out their arm for an immunization) or expressed
- consent is an ongoing process and can be withdrawn or changed after it is given, unless stopping a procedure would put the patient at risk of serious harm
- Health Care Consent Act (of Ontario) covers consent to treatment, admission to a facility, and personal assistance services (e.g. home care)

Four Basic Requirements of Valid Consent
1. Voluntary
   - consent must be given free of coercion or pressure (e.g. from parents or other family members who might exert ‘undue influence’)
   - the physician must not deliberately mislead the patient about the proposed treatment
2. Capable
   - the patient must be able to understand and appreciate the nature and effect of the proposed treatment
3. Specific
   - the consent provided is specific to the procedure being proposed and to the provider who will carry out the procedure (i.e. the patient must be informed if students will be involved in providing the treatment)
4. Informed
   - sufficient information and time must be provided to allow the patient to make choices in accordance with their wishes. This information should include:
     - the nature of the treatment or investigation proposed and its expected effects
     - all significant risks and special or unusual risks
     - alternative treatments or investigations and their anticipated effects and significant risks
     - the consequences of declining treatment
     - risks that are common sense need not be disclosed (i.e. bruising after venipuncture)
     - answers to any questions the patient may have
- the reasonable person test – the physician must provide all information that would be needed “by a reasonable person in the patient's position” to be able to make a decision
- disclose common adverse events (>1/200 chance of occurrence) and serious risks (e.g. death) even if remote
- it is the physician's responsibility to make reasonable attempts to ensure that the patient understands the information
- physicians should not withhold information about a legitimate therapeutic option based on personal conscience (e.g. not discussing the option of emergency contraception)

CPSO Policy Consent

Obtaining valid consent before carrying out medical, therapeutic and diagnostic procedures has long been recognized as an elementary step in fulfilling the doctor’s obligations to the patient.
Exceptions to Consent

1. Emergencies
   - treatment can be provided without consent where a patient is experiencing severe suffering, or where a delay in treatment would lead to serious harm or death and consent cannot be obtained from the patient or their substitute decision maker (SDM)
   - emergency treatment should not violate a prior expressed wish of the patient (e.g. a signed Jehovah’s Witness card)
   - if patient is incapable, MD must document reasons for incapacity and why situation is emergent
   - patients have a right to challenge a finding of incapacity as it removes their decision-making ability
   - if a SDM is not available, MD can treat without consent until the SDM is available or the situation is no longer emergent

2. Legislation
   - Mental Health legislation allows for:
     - the detention of patients without their consent
     - psychiatric outpatients may be required to adhere to a care plan in accordance with Community Treatment Orders (see Psychiatry, PS7)
   - Public Health legislation allows medical officers of health to detain, examine, and treat patients without their consent (e.g. a patient with TB refusing to take medication) to prevent transmission of communicable diseases (see Population Health and Epidemiology, PH19)

3. Special Situations
   - public health emergencies (e.g. an epidemic or communicable disease treatment)
   - warrant for information by police

Consequences of Failure to Obtain Valid Consent

- treatment without consent is battery (an offense in tort), even if the treatment is life-saving (excluding situations outlined in exceptions section above)
- treatment of a patient on the basis of poorly informed consent may constitute negligence, also an offense in tort
- the onus of proof that valid consent was not obtained rests with the plaintiff (usually the patient)

Capacity

- capacity is the ability to:
  - understand information relevant to a treatment decision
  - appreciate the reasonably foreseeable consequences of a decision or lack of a decision
  - capacity is specific for each decision (e.g. a person may be capable to consent to having a chest x-ray, but not for a bronchoscopy)
  - capacity can change over time (e.g. temporary incapacity secondary to delirium)
  - most Canadian jurisdictions distinguish capacity to make health care decisions from capacity to make financial decisions; a patient may be deemed capable of one, but not the other
  - a person is presumed capable unless there is good evidence to the contrary
  - capable patients are entitled to make their own decisions
  - capable patients can refuse treatment even if it leads to serious harm or death; however, decisions that put patients at risk of serious harm or death require careful scrutiny
  - capacity assessments must be conducted by a physician and, if appropriate, in consultation with other health care professionals (e.g. another physician, a mental health nurse)
  - clinical capacity assessment may include:
    - specific capacity assessment (i.e. capacity specific to the decision at hand)
      1. effective disclosure of information and evaluation of patient's reason for decision
      2. understanding of:
        - his/her condition
        - the nature of the proposed treatment
        - alternatives to the treatment
        - the consequences of accepting and rejecting the treatment
        - the risks and benefits of the various options (test: can the patient recite back what you have disclosed?)
      3. for the appreciation needed for decision making capacity, a person must:
        - acknowledge the condition that affects him/herself
        - be able to assess how the various options would affect him or her
        - be able to reach a decision and adhere to it, and make a choice, not based primarily upon delusional belief (test: are their beliefs responsive to evidence?)
    - general impressions
    - input from psychiatrists, neurologists, etc.
  - employ “Aid to Capacity Evaluation” (see Table 2)
Table 2. Aid to Capacity Evaluation

| Ability to understand the medical problem |
| Ability to understand the proposed treatment |
| Ability to understand the alternatives (if any) to the proposed treatment |
| Ability to understand the option of refusing treatment or of it being withheld or withdrawn |
| Ability to appreciate the reasonably foreseeable consequences of accepting the proposed treatment |
| Ability to appreciate the reasonably foreseeable consequences of refusing the proposed treatment |
| Ability to make a decision that is not substantially based on delusions or depression |

Adapted from Etchells, et al. 1996

- A decision of incapacity may warrant further assessment by psychiatrist(s), legal review boards (e.g. in Ontario, the Consent and Capacity Review Board), or the courts
- Judicial review is open to patients if found incapable

Treatment of the Incapable Patient in a Non-Emergent Situation
- Obtain informed consent from SDM
- An incapable patient can only be detained against his/her will to receive treatment if he/she meets criteria for certification under the Mental Health Act. In such a situation:
  - Document assessment in chart
  - Notify patient of assessment using appropriate mental health form(s) (Form 42 in Ontario)
  - Notify rights advisor

Substitute Decision Makers (SDMs)
- SDM must follow the following principles when giving informed consent:
  - Act in accordance with wishes previously expressed by the patient while capable
  - If wishes unknown, act in the patient’s best interest, taking the following into account:
    1. Values and beliefs held by the patient while capable
    2. Whether well-being is likely to improve with vs. without treatment
    3. Whether the expected benefit outweighs the risk of harm
    4. Whether a less intrusive treatment would be as beneficial as the one proposed
- The final decision of the SDM may and should be challenged by the MD if the MD believes the SDM is not abiding by the above principles

Figure 1. Ontario consent flowchart

Most provinces have legislated hierarchies for SDMs; the hierarchy in Ontario is:
- Legally appointed guardian
- Appointed attorney for personal care, if a power of attorney confers authority for treatment consent (see Powers of Attorney, ELOAM8)
- Representative appointed by the Consent and Capacity Board
- Spouse or partner
- Child (age 16 or older) or parent (unless the parent has only a right of access)
- Parent with only a right of access
- Sibling
- Other relative(s)
- Public guardian and trustee
INSTRUCTIONAL ADVANCE DIRECTIVES

• allow patients to exert control over their care once they are no longer capable
• the patient sets out their decisions about future health care, including who they would allow to make treatment decisions on their behalf and what types of interventions they would want
• takes effect once the patient is incapable with respect to treatment decisions
• in Ontario, a person can appoint a power of attorney for personal care to carry out his/her advance directives
• patients should be encouraged to review these documents with their family and physicians and to reevaluate them often to ensure they are current with their wishes

POWERS OF ATTORNEY

• all Guardians and Attorneys have fiduciary duties for the dependent person

Definitions

• Power of Attorney for Personal Care
  • a legal document in which one person gives another the authority to make personal care decisions (health care, nutrition, shelter, clothing, hygiene, safety) on their behalf if they become mentally incapable

• Guardian of the Person
  • someone who is appointed by the Court to make decisions on behalf of an incapable person in some or all areas of personal care, in the absence of a POA for personal care

• Continuing Power of Attorney for Property
  • a legal document in which a person gives another the legal authority to make decisions about their finances if they become unable to make those decisions

• Guardian of Property
  • someone who is appointed by the Public Guardian and Trustee or the Courts to look after an incapable person's property or finances

• Public Guardian and Trustee
  • acts as a SDM of last resort on behalf of mentally incapable people who do not have another individual to act on their behalf

• Pediatric Aspects of Capacity Covered by the HCCA, Ontario
  • no age of consent; consent depends on patient's decision-making capacity
  • QC has a specific age of consent, but common law and case law deem underage legal minors capable, allowing them to make their own choices; all other provinces and territories do not have an age of consent
  • infants and children are assumed to lack mature decision-making capacity for consent but they should still be involved (i.e. be provided with information appropriate to their comprehension level)
  • adolescents are usually treated as adults
  • preferably, assent should still be obtained from patient, even if not capable of giving consent
  • in the event that the physician believes the SDM is not acting in the child's best interest, an appeal must be made to the local child welfare authorities
  • under normal circumstances, parents have right of access to the child's medical record

Confidentiality and Reporting Requirements

• a full and open exchange of information between patient and physician is central to a therapeutic relationship
• privacy is a right of patients (which they may forego), while confidentiality is a duty of doctors (which they must respect barring patient consent or the requirements of the law)
• if inappropriate breached by a doctor, he/she can be sanctioned by the hospital, by the court or by his or her regulatory authority
• based on the ethical principal of patient autonomy, patients have the right to:
  • control their own information
  • expect information concerning them will receive proper protection from unauthorized access by others (see Privacy of Medical Records, ELOAM9)
• confidentiality may be ethically and legally breached in certain circumstances, e.g. the threat of harm to others
• unlike the solicitor-client privilege, there is no ‘physician-patient privilege’ by which a physician, even a psychiatrist, can promise the patient absolute confidentiality
• physicians should seek advice from their local health authority or the Canadian Medical Protective Association (CMPA) before disclosing HIV status of a patient to someone else
• many jurisdictions make mandatory not only the reporting of serious communicable diseases (e.g. HIV), but also the reporting of those who harbour the agent of the communicable disease
• physicians failing to abide by such regulations could be subject to professional or civil actions
• the legal duty to maintain patient confidentiality is imposed by provincial health information legislation and precedent-setting cases in the common law
Statutory Reporting Obligations
- legislation has defined specific instances where public interest overrides the patient right to confidentiality; varies by province, but may include:
  1. suspected child abuse or neglect – report to local child welfare authorities (e.g. Children’s Aid Society)
  2. fitness to drive a vehicle or fly an airplane – report to provincial Ministry of Transportation (see Geriatric Medicine, GM10)
  3. communicable diseases – report to local public health authority (see Population and Epidemiology, PH25)
  4. improper conduct of other physicians or health professionals – report to college or regulatory body of the health professional (sexual impropriety by physicians is required reporting in some provinces)
  5. vital statistics must be reported; reporting varies by province (in Ontario, births are required to be reported within 30 d to Office of Registrar General or local municipality; death certificates must be completed by a MD then forwarded to municipal authorities)
  6. reporting to coroners (see Physician Responsibilities Regarding Death, ELOAM13)
- physicians who fail to report in these situations are subject to prosecution and penalty, and may be liable if a third party has been harmed

Duty to Protect/Warn
- the physician has a duty to protect the public from a known dangerous patient; this may involve taking appropriate clinical action (e.g. involuntary detainment of violent patients for clinical assessment), informing the police, or warning the potential victim(s) if a patient expresses an intent to harm
- first established by a Supreme Court of California decision in 1976; supported by Canadian courts
- obliged by the CMA Code of Ethics and recognized by some provincial/territorial regulatory authorities
- concerns of breaching confidentiality should not prevent the MD from exercising the duty to protect; however, the disclosed information should not exceed that required to protect others
- applies in a situation where:
  1. there is a clear risk to identifiable person(s);
  2. there is a risk of serious bodily harm or death; and
  3. the danger is imminent (i.e. more likely to occur than not)

Disclosure for Legal Proceedings
- disclosure of health records can be compelled by a court order, warrant, or subpoena

Privacy of Medical Records
- privacy of health information is protected by professional codes of ethics, provincial and federal legislation, the Canadian Charter of Rights and Freedoms, and the fiduciary duty
- the federal government created the Personal Information Protection and Electronic Documents Act (PIPEDA), which established principles for the collection, use, and disclosure of information that is part of commercial activity (e.g. physician practices, pharmacies, private labs)
- PIPEDA has been superseded by provincial legislation in many provinces, such as the Ontario Personal Health Information Protection Act, which applies more specifically to health information

Duties of Physicians with Regards to the Privacy of Health Information
- inform patients of information-handling practices through various means (e.g. posting notices, brochures and pamphlets, and/or through discussions with patients)
- obtain the patient’s expressed consent to disclose information to third parties
  - under Ontario privacy legislation, the patient’s expressed consent need not be obtained to share information between health care team members involved in the “circle of care.” However, the patient may withdraw consent for this sharing of information and may put parts of the chart in a “lock box”
- provide the patient with access to their entire medical record; exceptions include instances where there is potential for serious harm to the patient or a third party
- provide secure storage of information and implement measures to limit access to patient records
- ensure proper destruction of information that is no longer necessary
Physician Competence and Professional Conduct

CanMEDS Competencies (Ethical/Policy Statement)
- a framework of professional competencies established by the Medical Council of Canada (MCC) as objectives for the Medical Council of Canada Qualifying Exam (MCCQE)
- further information on MCC objectives can be found at www.mcc.ca

1. Communicator
- display sensitivity to people of all ages, races, cultures, religions, sexual orientations, and genders
- accept or refuse patients without consideration of age, race, culture, religion, sexual orientation, and gender
- understand the variation in values and morals and their impact on approaches to care and decision-making
- elicit patients' beliefs, concerns, and expectations about their illness
- conduct patient-centered interviews, ensure patient comprehension

2. Collaborator
- respect all members of the health care team
- identify the roles and competencies of each member, and delegate tasks appropriately
- consult other physicians and health care professionals effectively and appropriately
- consult with patients and families regarding continuing care plans
- be able to outline co-ordination of services (e.g. Public Health, Home Care, Social Services, Workers' Compensation, Children's Aid Society, etc.)

3. Health Advocate
- identify determinants of health:
  - biological (e.g. genes, impact of lifestyle)
  - physical (e.g. food, shelter, working conditions)
  - social (education, employment, culture, access to care)
- influence public health and health policy to protect, maintain, and promote the health of individuals and the community

4. Manager
- meet regulatory requirements in an office practice (e.g. medical record-keeping, narcotic control, infection control, etc.)
- be prudent in utilization of health care resources, based on anticipated cost-benefit balance
- regulate work schedule such that time is available for continuing education

5. Professional
- maintain standards of excellence in clinical care and ethical conduct
- exhibit appropriate personal and interpersonal behaviour
- enhance clinical competence through lifelong learning
- accept responsibility for personal actions
- do not exploit the physician-patient relationship for personal advantage (e.g. financial, academic)

6. Scholar
- commitment to critical appraisal, constructive skepticism
- participate in the learning of peers and others (e.g. students, health care professionals, patients)

7. Medical Expert
- integration of all CanMEDS competencies to provide patient centred care
- combination of knowledge, clinical skills and judgment, procedural skills and professional behaviour for effective patient care

Legal Considerations
- the competence and conduct of physicians is legally regulated in certain respects to protect patients and society
- physicians are legally required to maintain a license with the appropriate authority
- physicians must ensure that patients have access to continuous on-call coverage and are never abandoned
- sexual conduct with patients, even when consented to by the patient, is a serious matter that can lead to criminal, civil, and disciplinary action
  - sexual conduct includes intercourse, undue touching, inappropriate reference to sexual matters, sexual jokes, and physician presence when capable patients undress or dress
- in some situations physicians may have a personal relationship with a patient provided a year has passed since the last therapeutic contact
Truth Telling

Ethical Basis
- helps to promote and maintain a trusting physician-patient relationship
- patients have a right to be told important information that physicians have regarding their care
- enables patients to make informed decisions about health care and their lives

Legal Basis
- required for valid patient consent (see Consent and Capacity, ELOAM5)
  - goal is to disclose information that a reasonable person in the patient's position would need in order to make an informed decision ("standard of disclosure")
- withholding information can be a breach of fiduciary duty and duty of care
- obtaining consent on the basis of misleading information can be seen as negligent

Evidence about Truth Telling
- most patients want to know what is wrong with them
- although many patients want to protect family members from bad news, they themselves would want to be informed in the same situation
- truth telling improves compliance and health outcomes
- informed patients are more satisfied with their care
- negative consequences of truth telling can include decreased emotional well-being, anxiety, worry, social stigmatization, and loss of insurability

Challenges in Truth Telling

Medical Error
- medical error may be defined as 'preventable adverse events' caused by the patient's medical care and not the patient's underlying illness. Some errors may be identified before they harm the patient, so not all error is truly 'adverse'
- many jurisdictions and professional associations expect and require physicians to disclose medical error; that is, any event that harms or threatens to harm patients must be disclosed to the patient or the patient's family and reported to the appropriate health authorities
- physicians should disclose to patients the occurrence of adverse events or errors caused by medical management, but should not suggest that they resulted from negligence because:
  - a) negligence is a legal determination
  - b) error is not equal to negligence (see Negligence, ELOAM4)
- disclosure allows the injured patient to seek appropriate corrective treatment promptly
- physicians should avoid simple attributions as to cause and sole responsibility of others or oneself
- physicians should offer apologies or empathic expressions of regret ("I wish things had turned out differently") as these can increase trust and are not admissions of guilt or liability
- Apology Acts across Canada protect apologies, both as expressions of regret and admissions of responsibility, from being used as evidence of liability and negligence

Breaking Bad News
- 'bad news' may be any information that reveals conditions or illnesses threatening the patient's sense of well-being
- caution patients in advance of serious tests about possible bad findings
- give warnings of impending bad news (see sidebar for example) and make sure you provide time for the patient
- poorly done disclosure may be as harmful as non-disclosure
- truth-telling may be a process requiring multiple visits
- adequate support should be provided along with the disclosure of difficult news
- SPIKES protocol was developed to facilitate "breaking bad news"
Arguments Against Truth Telling
- may go against certain cultural norms and expectations
- may lead to patient harm and increased anxiety
- 10-20% of patients prefer not to be informed
- medical uncertainty may result in the disclosure of uncertain or inaccurate information

Exceptions to Truth Telling
- patients may 'waive' the right to know: patient declines information that would normally be disclosed
- a patient may waive their right to know the truth about their situation when
  - the patient clearly declines to be informed
  - there is a strong cultural component that should be respected and acknowledged
  - the patient may wish others to be informed and make the medical decisions for him/her
  - the more weighty the consequences for the patient from non-disclosure, the more carefully one must consider the right to ignorance
- 'Emergencies': an urgent need to treat may legitimately delay full disclosure; the presumption is that most people would want such treatment and the appropriate SDM cannot be found
- 'Therapeutic privilege'
  - withholding information by the clinician in the belief that disclosure of the information would itself lead to severe anxiety, psychological distress or physical harm to the patient
  - clinicians should avoid invoking therapeutic privilege due to its paternalistic overtones and is a defense of non-disclosure that is rarely accepted anymore. It is often not the truth that is unpalatable; it is how it is conveyed that can harm the patient

Research Ethics
- involves the systematic analysis of ethical dilemmas arising during research involving human subjects to ensure that:
  - study participants are protected
  - clinical research is conducted to serve the interests of the participants and/or society as a whole
- major ethical dilemmas arise when a physician's obligation to the patient comes into conflict with other obligations and incentives
- any exceptions to disclosure for therapeutic consent do not apply in an experimental situation

Table 3. Ethical Principles for Research Involving Human Subjects
- Patient’s participation in research should not put him/her at a known or probable disadvantage with respect to medical care (i.e. cannot deny participants in research ‘known effective care’, for example, unethical to randomize some patients who are depressed to a placebo arm)
- Participant’s voluntary and informed choice is usually required
- Consent may not be required in special circumstances: chart reviews without patient contact; emergency situations for which there is no accepted or helpful standard of care and the proposed intervention is not likely to cause more harm than such patients already face
- Access to the treatment that is considered standard
  - Placebo-controlled trials are generally acceptable where patients still receive the standard of care and are informed about the placebo arm and what that entails
- Must employ a scientifically valid design to answer the research question
  - Scientific rigour ensured via peer review, expert opinion
- Must demonstrate sufficient value to justify the risk posed to participants
- Must be conducted honestly (i.e. carried out as stated in the approved protocol)
- Findings must be reported promptly and accurately without exaggeration, to allow practicing clinicians to draw reasonable conclusions
- Patients must not be enticed into risky research by the lure of money and investigators must not trade the interests of patients for disproportionate recompense by a sponsor; both participants and investigators are due fair recompense for their time and efforts
- Any significant interventional trial ought to have a data safety monitoring board that is independent of the sponsor and can ensure safety of the ongoing trial

Physician-Industry Relations
- health care delivery in Canada involves collaboration between physicians and the pharmaceutical and health supply industries in the areas of research, education, and clinical evaluation packages (e.g. product samples)
- physicians have a responsibility to ensure that their participation in such collaborative efforts is in keeping with their duties to their patients and society
- gifts or free products from the pharmaceutical industry are inappropriate
  - sponsorship for travel and fees for conference attendance may be accepted only where the physician is a conference presenter and not just in attendance
- physicians receiving such sponsorship must disclose this at presentations or in written articles

Guiding Principles for Research Ethics
- Respect for persons: informed consent
- Beneficence: harm vs. benefit
- Justice: avoid exploitation/unjustified exclusion

Informed Consent for Research
- Purpose of study
- Sum of funding
- Name and probability of harm and benefits
- Nature of physician’s participation including compensation

CMA and CPSO Guidelines for Ethically Appropriate Physician-Industry Relations:
- The primary goal should be the advancement of the health of Canadians
- Relationships should be guided by the CMA Code of Ethics
- The physician’s primary obligation is to the patient
- Physicians should avoid any self-interest in their prescribing and referral practices
- Physicians should always maintain professional autonomy, independence, and commitment to the scientific method

The AMA Code of Medical Ethics has a number of opinions on “Practice Matters” including “Industry representatives in clinical settings,” “Financial incentives and the practice of medicine,” and “Gifts to physicians from industry,” (see http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics.shtml).
**Physician Responsibilities Regarding Death**

- physicians are required by law to complete a medical certificate of death unless the coroner needs notification; failure to report death is a criminal offence

**Role of the Coroner**

- *Coroner's Act* (specific to Ontario, similar in other provinces) requires physicians to notify a coroner or police officer if death occurs:
  - due to violence, negligence, misconduct, misadventure, or malpractice
  - during pregnancy or is attributable to pregnancy
  - suddenly and unexpectedly
  - from disease which was not treated by a legally qualified medical practitioner
  - from any cause other than disease
  - under suspicious circumstances
- coroner investigates these deaths, as well as deaths that occur in psychiatric institutions, jails, foster homes, nursing homes, hospitals to which a person was transferred from a facility, institution or home, etc.
- in consultation with forensic pathologists and other specialists, the coroner establishes:
  - the identity of the deceased
  - where and when the death occurred
  - the medical cause of death
  - the means of death (i.e. natural, accidental, suicide, homicide or undetermined)
- coroners do not make decisions regarding criminality or legal responsibility

**Palliative and End-of-Life Care**

- focus of care is comfort and respect for person nearing death and maximizing quality of life for patient, family, loved ones
- appropriate for any patient at any stage of a life-threatening illness
- may occur in a hospital, hospice, in the community or at home
- often an interdisciplinary team of caregivers
- addresses the medical, psychosocial, and spiritual dimensions of care

**Euthanasia and Physician-Assisted Suicide**

- euthanasia: a deliberate act undertaken by one person with the intention of ending the life of another person to relieve that person's suffering where the act is the cause of death
- physician-assisted suicide: the act of intentionally killing oneself with the assistance of a physician who deliberately provides the knowledge and/or the means
- ethical issues and arguments:
  - right to make autonomous choices about the time and manner of own death
  - belief that there is no ethical difference between the acts of euthanasia/assisted suicide and foregoing life-sustaining treatments
  - belief that these acts benefit terminally ill patients by relieving suffering
  - patient autonomy has limits
  - death should be the consequence of the morally justified withdrawal of life-sustaining treatments only in cases where there is a fatal underlying condition, and it is the condition (not the withdrawal of treatment) that causes death
- the use of palliative sedation with opioids in end-of-life care, knowing that death may occur as an unintended consequence (principle of double effect) is distinguished from euthanasia and assisted suicide where death is the primary intent
- the appropriate withdrawal of life-support is distinguished from euthanasia and assisted suicide as it is seen as allowing the underlying disease to take its 'natural course'
- despite all this, refusals of care by the patient that may lead to death ought to be carefully explored by the physician to rule out any ‘reversible factors’ (such as depression, pain, loneliness, isolation) that may be hindering authentic choice
- law
  - Canada: euthanasia and physician-assisted suicide are punishable offences under the Criminal Code of Canada
  - United States: euthanasia is punishable under general homicide laws; Oregon, Washington, and Montana are the only states to have enacted legislation allowing physicians to actively assist patients who wish to end their lives
Reproductive and Sexual Health Law and Ethics

Maternal-Fetal Relationship
- in general, maternal and fetal interests align
- in some situations a conflict between maternal autonomy and the best interests of the fetus may arise

Ethical Issues and Arguments
- principle of reproductive freedom: women have the right to make their own reproductive choices
- coercion of a woman to accept efforts to promote fetal well-being is an unacceptable infringement of her personal autonomy

Legal Issues and Arguments
- law: upholds a woman’s right to life, liberty, and security of person and does not recognize fetal rights
  - if a woman is competent and refuses medical advice, her decision must be respected even if the fetus will suffer
  - the fetus does not have legal rights until it is born alive and with complete delivery from the body of the woman
- Royal Commission on New Reproductive Technologies recommendations:
  - medical treatment must never be imposed upon a competent pregnant woman against her wishes
  - no law should be used to confine a pregnant woman in the interest of her fetus
  - the conduct of a pregnant woman in relation to her fetus should not be criminalized
  - child welfare should never be used to control a woman’s behaviour during pregnancy
  - civil liability should never be imposed upon a woman for harm done to her fetus during pregnancy
- examples of implications
  - a woman is permitted to refuse HIV testing during pregnancy, even if vertical transmission to fetus results
  - a woman is permitted to refuse Caesarean section in labour that is not progressing, despite evidence of fetal distress

Advanced Reproductive Technologies (ART)
- includes non-coital insemination, hormonal ovarian stimulation, and in vitro fertilization (IVF)
- ethical issues and arguments
  - donor anonymity vs. child-centred reproduction (i.e. knowledge about genetic medical history)
  - preimplantation genetic testing for diagnosis before pregnancy
  - lack of sufficient data regarding efficacy and complications to provide the full disclosure needed for truly informed consent
  - use of new techniques without patients appreciating their experimental nature
  - embryo status – the Supreme Court of Canada maintains that fetuses are “unique” but not persons under law; this view would likely apply to embryos as well
  - access to ART
    - private vs. public funding
    - social factors limiting access to ART (e.g. same-sex couples)
  - against the ‘commercialization’ of reproduction; e.g. payment of gamete donors is currently illegal in Canada
  - however, no regulations as yet means the ART Act is not being enforced; caught in the legal web as to whether such regulations are a provincial or federal responsibility

Fetal Tissue
- pluripotent stem cells have been derived from human embryonic and fetal tissue
- potential uses of stem cells in research:
  - studying human development and factors that direct cell specialization
  - evaluating drugs for efficacy and safety in human models
  - cell therapy: using stem cells grown in vitro to repair or replace degenerated/destroyed/malignant tissues (e.g. Parkinson’s disease)
  - genetic treatment aimed at altering somatic cells (i.e. myocardial or immunological cells) is acceptable and ongoing
  - genetic treatment aimed at altering germ cells is prohibited in Canada and elsewhere
  - embryo research is permitted up to 14 d post-fertilization
  - embryos created for reproductive purposes that are no longer required may be used
  - gamete providers must give free and informed consent for research use
  - no commercial transactions in the creation and use of the embryos is permitted

The fetus does not have legal rights until it is born alive and with complete delivery from the body of the woman.

Once outside the mother’s body, the neonate becomes a member of society with all the rights and protections other vulnerable persons receive.
- Non-treatment of a neonate born alive is only acceptable if <22 wk gestational age (GA)
- 23-25 wk GA: treatment should be a consensual decision between physician and parents
- 25 wk GA and more: neonate should receive full treatment unless major anomalies or conditions incompatible with life are present
Source: Paed Child Health 2012;443

Advanced Reproductive Technologies: Ethically Appropriate Actions
- Educate patients and address contributors to infertility (e.g. stress, alcohol, medications, etc.)
- Investigate and treat underlying health problems causing infertility
- Wait at least 1 yr before initiating treatment with ART (exceptions – advanced age or specific indicators of infertility)
- Educate and prepare patients for potential negative outcomes of ART

Surrogate mothers cannot be paid or offered compensation beyond a reimbursement of their expenses.
Source: Assisted Human Reproduction Act

No one under age 18 can donate sperm or eggs, except for the purpose of creating a child that the donor plans to raise themselves (example: young patients receiving radiation therapy for cancer that may cause infertility).
Source: Semen Regulations of the Food and Drug Act

The CMA remains neutral on the issue of embryonic stem cell research.
creation of embryos solely for research purposes is prohibited
human cloning is strictly prohibited
• risks of coercion must be minimized:
  • may not pressure fertility treatment team to generate more embryos than necessary
  • only discuss option of using fetal tissue for research after free and informed choice to have a therapeutic abortion has been made
  • physicians responsible for fertility treatment may not be part of a stem cell research team

Induced Abortion
• CMA definition of induced abortion: the active termination of a pregnancy before fetal viability
  • fetal viability: fetus >500 g, or >20 wk gestational age
• CMA policy on induced abortion:
  • induced abortion should not be used as an alternative to contraception
  • counselling on contraception must be readily available
  • full and immediate counselling services must be provided in the event of unwanted pregnancy
  • there should be no delay in the provision of abortion services
  • no patient should be compelled to have a pregnancy terminated
  • physicians should not be compelled to participate in abortion – if morally opposed, the physician should inform the patient so she may consult another physician
  • no discrimination should be directed towards either physicians who do not perform or assist at induced abortions or physicians who do
  • induced abortion should be uniformly available to all women in Canada and health care insurance should cover all the costs (N.B. the upper limit of gestational age for which coverage is provided varies between provinces)
  • elective termination of pregnancy after fetal viability may be indicated under exceptional circumstances
• ethical and legal issues and arguments:
  • according to common law, the rights of a fetus are not equal to those of a human being
  • no law currently regulates abortion in Canada – it is a woman's medical decision to be made in consultation with whom she wishes; no mandatory role for spouse/family
  • 2nd and even 3rd trimester abortions are not illegal in Canada, but are usually only carried out when there are serious risks to the woman's health or if the fetus has died in utero or has major malformations (e.g. anencephaly)

Prenatal/Antenatal Genetic Testing
• uses:
  • confirm a clinical diagnosis
  • detect genetic predisposition to a disease
  • allows preventative steps to be taken and helps patient prepare for the future
  • give parents the option to terminate a pregnancy or begin early treatment
• ethical dilemmas arise because of the nature of genetic information:
  • it has individual and familial implications
  • it pertains to future disease
  • it often identifies disorders for which there are no effective treatments or preventive steps
  • also can be used to identify the sex of the fetus leading to termination of pregnancy if the fetus is of the unwanted sex; this is considered inappropriate by some but is entirely legal as a woman can request an abortion for any reason
• ethical issues and arguments:
  • obtaining informed consent is difficult due to the complexity of genetic information
  • doctor's duty to maintain confidentiality vs. duty to warn family members
  • risk of social discrimination (e.g. insurance) and psychological harm
• law:
  • no current specific legislation exists
  • testing requires informed consent
  • no standard of care exists for clinical genetics but physicians are legally obligated to inform patients that prenatal testing exists and is available
  • breach of confidentiality – duty to warn family members
  • only acceptable if can likely prevent serious harm, such as if treatment or prevention is available (e.g. familial adenomatous polyposis)

Organization of Health Care in Canada
• one federal, three territorial, and ten provincial systems
• federal system provides care to Aboriginal groups, the RCMP, and the armed forces
• financed by both the public (70%) and private (30%) sectors
• each provincial plan must cover all medically necessary health services delivered in hospitals and by physicians; may choose to cover services such as home care and prescription drugs
• non-insured health services and fees are either covered by private insurance or by the individual
• workers’ compensation funds cover treatment for work-related injuries and diseases
Legal Foundation

The legal foundation of the Canadian health system is based on two constitutional documents:
1. **Constitution Act** (1867): deals primarily with the jurisdictional power between federal and provincial governments
2. **The Canadian Charter of Rights and Freedoms** (1982): does not guarantee a right to health care but, given government's decision to finance health care, they are constitutionally obliged to do so consistently with the rights and freedoms outlined in the Charter (including the right to equality, physician's mobility rights, etc.)

And two statutes:
1. **Canada Health Act** (1984): outlines the national terms and conditions that provincial health systems must meet in order to receive federal transfer payments
2. **Canada Health and Social Transfer Act** (1996): federal government gives provinces a single grant for health care, social programs, and post-secondary education; division of resources at provinces' discretion

History

1867  **British North America Act** (now **Constitution Act**) establishes Canada as a confederacy
   - government has minimal role in health care at this time
   - "establishment, maintenance, and management of hospitals" under provincial jurisdiction

1947  Saskatchewan introduces universal hospital insurance
   - based on taxes and premiums
   - other provinces follow

1957  Federal government passes **Hospital Insurance and Diagnostic Services Act**
   - provinces with universal hospital insurance receives federal funds
   - federal government pays for approximately 50% of insured services

1962  Saskatchewan implements universal medical care insurance
   - physician services included

1965  **Royal Commission on Health Services** (**Hall Commission**) recommends federal leadership and financial support with provincial government operation

1966  **Medical Care Act** passed by federal government
   - federal government contribution maintained at 50% on average, with poorer provinces receiving more funds
   - medical insurance must be comprehensive, portable, universal, and publicly administered

1977  **Established Programs Financing Act** passed by federal government
   - federal government gives "tax points" to provinces by reducing federal taxes and allowing provinces to collect more
   - funding no longer tied to direct services → federal influence wanes
   - provinces bear greater costs and impose restrictions on physicians
   - physicians respond with "extra-billing"; patients pay a supplementary fee

1984  **Canada Health Act** passed by federal government
   - replaced **Medical Care Act** and **Hospital Insurance and Diagnostic Services Act**
   - extra-billing banned by new fifth criterion: Accessibility

1996  **Canada Health and Social Transfer Act** passed by federal government
   - federal government gives provinces a single grant for health care, social programs, and post-secondary education; division of resources at provinces' discretion

1999  **Social Union Framework Agreement** signed by the Prime Minister and all Premiers and territorial leaders except Quebec
   - federal and provincial/territorial governments vow to concentrate their efforts to modernize Canadian social policy

2001  **Kirby and Romanow Commissions** appointed
   **Kirby Commission** (final report, October 2002)
   - one-member committee of the Senate: examined history of health care system in Canada, pressures and constraints of current health care system, role of federal government, and health care systems in foreign jurisdictions
   **Romanow Commission** (final report, November 2002)
   - one-member royal commission (former Saskatchewan Premier Roy Romanow) appointed by the Prime Minister to inquire into and undertake dialogue with Canadians on the future of Canada's public health care system
2003  *First Ministers' Accord on Health Care Renewal* signed  
- First Ministers agreed on an action plan to improve access to quality care for all Canadians and to prepare an annual public report on primary and home care  
- First Health Council (composed of government and expert/public representatives) appointed to improve accountability in the health care system

2004  *First Ministers' Meeting on the Future of Health Care* produces a 10-yr plan  
- priorities include reductions in waiting times, development of a national pharmacare plan, and primary care reform

2005  *Chaoulli v. Quebec*, Supreme Court of Canada Decision  
- ruled that Quebec's banning of private insurance would be unconstitutional under the Quebec Charter of Rights, given that patients do not have access to those services under the public system in a timely way  
- Quebec government was given one year to respond

2011  First progress report by the Health Council reviews progress towards 2004 First Ministers' 10 yr plan  
- significant reductions in wait times for specific areas (such as cancer, joint replacement and sight restoration) while these reductions may have inadvertently caused increases in wait times of other services  
- despite large investments into electronic medical records (EMRs), Canada continues to have very low uptake, ranking last in the Commonwealth Fund International Health Policy survey, with use of only 37% use by primary care physicians  
- little progress in creating a national strategy for equitable access to pharmaceuticals; however, there has been some success in increasing pharmacists’ scope of practice, reducing generic drugs costs and implementing drug info systems

Federal Government announces that it will not renew *2004 First Ministers' Accord on Health Care Renewal*  
- increases in funding to provinces at 6% per annum until the 2016-2017 fiscal year, from then onwards, increases tied to nominal GDP at a minimum of 3% per annum

2012  Second progress report by the Health Council reviews progress towards 2004 First Ministers' 10 yr plan  
- funding is sufficient; however, more innovation is needed including incentivizing through models of remuneration  
- 46 recommendations were made to address the lack of progress in prevention, access to primary-care physicians, long-term, respite and palliative care services, wait-time benchmarks, accountability, IT, Aboriginal health and more

2013  Federal Government announces that it will stop funding the Health Council of Canada in 2014  
- the council (born in 2004) will close in 2014 leaving no other independent national body to assess the performance of the Canadian health care system

2014  Expiry of current *10 Year Health Care Funding Agreement* between Federal and Provincial governments

### Key Principles of the Canada Health Act

1. Public Administration  
   - provincial health insurance programs must be administered by public authorities
2. Comprehensiveness  
   - provincial health insurance programs must cover all necessary diagnostic, physician, and hospital services
3. Universality  
   - all eligible residents must be entitled to health care services
4. Portability  
   - emergency health services must be available to Canadians who are outside their home province, paid for by the home province
5. Accessibility  
   - user fees, charges, or other obstructions to insured health care services are not permitted

The federal government can reduce its contributions to provinces that violate the key principles of the Canada Health Act.

**Principles of Canada Health Act**  
- Public Administration  
- Comprehensiveness  
- Universality  
- Portability  
- Accessibility
Health Care Expenditure and Delivery in Canada

- projected total health care expenditure in 2009 was $182.1 billion, 11.9% of the GDP, approx. $4,363 USD per capita (Canadian Institute of Health Information)
- 2009 Canadian health care expenditure as a percentage of GDP ranked 6 out of 29 for Organization for Economic Cooperation and Development (OECD) member nations (Canadian Institute of Health Information)
- 70.9% of health care spending came from public sector sources in 2009 as compared to 47.7% in the US
- in 2006 there were 2.1 physicians per 1000 population, ranking 26th out of OECD member countries

Delivery of Health Care

- hospital services in Canada are publicly funded but delivered through private, not-for-profit institutions owned and operated by communities, religious organizations, and regional health authorities
- this differs from other countries, such as the US (a mix of public and private funding, as well as private-for-profit and private not-for-profit delivery) and the UK (primarily public funding and delivery)

Ethical Considerations in Resource Allocation and Physicians’ Role

- the distribution of goods and services to programs and people
- physicians have the duty to inform patients about therapeutic options even if they are not available
- distributive justice: physicians must make health care resources available to patients in a manner which is fair and equitable, without bias or discrimination
  - need and benefit are morally relevant criteria for resource allocation
  - gender, sexual orientation, religion, level of education or age alone are morally irrelevant criteria
- ethical dilemmas that arise when deciding how best to allocate resources
- fair chances versus best outcome: favouring best outcome vs. giving all patients fair access to limited resources (e.g. transplant list prioritization)
- priorities problem: how much priority should the sickest patients receive?
- aggregation problem: modest benefits to many vs. significant benefits to few
- democracy problem: when to rely on a fair democratic process to arrive at a decision
- guidelines for appropriately allocating resources
- the physician’s primary obligation is to protect and promote the welfare and best interests of his or her patients
- choose interventions known to be beneficial on the basis of evidence of effectiveness
- seek the tests or treatments that will accomplish the diagnostic or therapeutic goal for the least cost
- advocate for one’s patients but avoid manipulating the system to gain unfair advantage for them
- resolve conflicting claims for scarce resources justly, on the basis of morally relevant criteria such as need and benefit, using fair and publicly defensible procedures
- inform patients of the impact of cost constraints on care, but in a sensitive way
- seek resolution of unacceptable shortages at the level of hospital management or government

Figure 2. Health expenditure in Canada by use of funds (billions of dollars), 2009
Source: Canadian Institute for Health Information. National Health Expenditure Trends. 1975 to 2011

Figure 3. Canadian health care dollars by source of funds, 2007
Source: Canadian Institute for Health Information. National Health Expenditure Trends. 1975 to 2009

Payments for Care at Private For-Profit and Private Not-For-Profit Hospitals: A Systematic Review and Meta-analysis
CMAJ 2004;170:1817-1824
Meta-analysis of 8 US observational studies involving more than 350,000 patients. Concluded that care provided by private for-profit hospitals was more expensive (Relative payments for care = 1.19; 95% CI = 1.07-1.33; p = 0.001). If half of Canadian hospitals were converted to private for-profit institutions, an extra $3.6 billion would be paid annually.
Role of the Provincial Licensing Authorities

- the medical profession in Canada self-regulates under the authority of provincial legislation;
- physicians in each province are self-regulated by a licensing authority (e.g. College of Physicians and Surgeons of Ontario, the CPSO); membership is mandatory to practice in that province;
- self-regulation is based on the premise that the licensing authority must act first and foremost in the interest of the public;
- licensing authority functions include:
  - provincial licensing authorities provide non-transferable licensure to physicians
  - issuing non-transferable licenses allow doctors to practice only in that province
  - maintaining ethical, legal, and competency standards and developing policies to guide doctors
  - investigating complaints against doctors
  - disciplining doctors guilty of professional misconduct or incompetence
  - at times of license investiture and renewal, physicians must disclose if they have a condition (such as HIV positivity or drug addiction or other illness that may impact their ability to practice safely)
- in an evolving area of responsibility, physicians may be required to report colleagues who may be a hazard to patients (e.g. the inebriated colleague)

Licensure and Certification

- the Medical Council of Canada (MCC) certifies physicians
  - certification is known as the Licentiate of the MCC (LMCC)
  - LMCC is acquired by passing the MCC Qualifying Examination Parts I and II
- the Royal College of Physicians and Surgeons of Canada (RCPSC) certifies specialists who complete an accredited residency program and pass the appropriate exam
  - voluntary membership of RCPSC is designated FRCPC or FRCSC (Fellow of the Royal College of Physicians/Surgeons of Canada)
- the College of Family Physicians of Canada (CFPC) certifies family physicians who complete an accredited residency program and pass the Certification Examination in Family Medicine
- the RCPSC and CFPC are responsible for monitoring ongoing continuing medical education (CME) and professional development

Role of Professional Associations

- membership in a provincial or national association is voluntary
- provincial medical associations represent the economic and professional interests of doctors
- the Canadian Medical Association (CMA) is a national association that provides leadership to doctors and advocates for access to high quality health care in Canada
- the CMA represents physician and population concerns at the national level, while the provincial medical associations negotiate fee and benefit schedules with provincial governments
- medical residents are represented nationally by the Canadian Association of Interns and Residents, and provincially by Provincial Housestaff Organizations, which uphold the economic and professional interests of residents
- medical students are represented at their universities by student societies; these bodies collectively form the Canadian Federation of Medical Students; francophone medical schools participate in the Federation of Quebec Medical Student Societies
- the Canadian Medical Protective Association (CMPA), a physician-run organization, is a voluntary insurance association that protects the integrity of member physicians by providing legal defense against allegations of malpractice or negligence and by providing risk management and educational programs, and general advice

The US Health Care System

- the United States health care system is more market-based than the Canadian system
- it is funded and delivered by a mixture of the public, private, and voluntary sectors; private-for-profit is the prevailing method of delivery
- public funding is derived from taxes raised at both the federal and state government levels
History

1850 Franklin Health Insurance Company of Massachusetts
- offers accident insurance to cover injuries acquired during railroad or steamboat travel
- informal "sickness insurance" evolved from this to cover different injuries or diseases

1901 American Medical Association established as the national organization of state and local medical groups

1929 Baylor Plan developed
- created by Dr. Justin Ford Kimball to ensure that teachers could pay their medical bills
- teachers pay 50 cents/month in exchange for guarantee of medical services for 21 days

1930s More hospitals adopt medical insurance plans as per the Baylor Plan
- emergence of private, commercial, health insurance as a service of life insurance companies

1939 Community hospitals work together to create health care plans
- American Hospital Association (AHA) uses the term “Blue Cross” to describe health care plans that meet their standards
- emergence of prepaid plans covering physician and surgeon services

1940s and 1950s
- employee benefit plans increase in number with more comprehensive health care insurance packages
- companies compete for employees using the proposed health care plan
- reason why workplace is currently main source of health care insurance

1946 Blue Shield created and represents physician sponsored health care plans

1954 Social Security coverage begins to include disability benefits

1960 Blue Cross becomes the official designation for AHA health care plans

1965 Medicare and Medicaid programs introduced government funded health care plans

1971 Blue Cross and Blue Shield merge into one company

1970s and 1980s
- emergence of Health Maintenance Organizations (HMOs)
- HMOs offer managed care plans: health care packages that are provided by an HMO approved network of health care providers

1993 Universal health care system proposed but rejected by congress

1996 Mental Health Parity Act passed
- invoked to decrease discrimination in health care coverage for mental health illnesses
- aggregate annual and lifetime limits for mental health services must match aggregate annual and lifetime limits for medical and surgical services

1996 Health Insurance Portability and Accountability Act passed
- Title 1: Health Care Access, Portability, and Renewability
  - provides protection of health care coverage to employees and their families if they change or lose their job
- Title 2: Preventing Health Care Fraud and Abuse; Administrative Simplification; Medical Liability Reform
  - addresses and establishes national standards for electronic health care transactions and security and privacy of health data

1997 State Children’s Health Insurance Program (SCHIP) created
- states extend health coverage to uninsured children

1999 Ticket to Work and Work Incentives Improvement Act
- enables people with disabilities to be employed without affecting their Medicaid or Medicare coverage

2010 Affordable Care Act
- reform to health care to improve access to affordable health coverage and creates regulations on activities of private health insurance providers
Health Care Expenditure and Delivery in the US

- health care spending in the US represents a large economic sector
  - health care comprises over 17.4% of the gross domestic product (GDP) (highest in the OECD), amounting to $7960 USD per capita in 2009
  - one advantage is the widespread availability of technology – the US has 4 times as many MRI machines per capita than Canada
- the US scores poorly on some indicators of population health, with a life expectancy below the OECD average and infant mortality above the OECD average. Possible factors that account for this discrepancy are:
  - poor health of large uninsured population
  - high cost of health care administration
  - the provision of inefficient high-cost, high-intensity care
    - the higher-spending regions in the US do not provide any better quality of care, access to care, health outcomes or satisfaction with care when compared to the lower-spending regions
- the US has the highest level of obesity of all OECD nations at 34.3%; this has major implications for future health care spending

Access to Health Services

- 70% of Americans under the age of 65 have private health insurance, either employer-sponsored or individually purchased; 12% receive health care through public health insurance; 18%, mainly the poor, have no health insurance
- access to publicly funded health services occurs primarily through two programs, Medicare and Medicaid, which were created by the 1965 Social Security Act
- other federal government-funded health programs include the Military Health Services System, the Veterans Affairs Health Services System, the Indian Health Service, and the Prison Health Service

Table 4. Medicare and Medicaid Program Information

<table>
<thead>
<tr>
<th></th>
<th>Medicare</th>
<th>Medicaid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eligibility</strong></td>
<td>People over the age of 65</td>
<td>People who receive funds through social assistance programs</td>
</tr>
<tr>
<td></td>
<td>People with end stage renal disease</td>
<td>Pregnant women</td>
</tr>
<tr>
<td></td>
<td>People of any age meeting the Medicare definition of disability</td>
<td>People with developmental disabilities</td>
</tr>
<tr>
<td><strong>Coverage</strong></td>
<td>Basic &quot;Part A&quot; providing inpatient hospital care, home care, limited skilled nursing facility care, and hospice care</td>
<td>Basic coverage involves inpatient and outpatient hospital care, laboratory and x-ray services, skilled nursing care, home care, physician services, dental services, and family planning</td>
</tr>
<tr>
<td></td>
<td>Supplemental “Part B” covers outpatient physician and clinic services, and requires payment of a further monthly fee</td>
<td>Financing for Medicaid is provided jointly by the federal and state governments, and program details vary greatly between states</td>
</tr>
<tr>
<td><strong>Co-payment</strong></td>
<td>To help pay for out-of-pocket expenditures, and to cover many of the services not insured by Medicare, the majority of Medicare beneficiaries buy supplemental private health insurance</td>
<td>States may impose deductibles, coinsurance, or co-payments on some Medicaid recipients for certain services</td>
</tr>
</tbody>
</table>


Health Care Reform

- Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act of 2010 are federal statutes signed into law in March 2010 that include a number of new health care provisions to be implemented over 8 yr
  - expand Medicaid eligibility, provide subsidies for insurance premiums and incentives for businesses to provide health care benefits, prohibit denial of coverage/claims for pre-existing conditions, and establish health-insurance exchanges
  - costs are offset by a number of health care related taxes, including a tax penalty for citizens with no health insurance (low income persons are exempt)
Anesthesia and Peri-Operative Medicine

Gavin Hamilton and Ashwin Sankar, chapter editors
Maria Jogova and Howard Meng, associate editors
Melini Gupta, EBM editor
Dr. Isabella Devito and Dr. Diana Tamir, staff editors

Anesthesia Basics ........................................ 2
Pre-Operative Assessment ............................. 2
History and Physical
Pre-Operative Investigations
Fasting Guidelines
American Society of Anesthesiology (ASA)
Classification
Pre-Operative Optimization ......................... 4
Medications
Hypertension
Coronary Artery Disease (CAD)
Endocrine Disorders
Respiratory Diseases
Aspiration
Monitoring .............................................. 5
Induction Agents ............................... 6
Intravenous Agents
Volatile Inhalational Agents
Muscle Relaxants and Reversing Agents
Airway Management ...................... 7
Airway Anatomy Review
Tracheal Intubation
Routine Induction vs. Rapid Sequence
Induction (RSI)
Difficult Airway
Intraoperative Management ............ 10
Oxygen Therapy
Ventilation
Temperature
Heart Rate
Blood Pressure
Fluid Balance and Resuscitation
IV Fluids
Blood Products
Extubation ........................................ 17
Post-Operative Care ............. 17
Pain Management .................... 18
Regional Anesthesia ............. 19
Definition of Regional Anesthesia
Preparation for Regional Anesthesia
Epidural and Spinal Anesthesia
Peripheral Nerve Blocks
Local Anesthesia .................... 21
Local Anesthetic Agents (LA)
Local Infiltration and Hematoma Blocks
Topical Anesthetics
Obstetrical Anesthesia .......... 22
Pediatric Anesthesia ............. 23
Uncommon Complications ....... 24
Malignant Hyperthermia (MH)
Abnormal Pseudocholinesterase
Common Medications ............. 25
Intravenous Induction Agents
Opioids
Volatile Inhalational Agents
Depolarizing Muscle Relaxants
Non-Depolarizing Muscle Relaxants
Reversal Agents for Non-Depolarizing Relaxants
Local Anesthetic Agents
Advance Cardiac Life Support
(ACLS) Guidelines .............. 28
References ..................... 30

Acronyms

2,3-SPG 2,3-Diphosphoglycerate
ACC American College of Cardiology
ACH acetylcholine
ACOE acetylcholineesterase
AHA American Heart Association
ALS amyotrophic lateral sclerosis
ARDS acute respiratory distress syndrome atm atmosphere
CCS Canadian Cardiovascular Society
CK creatine kinase
CO cardiac output
CSF cerebrospinal fluid
CVP central venous pressure
DIC disseminated intravascular coagulopathy
DPG diphosphoglycerate
ETCO₂ End Tidal CO₂
ETT endotracheal tube
FIO₂ fraction of oxygen in inspired air
FiO₂ fraction of oxygen in inspired air
FiO₂ fresh frozen plasma
FiO₂ functional residual capacity
FiO₂ general anesthetic
FiO₂ gastrinostemal reflux disease
FiO₂ initial hematocrit
FiO₂ New York Heart Association
FiO₂ operating room
FiO₂ arterial partial pressure of carbon dioxide
FiO₂ arterial partial pressure of oxygen
FiO₂ patient-controlled
FiO₂ positive end-expiration pressure
FiO₂ parasympathetic nervous system
FiO₂ post-operative nausea and vomiting
FiO₂ positive pressure ventilation
FiO₂ rapid sequence induction
FiO₂ short-acting β-agonist
FiO₂ succinylcholine
FiO₂ syndrome of inappropriate antidiuretic hormone
FiO₂ sympathetic nervous system
FiO₂ stroke volume
FiO₂ systemic vascular resistance
FiO₂ total body water
FiO₂ total intravenous anesthetic
FiO₂ transurethral resection of prostate
FiO₂ ventilation/perfusion
FiO₂ ventricular tachycardia
FiO₂ venous thromboembolism

LOC level of consciousness
MAC minimum alveolar concentration
MAP mean arterial pressure
MAH malignant hyperthermia
MS multiple sclerosis
MJN neuromuscular junction
NMA New York Heart Association
OCS oral corticosteroids
OR operating room
PaCO₂ arterial partial pressure of carbon dioxide
PaO₂ arterial partial pressure of oxygen
PAC patient controlled analgesia
PEP positive end-expiration pressure
PNS parasympathetic nervous system
POJV post-operative nausea and vomiting
PPV positive pressure ventilation
RSI rapid sequence induction
SABA short-acting β-agonist
SCH succinylcholine
SIADH syndrome of inappropriate antidiuretic hormone
SNS sympathetic nervous system
SV stroke volume
SVR systemic vascular resistance
TBW total body water
TIA total intravenous anesthetic
TURP transurethral resection of prostate
V/Q ventilation/perfusion
VTI ventricular tachycardia
VTE venous thromboembolism

A1 Anesthesia

Toronto Notes 2014
**Anesthesia Basics**

### Types of Anesthesia

- **general**
  - general anesthesia (GA)
  - total IV anesthesia (TIVA)
- **regional**
  - spinal, epidural
  - peripheral nerve block
  - IV regional
- **local**
  - local infiltration
  - topical
- **sedation**
  - monitored anesthesia care
  - note that different types of anesthesia can be combined (e.g. general + regional)

### Pre-Operative Assessment

- to identify the patient's medical and surgical issues
- to allow for the arrangement of further investigations, consultations and treatments for patients not yet optimized
- to plan and consent for anesthetic techniques

### History and Physical

#### History

- indication for surgery
- surgical/anesthetic Hx: previous anesthetics/complications, previous intubations, medications, drug allergies
- PMHx:
  - CNS: seizures, strokes, raised ICP, spinal disease
  - CVS: CAD, MI, CHF, HTN, valvular disease, dysrhythmias, peripheral vascular disease (PVD), conditions requiring endocarditis prophylaxis, exercise tolerance, CCS class, NYHA class (see Cardiology and Cardiovascular Surgery, C31 for NYHA classification)
  - respiratory: smoking, asthma, COPD, recent upper respiratory tract infection, sleep apnea
  - GI: GERD, liver disease
  - renal: insufficiency, dialysis, chronic kidney disease
  - hematologic: anemia, coagulopathies, blood dyscrasias
  - MSK: conditions associated with difficult intubations – arthriitis (e.g. rheumatoid arthritis), cervical tumours, cervical infections/abscesses, trauma to cervical spine, previous cervical spine surgery, Down syndrome, scleroderma, obesity, conditions affecting neuromuscular junction (e.g. myasthenia gravis)
  - endocrine: diabetes, thyroid disorders, adrenal disorders
  - other: morbid obesity, pregnancy, ethanol/other drug use
- FHx: malignant hyperthermia, atypical cholinesterase (pseudocholinesterase), other abnormal drug/anesthetic reactions

#### Physical Examination

- examination of organ systems
  - focused physical exam of the CNS, CVS and respiratory systems
  - general assessment of nutrition, hydration and mental status
  - pre-existing motor and sensory deficits
- oropharynx and airway assessment to determine the likelihood of difficult intubation
  - no single test is specific or sensitive – all aid in determining the ease of intubation
  - ability to assume “sniffing position” – upper cervical spine extension, lower cervical spine flexion, previous cervical spine surgery
  - Mallampati classification (Figure 1)
  - "3-2-1 rule"
    - thyromental distance (the distance of the lower mandible in the midline from the mentum to the thyroid notch); <3 finger breadths (<6 cm) is associated with difficult intubation
    - mouth opening (<2 finger breadths is associated with difficult intubation)
    - anterior jaw subluxation (<1 finger breadth is associated with difficult intubation)
  - tongue size
  - dentition, dental appliances/prosthetic caps – must inform patients of the rare possibility of damage
  - nasal passage patency (if planning nasotracheal intubation)
- examination of anatomical sites relevant to lines and blocks
  - bony landmarks and suitability of anatomy for regional anesthesia (if relevant)
  - sites for IV, central venous pressure (CVP) and pulmonary artery (PA) catheters
Pre-Operative Investigations

Table 1. Suggested Indications for Specific Investigations in the Pre-Operative Period

<table>
<thead>
<tr>
<th>Test</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Major surgery requiring group and screen or cross and match; chronic cardiovascular, pulmonary, renal, or hepatic disease; malignancy; known or suspected anemia; bleeding diathesis or myelosuppression; patient less than 1 yr of age</td>
</tr>
<tr>
<td>Sickle cell screen</td>
<td>Genetically predisposed patient (hemoglobin electrophoresis if screen is positive)</td>
</tr>
<tr>
<td>INR, aPTT</td>
<td>Anticoagulant therapy, bleeding diathesis, liver disease</td>
</tr>
<tr>
<td>Electrolytes and creatinine</td>
<td>Hypertension, renal disease, diabetes, pituitary or adrenal disease; digoxin, diuretic or other drug therapies affecting electrolytes</td>
</tr>
<tr>
<td>Fasting glucose level</td>
<td>Diabetes (repeat on day of surgery)</td>
</tr>
<tr>
<td>Pregnancy (ß-HCG)</td>
<td>Women who may be pregnant</td>
</tr>
<tr>
<td>ECG</td>
<td>Heart disease, diabetes, other risk factors for cardiac disease; subarachnoid or intracranial hemorrhage, cerebrovascular accident, head trauma</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Cardiac or pulmonary disease, malignancy</td>
</tr>
</tbody>
</table>


Fasting Guidelines

Fasting Guidelines Prior to Surgery (Canadian Anesthesiologists’ Society)
- **8 hours** after a meal that includes meat, fried or fatty foods
- **6 hours** after a light meal (such as toast or crackers) or after ingestion of infant formula or nonhuman milk
- **4 hours** after ingestion of breast milk or Jello
- **2 hours** after clear fluids (water, black coffee, tea, carbonated beverages, juice without pulp)

American Society of Anesthesiology (ASA) Classification

- common classification of physical status at the time of surgery
- a gross predictor of overall outcome, NOT used as stratification for anesthetic risk (mortality rates)
- **ASA 1**: a healthy, fit patient
- **ASA 2**: a patient with mild systemic disease
  - e.g. controlled type 2 diabetes mellitus (DM), controlled essential HTN, obesity, smoker
- **ASA 3**: a patient with severe systemic disease that limits activity
  - e.g. stable CAD, COPD, DM, obesity
- **ASA 4**: a patient with incapacitating disease that is a constant threat to life
  - e.g. unstable CAD, renal failure, acute respiratory failure

Impact of Anesthesia Management Characteristics on Severe Morbidity and Mortality

Anesth 2005;102:257-268

Study: Case-control study of patients undergoing anesthesia.
 Patients: 807 cases and 883 controls were analyzed among a cohort of 869,483 patients undergoing anesthesia between 1995-1997. Cases were defined as patients who either remained comatose or died within 24 h of receiving anesthesia. Controls were defined as patients who neither remained comatose nor died within 24 h of receiving anesthesia.

Intervention: General, regional or combined anesthesia to patients undergoing a surgical procedure.

Main Outcome: Coma or death within 24 h of receiving anesthesia.

Results: The incidence of 24 h postoperative death was 8.8 per 10,000 anesthetics (95% CI, 8.2-9.5) and the incidence of coma was 0.5 (95% CI, 0.3-0.6). Anesthesia management risk factors that were associated with a decreased risk of morbidity and mortality were equipment check with protocol and documentation, directly available anesthesiologist with no change during anesthesia, 2 persons present at emergence of anesthesia, reversal of muscle relaxation and postoperative pain medication.
• ASA 5: a moribund patient not expected to survive 24 h without surgery
  e.g. ruptured abdominal aortic aneurysm (AAA), head trauma with increased ICP
• ASA 6: declared brain dead, a patient whose organs are being removed for donation purposes
  for emergency operations, add the letter E after classification (e.g. ASA 3E)

Pre-Operative Optimization

• in general, any fluid and/or electrolyte imbalance should be corrected prior to elective surgery

Medications

• pay particular attention to cardiac and respiratory medications, opioids and drugs with many side effects and interactions
• pre-operative medications to consider
  • prophylaxis
    • risk of GE reflux: sodium citrate 30 mL PO or ranitidine 150-300 mg PO or metoclopramide 10 mg PO 30 min to 1 h pre-op
    • risk of infective endocarditis, GI/GU interventions: antibiotics
    • risk of adrenal suppression: steroid coverage
    • consider benzodiazepines for the anxious patient
    • bronchodilators (COPD, asthma)
    • nitroglycerin and β-blockers (CAD risk factors)
• pre-operative medications to stop
  • oral hypoglycemics: stop on morning of surgery
  • antidepressants: stop on morning of surgery
  • ACE inhibitors and angiotension receptor blockers: stop on morning of surgery
  • warfarin (consider bridging with heparin), anti-platelet agents (e.g. clopidogrel)
• pre-operative medication to adjust
  • insulin (consider insulin/dextrose infusion), prednisone, bronchodilators

Hypertension

• mild to moderate HTN is not an independent risk factor for peri-operative cardiovascular complications
• target sBP <180 mmHg, dBP <110 mmHg
• assess for end-organ damage and treat accordingly

Coronary Artery Disease (CAD)

• ACC/AHA Guidelines (2007) recommend postponing elective surgery 4-6 wk following an MI
• this period carries an increased risk of reinfarction/death
  • ≤3 mo after MI – 37% patients may reinfarct
  • 3-6 mo after MI – 15%
  • >6 mo after MI – risk remains constant at 5%
• if operative procedure is essential and cannot be delayed, invasive intra- and post-operative ICU monitoring reduces the risk to 6%, 2% and 1% respectively for the above time periods
• mortality with peri-operative MI is 20-50%
• initiation of peri-operative β-blockade previously advocated; currently, some recent studies have suggested an increased risk of stroke
  • β-blockade should be continued if already started
  • initiate β-blockade if inducible ischemia, CAD or multiple cardiac risk factors and undergoing high risk surgery
  • consider initiating and optimizing β-blockade if CAD or multiple cardiac risk factors and undergoing intermediate risk surgery

Endocrine Disorders

• diabetes mellitus
  • hypoglycemia
    • caused by drugs and surgical stresses and masked by anesthesia
    • appropriate use of dextrose/insulin infusion and blood glucose monitoring
  • end organ damage: be aware of damage to CVS, renal and nervous systems, including autonomic neuropathy

Effects of Extended-Release Metoprolol Succinate in Patients Undergoing Non-Cardiac Surgery (POISE Trial): A Randomized Controlled Trial
Lancet 2008;371:1839-1847
Purpose: To investigate the role of β-blockers (metoprolol) peri-operatively in patients with known vascular disease undergoing non-cardiac surgery.
Methods: Patients from 190 centres in 23 countries were eligible if they were age >45, undergoing non-cardiac surgery and were known to have significant vascular disease. Patients were randomized to either the metoprolol group or placebo. Participants received metoprolol (or placebo) 100 mg 2-4 h prior to surgery, 6 h after surgery, and then 20 mg daily for 30 d. The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal cardiac arrest. Analysis was by intention to treat.
Results: 8351 patients were recruited into the study, with 8331 completing the 30 d course. Use of metoprolol was found to significantly reduce the risk of cardiovascular death, non-fatal MI or non-fatal cardiac arrest vs. placebo (hazard ratio 0.84, p<0.05) but significantly increased the rate of stroke (hazard ratio 2.17, p<0.01) and overall risk of death (hazard ratio 1.33, p<0.05).
Conclusion: Use of peri-operative β-blockers (metoprolol) in patients with known vascular disease provides both risks and benefits, and these must be considered for each patient individually.
• hyperthyroidism
  • can experience sudden release of thyroid hormone (thyroid storm)
  • treatment: β-blockers and pre-op prophylaxis
• adrenocortical insufficiency (e.g. Addison’s, exogenous steroid use)
  • consider steroid coverage if steroid use of >1 wk in past 6 mo

## Respiratory Diseases

• smoking
  • adverse effects: altered mucus secretion and clearance, decreased small airway caliber and altered immune response
  • abstain at least 8 wk pre-op if possible
  • if unable, abstaining even 24 h pre-op has shown benefit
• asthma
  • increased risk of bronchospasm from intubation, delivery of desflurane
  • pre-op management depends on degree of baseline asthma control
  • pre-op SABA, LABA, ICS, OCS may be used up to 1 wk pre-op to achieve adequate asthma control
  • avoid non-selective β-blockers; cardioselective β-blockers (e.g. metoprolol, atenolol) do not increase risk of bronchospasm in the short term
  • cancel/delay elective surgery for poorly controlled asthma (increased cough or sputum production, active wheezing)
• COPD
  • anesthesia, surgery and analgesia predispose the patient to atelectasis, bronchospasm, pneumonia, prolonged need for mechanical ventilation and respiratory failure
  • cancel/delay elective surgery for acute exacerbation
  • optimize with bronchodilators ± ICS ± antibiotics

## Aspiration

• conditions with increased risk of aspiration:
  • decreased LOC
  • trauma
  • meal within 8 h
  • suspected sphincter incompetence (GERD, hiatus hernia, nasogastric tube)
  • increased abdominal pressure (pregnancy, obesity, bowel obstruction, acute abdomen)
• management: reduce gastric volume and acidity, delay inhibiting airway reflexes, employ rapid sequence induction if increased risk (see Rapid Sequence Induction, A9)
  • increased risk with laryngeal mask instead of endotracheal tube (ETT)

## Monitoring

### Canadian Guidelines to the Practice of Anesthesia and Patient Monitoring

• an anesthetist present: “the only indispensable monitor”
• a completed pre-anesthetic checklist: including ASA class, NPO policy, Hx and investigations
• a peri-operative anesthetic record: HR and BP every 5 min, dose and route of drugs and fluids
• continuous monitoring: see Routine Monitors below

### Routine Monitors for All Cases

• pulse oximeter, apparatus to measure BP, electrocardiography, capnography for general anesthesia and sedation (Ramsey Sedation Scale 4-6), agent-specific anesthetic gas monitor when inhalation anesthetic agents are used
• the following must also be available: temperature probe, peripheral nerve stimulator, stethoscope, appropriate lighting, spirometer

### Elements to Monitor

• anesthetic depth
  • inadequate: blink reflex present when eyelashes lightly touched, HTN, tachycardia, tearing or sweating
  • excessive: hypotension, bradycardia
• oxygenation: pulse oximetry, fraction of inspired O₂ (FiO₂)
• ventilation: verify correct position of ETT, chest excursions, breath sounds, ETCO₂ analysis, end tidal inhaled anesthesia analysis
• circulation: pulse, heart sounds, BP, telemetry, oximetry, CVP, pulmonary capillary wedge pressure
• temperature: temperature probe
Intravenous Agents

- IV induction agents include a selection of non-opioid drugs used to provide amnesia and blunt reflexes
- these are initially used to draw the patient into the maintenance phase of general anesthesia rapidly, smoothly and with little adverse effects
- e.g. propofol, sodium thiopental (not available in North America) or ketamine
- a continuous propofol infusion may also be used for the maintenance phase of GA

Volatile Inhalational Agents

- see Table 15, A26
- general concepts of volatile agents are discussed below
  - e.g. sevoflurane, desflurane, isoflurane, enflurane, halothane and nitrous oxide

MAC (minimum alveolar concentration)

- definition: the alveolar concentration of an agent at one atmosphere (atm) of pressure that will prevent movement in 50% of patients in response to a surgical stimulus (e.g. abdominal incision)
- often 1.2-1.3 times MAC will ablate response to stimuli in the general population
- potency of inhalational agents is compared using MAC
- MAC values are roughly additive when mixing N₂O with another volatile agent (i.e. 0.5 MAC of a potent agent + 0.5 MAC of N₂O = 1 MAC of potent agent; however, this only applies to movement, not other effects such as BP changes and does not hold over the entire N₂O dose range)
- MAC-intubation: the MAC of anesthetic that will inhibit movement and coughing during endotracheal intubation, generally 1.3 MAC
- MAC-block adrenergic response (MAC-BAR): the MAC necessary to blunt the sympathetic response to noxious stimuli, generally 1.5 MAC
- MAC-awake: the MAC of a given volatile anesthetic at which a patient will open their eyes to command, usually 0.3-0.4 of the usual MAC value

Table 2. Ramsay Sedation Scale

<table>
<thead>
<tr>
<th>Value</th>
<th>Description</th>
<th>Test to Follow</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Awake: Patient is anxious and agitated, or restless, or both</td>
<td>Observe the patient</td>
</tr>
<tr>
<td>2</td>
<td>Awake: Patient is co-operative, orientated, and tranquil</td>
<td>Observe the patient. Does patient make eye contact and respond to commands?</td>
</tr>
<tr>
<td>3</td>
<td>Awake: Patient responds to commands only</td>
<td>Talk to the patient. Does patient make eye contact and respond to commands?</td>
</tr>
<tr>
<td>4</td>
<td>Asleep: Patient reacts with a brisk response to a light glabellar tap or a loud auditory stimulus</td>
<td>Physically stimulate the patient by shaking the shoulder while Speaking loudly. Does patient respond within 10 s?</td>
</tr>
<tr>
<td>5</td>
<td>Asleep: Patient reacts with a sluggish response to a light glabellar tap or a loud auditory stimulus</td>
<td>Physically stimulate the patient by shaking the shoulder while Speaking loudly. Does patient respond after 10 s?</td>
</tr>
<tr>
<td>6</td>
<td>Asleep: Patient does not respond to pain</td>
<td>Use painful stimuli. No response</td>
</tr>
</tbody>
</table>
Muscle Relaxants and Reversing Agents

- see Tables 16 and 17, A27; Table 18, A28
- depolarizing muscle relaxants: succinylcholine (SCh)
- non-depolarizing muscle relaxants: rocuronium, mivacurium, vecuronium, cistracurium, pancuronium

**Figure 3. Anatomy and physiology of the neuromuscular junction (NMJ)**

**Muscle Relaxants**
- never use without adequate preparation and equipment to maintain airway and ventilation
- muscle relaxation produces the following desired effects:
  1. facilitates intubation
  2. assists with mechanical ventilation
  3. prevents muscle stretch reflex and decreases muscle tone
  4. allows access to the surgical field (intracavitary surgery)
- blocks nicotinic cholinergic receptors in NMJ
- provides skeletal muscle paralysis, including the diaphragm, but spares involuntary muscles such as the heart and smooth muscle
- nerve stimulator is used intraoperatively to assess the degree of nerve block; no twitch response seen with complete neuromuscular blockade

**Reversing Agents for Non-Depolarizing Muscle Relaxants** *(e.g. neostigmine, pyridostigmine, edrophonium)*
- reversal agents are acetylcholinesterase inhibitors
  - inhibits enzymatic degradation of ACh; increases amount of ACh at nicotinic and muscarinic receptors, displacing non-depolarizing muscle relaxant
  - administer reversal agents when there has been some recovery of blockade (i.e. muscle twitch)
- anticholinergic agents (e.g. atropine, glycopyrrolate) are simultaneously administered to minimize muscarinic effect of reversal agents (i.e. bradycardia, salivation and increased bowel peristalsis)

**Airway Anatomy Review**

- normal airway: nares → nasal cavities → nasal pharynx → laryngeal pharynx → trachea
- resistance to airflow through nasal passages accounts for approximately 2/3 of total airway resistance
- pharyngeal airway extends from posterior aspect of the nose to cricoid cartilage
- glottic opening (triangular space formed between the true vocal cords) is the narrowest segment of the laryngeal opening in adults
- when intubating, the glottic opening is used as the space through which one visualizes proper placement of the ETT
- the trachea begins at the level of the thyroid cartilage at the level of C6
- the trachea bifurcates into the right and left main bronchi at the level of T5 (approximately at the sternal angle)
Table 3. Methods of Supporting the Airway

<table>
<thead>
<tr>
<th>Bag and Mask</th>
<th>Laryngeal Mask Airway (LMA)</th>
<th>Endotracheal Tube (ETT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages/Indications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic</td>
<td>Easy to insert</td>
<td>Indications for intubation (5 Ps):</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>Less airway trauma/irritation than ETT</td>
<td>• Patent airway</td>
</tr>
<tr>
<td>Readily available</td>
<td>Frees up hands (vs. face mask)</td>
<td>• Protects against aspiration</td>
</tr>
<tr>
<td></td>
<td>Primarily used in spontaneously ventilating patient</td>
<td>• Positive pressure ventilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pulmonary toilet (suction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pharmacologic administration also hemodynamic instability</td>
</tr>
</tbody>
</table>

| **Disadvantages/Contraindications** | | |
| Risk of aspiration if decreased LOC | Risk of gastric aspiration | Insertion can be difficult |
| Cannot ensure airway patency | PPV < 20 cm H2O needed | Muscle relaxant usually needed |
| Inability to deliver precise tidal volume | Oropharyngeal/retropharyngeal pathology or foreign body | Most invasive – see Complications During Laryngoscopy and Intubation, A9 |

| **Other** | | |
| Facilitate airway patency with jaw thrust and chin lift | Does NOT protect against laryngospasm or gastric aspiration | Auscultate to avoid endobronchial intubation |
| Can use oropharyngeal/retropharyngeal airway | Sizing by body weight (approx): | Sizing (approx): |
| 40-50 kg: 3 | Male: 8.0-9.0 mm | Male: 8.0-9.0 mm |
| 50-70 kg: 4 | Female: 7.0-8.0 mm | Female: 7.0-8.0 mm |
| 70-100 kg: 5 | Pediatric: (age/4) + 4 mm | Pediatric: (age/4) + 4 mm |

**Tracheal Intubation**

**Preparing for Intubation**
- failed attempts at intubation can make further attempts more difficult due to tissue trauma
- plan, prepare and assess for potential difficulties (see Pre-Operative Assessment, A2)
- ensure equipment is available and working (e.g. test ETT cuff, check laryngoscope light, machine check)
- pre-oxygenate/denitrogenate: patient breathes 100% O2 for 3-5 min or for 4 vital capacity breaths
- may need to suction mouth and pharynx first

**Proper Positioning for Intubation**
- “sniffing position”: flexion of lower C-spine (C5,6), i.e. bow head forward and extension of upper C-spine at atlanto (C1)-occipital joint, i.e. nose in the air
- contraindicated in known/suspected C-spine fracture/instability
- aligns the three axes of mouth, pharynx and larynx to allow visualization from the oral cavity to the glottis (Figure 5)
- proper position for laryngoscope tip to visualize cords is in the epiglottic vallecula
- contraindicated in known/suspected C-spine fracture/instability

**Tube Insertion**
- ETT insertion can incite a significant sympathetic response due to a “foreign body reflex” in the trachea, including tachycardia, dysrhythmias, myocardial ischemia, increased BP and coughing
- a malpositioned ETT is a potential hazard for the intubated patient
  - if too deep, may result in right endobronchial intubation, which is associated with left-sided atelectasis and right-sided tension pneumothorax
  - if too shallow, may lead to accidental extubation, vocal cord trauma or laryngeal paralysis as a result of pressure injury by the ETT cuff
- the tip of ETT should be located at the midpoint of the trachea at least 2 cm above the carina and the proximal end of the cuff should be placed at least 2 cm below the vocal cords
  - approximately 20-23 cm mark at the right corner of the mouth for men and 19-21 cm for women

**Confirmation of Tracheal Placement of ETT**
- direct
  - visualization of ETT passing through cords
  - bronchoscopic visualization of ETT in trachea
- indirect
  - \( \text{ET}_{\text{CO}_2} \), in exhaled gas measured by capnography
  - auscultate for equal breath sounds bilaterally and absent breath sounds over epigastrium
  - bilateral chest movement, condensation of water vapour in ETT visible during exhalation and no abdominal distention
  - refilling of reservoir bag during exhalation
  - CXR (rarely done): ETT tip at midpoint of thoracic inlet and carina (lateral CXR more sensitive and specific)
- esophageal intubation suspected when
  - \( \text{ET}_{\text{CO}_2} \) zero or near zero on capnograph

**Figure 5. Anatomic considerations in laryngoscopy**
A. Neutral position
B. C-spine flexion
C. C-spine flexion with atlanto-occipital extension
• abnormal sounds during assisted ventilation
• impairment of chest excursion
• hypoxia/cyanosis
• presence of gastric contents in ETT
• distention of stomach/epigastrium with ventilation

### Complications During Laryngoscopy and Intubation
- dental damage
- laceration (lips, gums, tongue, pharynx, esophagus)
- laryngeal trauma
- esophageal or endobronchial intubation
- accidental extubation
- insufficient cuff inflation or cuff laceration: results in leaking and aspiration
- laryngospasm (see *Exubtion*, A17 for definition)
- bronchospasm

### Routine Induction vs. Rapid Sequence Induction (RSI)

- RSI is indicated in patients at risk of regurgitation/aspiration (see *Aspiration*, A5)

#### Table 4. Comparison of Routine Induction vs. RSI

<table>
<thead>
<tr>
<th>Steps</th>
<th>Routine Induction</th>
<th>RSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Equipment Preparation</td>
<td>Check equipment, drugs, suction, and monitors. Prepare an alternative laryngoscope blade and a second ETT tube one size smaller</td>
<td>Check equipment, drugs, suction, and monitors. Prepare an alternative laryngoscope blade and a second ETT tube one size smaller</td>
</tr>
<tr>
<td>2. Pre-Oxygenation/Denitrogenation</td>
<td>100% O₂ for 3 min or 4 vital capacity breaths</td>
<td>100% O₂ for 3 min or 4 vital capacity breaths</td>
</tr>
<tr>
<td>3. Pre-Treatment Agents</td>
<td>Use agent of choice to blunt physiologic responses to airway manipulation 3 min prior to laryngoscopy</td>
<td>Use agent of choice to blunt physiologic responses to airway manipulation. If possible, give 3 min prior to laryngoscopy but can skip this step in an emergent situation.</td>
</tr>
<tr>
<td>4. Induction Agents</td>
<td>Use IV or inhalation induction agent of choice</td>
<td>Use fast acting induction agent of choice</td>
</tr>
<tr>
<td>5. Ventilation</td>
<td>Bag-mask ventilation</td>
<td>DO NOT bag ventilate – can increase risk of aspiration</td>
</tr>
<tr>
<td>6. Cricoid Pressure</td>
<td>Backwards upwards rightwards pressure (BURP) to assist visualization if indicated</td>
<td>Sellick maneuver, also known as cricoid pressure, to prevent regurgitation and assist in visualization (2 kg pressure with drowsiness, 3 kg with loss of consciousness)</td>
</tr>
<tr>
<td>7. Intubation</td>
<td>Intubate, inflate cuff, confirm ET Tposition</td>
<td>Intubate once paralyzed (~45 s after Sch given), inflate cuff, confirm ET Tposition. Cricoid pressure maintained until ET T cuff inflated and placement confirmed</td>
</tr>
</tbody>
</table>

### Difficult Airway

- difficulties with bag-mask ventilation, supraglottic airway, endotracheal intubation, infraglottic airway or surgical airway
- algorithms exist for difficult airways (e.g. *Anesthesiology* 2003;98:3273, *Anaesthesia* 2004;59:675)
- pre-op assessment (history of previous difficult airway, airway examination) and pre-oxygenation are important preventative measures
- if difficult airway expected, consider:
  - awake intubation
  - intubating with bronchoscope, trachlight (lighted stylet), fibre optic laryngoscope, glidescope, etc.
Intraoperative Management

Oxygen Therapy

- in general, the goal of oxygen therapy is to maintain oxygen saturation (\(\text{SaO}_2\)) >90%
- below an \(\text{SaO}_2\) of 90%, a small decrease in saturation corresponds to a large drop in \(\text{PaO}_2\)
- in intubated patients, oxygen is delivered via the ETT
- in patients not intubated, there are many oxygen delivery systems available; the choice depends on oxygen requirements (FiO\(_2\)) and the degree to which precise control of delivery is needed
- cyanosis can be detected at \(\text{SaO}_2\) <85%, frank cyanosis at \(\text{SaO}_2\) = 67%

Low Flow Systems

- acceptable if tidal volume 300-700 mL, respiratory rate (RR) <25, consistent ventilation pattern
- provide O\(_2\) at flows between 0-10 L/min
- dilution of oxygen with room air results in a decrease in FiO\(_2\)
- an increase in minute ventilation (tidal volume x RR) results in a decrease in FiO\(_2\)
- e.g. nasal canula (prong)
  - well tolerated if flow rates <5-6 L/min; drying of nasal mucosa at higher flows
  - nasopharynx acts as an anatomic reservoir that collects O\(_2\)
  - delivered oxygen concentration (FiO\(_2\)) can be estimated by adding 4% for every additional litre of O\(_2\) delivered (e.g. at normal tidal volume and RR, flow rate of 1-6 L/min equates to FiO\(_2\) of 24-44%)

Reservoir Systems

- use a volume reservoir to accumulate oxygen during exhalation thus increasing the amount of oxygen available for the next breath
- simple face mask (Hudson face mask)
  - covers patient's nose and mouth and provides an additional reservoir beyond nasopharynx
  - fed by small bore O\(_2\) tubing at a rate of at least 6 L/min to ensure that exhaled CO\(_2\) is flushed through the exhalation ports and not rebreathed
  - FiO\(_2\) of 55% can be achieved at O\(_2\) flow rates of 10 L/min
- non-rebreather mask
  - reservoir bag and a series of one-way valves direct gas flow from the bag on inhalation and allow release of expired gases on exhalation, thus allowing for oxygen accumulation during intubation
  - O\(_2\) flow rates of 10-15 L/min are needed to maintain the reservoir bag inflation and should deliver FiO\(_2\) >80%

High Flow Systems

- generates flows of up to 50-60 L/min
- meets/exceeds patient's inspiratory flow requirement
- delivers consistent and predictable concentration of O\(_2\)
- Venturi mask
  - delivers specific percentages of oxygen by varying the size of air entrainment
  - port determines the oxygen concentration (i.e. can vary to achieve 24%, 28%, 35%, 50%)
  - enables control of gas humidity
- Puritan mask
  - delivers the highest level of humidified oxygen

Ventilation

- in patients given muscle relaxants, ventilation is maintained with PPV
- if no muscle relaxant is given, patients may have sufficient spontaneous respirations to maintain ventilation or assisted/controlled ventilation can be used
- other indications for mechanical ventilation:
  - apnea
  - hypoventilation
  - intraoperative positioning limiting respiratory excursion (e.g. prone, Trendelenburg)
  - required hyperventilation (to lower ICP)
A11 Anesthesia  Intraoperative Management  Toronto Notes 2014

- deliver positive end expiratory pressure (PEEP)
- increased intrathoracic pressure (e.g. laparoscopic procedure)
- complications of mechanical ventilation:
  - decreased CO₂ due to hyperventilation
  - decreased BP due to decreased venous return from increased intrathoracic pressure
  - alkalemia with over correction of chronic hypercarbia
  - nosocomial pneumonia/bronchitis
- see Respirology, R26 for ventilatory modes

**Causes of Hypocapnea (decreased CO₂)**
- hyperventilation
- hypothermia (decreased metabolic rate)
- decreased pulmonary blood flow (e.g. decreased cardiac output)
- incorrect placement of sampling catheter
- inadequate sampling volume
- V/Q mismatch
  - pulmonary thromboembolism
  - incipient pulmonary edema
  - air embolism

**Causes of Hypercapnea (increased CO₂)**
- hypoventilation
- hyperthermia
- improved pulmonary blood flow after resuscitation or hypotension
- low bicarbonate
- water in capnography device
- anesthetic breathing circuit error
  - inadequate fresh gas flow
  - rebreathing
  - exhausted soda lime
  - faulty circuit absorber valves

**Temperature**

**Causes of Hypothermia (<36.0°C)**
- intraoperative temperature losses are common (e.g. 90% of intraoperative heat loss is transcutaneous), due to:
  - OR environment (cold room, IV fluids, instruments)
  - open wound
- prevent with inflated warming blanket and warmed IV fluids (if giving platelet transfusion, put through a line that does not go through warmer because warmer distorts viability of platelets)

**Causes of Hyperthermia (>37.5-38.3°C)**
- drugs (e.g. atropine)
- blood transfusion reaction
- infection/sepsis
- medical disorder (e.g. thyrotoxicosis)
- malignant hyperthermia (see Uncommon Complications, A24)
- over-zealous warming efforts

**Heart Rate**

**Cardiac Arrest**
- pulseless arrest occurs due to 4 cardiac rhythms divided into shockable and non-schockable rhythms
  - shockable: ventricular fibrillation (VF) and ventricular tachycardia (VT)
  - non-shockable: asystole and pulseless electrical activity (PEA)
- for VF/VT, key to survival is good early CPR and defibrillation
- for asystole/PEA, key to survival is good early CPR and exclude all reversible causes
- reversible causes of PEA arrest (5 Hs and 5 Ts):
  - 5 Hs: hypothermia, hypovolemia, hypoxia, hydrogen ions (acidosis), hypo/hyperkalemia
  - 5 Ts: tamponade (cardiac), thrombosis (pulmonary), thrombosis (coronary), tension pneumothorax, toxins (overdose/poisoning)
- for management of cardiac arrest, see ACLS Guidelines (Figure 13), A28

**Intraoperative Tachycardia**
- tachycardia = HR >150 bpm; divided into narrow complex supraventricular tachycardias (SVT) or wide complex tachycardias
- SVT: sinus tachycardia, atrial fibrillation/flutter, accessory pathway mediated tachycardia, paroxysmal atrial tachycardia
- wide complex tachycardia: VT, SVT with aberrant conduction

---

**Causes of Intraoperative Hypoxia**
- **Inadequate oxygen supply**: e.g. breathing system disconnection, obstructed or malpositioned ETT, leaks in the anesthetic machine, loss of oxygen supply.
- **Hyperventilation**
  - Ventilation-perfusion inequalities: e.g. atelectasis, pneumonia, pulmonary edema, pneumothorax.
- **Reduction in oxygen carrying capacity**: e.g. anemia, carbon monoxide poisoning, methemoglobinemia, hemoglobinopathy.
- **Leftward shift of the hemoglobin-oxygen saturation curve**: e.g. hypothermia, decreased 2,3-DPG, alkalosis, hypocarbia, carbon monoxide poisoning.
- **Right-to-left cardiac shunt**

**Hypothermia (32°-35.9°C)**
- Impact on Outcomes
  - Increased risk of wound infections due to impaired immune function.
  - Increases the period of hospitalization by delaying healing.
  - Reduces platelet function and impairs activation of coagulation cascade increasing blood loss and transfusion requirements.
  - Triples the incidence of VT and morbid cardiac events.
  - Decreases the metabolism of anesthetic agents prolonging post-op recovery.
• causes of sinus tachycardia:
  - shock/hypovolemia/blood loss
  - anxiety/pain/light anesthesia
  - full bladder
  - anemia
  - febrile illness/sepsis
  - drugs (e.g. atropine, cocaine, dopamine, epinephrine, ephedrine, isoflurane, isoproterenol, pancuronium)
  - Addisonian crisis, hypoglycemia, transfusion reaction, malignant hyperthermia
  - for management of tachycardia, see ACLS Guidelines (Figure 14), A29

**Intraoperative Bradycardia**
• bradycardia = HR <50 bpm; most concerning are 2nd degree (Type 2 Mobitz) and 3rd degree heart block, which can both degenerate into asystole
• causes of sinus bradycardia:
  - increased parasympathetic tone vs. decreased sympathetic tone
  - must rule out hypoxemia
  - arrhythmias (see Cardiology and Cardiovascular Surgery, C12)
  - baroreceptor reflex due to increased ICP or increased BP
  - vagal reflex (oculocardiac reflex, carotid sinus reflex, airway manipulation)
  - drugs (e.g. Sch, opioids, edrophonium, neostigmine, halothane, digoxin, β-blockers)
  - high spinal/epidural anesthesia
  - for management of bradycardia, see ACLS Guidelines (Figure 15), A29

**Blood Pressure**

**Causes of Intraoperative Hypotension/Shock** (sBP <90 mmHg or MAP <60 mmHg)
  a) hypovolemic/hemorrhagic shock
    - most common form of shock, due to blood loss or dehydration

<table>
<thead>
<tr>
<th>Class</th>
<th>Percentage blood loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0-15%</td>
</tr>
<tr>
<td>II</td>
<td>15-30%</td>
</tr>
<tr>
<td>III</td>
<td>30-40%</td>
</tr>
<tr>
<td>IV</td>
<td>&gt;40%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class</th>
<th>Percentage TBW loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0-3%</td>
</tr>
<tr>
<td>II</td>
<td>3-6%</td>
</tr>
<tr>
<td>III</td>
<td>6-9%</td>
</tr>
<tr>
<td>IV</td>
<td>&gt;9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class</th>
<th>Heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;100</td>
</tr>
<tr>
<td>II</td>
<td>&gt;100</td>
</tr>
<tr>
<td>III</td>
<td>&gt;120</td>
</tr>
<tr>
<td>IV</td>
<td>&gt;140</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Rapid infusion of 1-2 L of crystalloid (e.g. Ringer’s lactate), maintenance fluids or 2 L of crystalloid and re-evaluate</td>
</tr>
<tr>
<td>Normal</td>
<td>Rapid infusion of 2 L of crystalloid, replace losses with crystalloid (1:1) or pRBCs, colloid (1:1)</td>
</tr>
<tr>
<td>Decreased</td>
<td>Rapid infusion of 2 L of crystalloid, replace losses with crystalloid (1:1) or pRBCs, colloid (1:1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal is to maintain urine output at &gt;0.5 mL/kg/h</td>
</tr>
</tbody>
</table>

b) obstructive shock
  - obstruction of blood into or out of the heart
  - increased JVP, distended neck veins, increased systemic vascular resistance, insufficient cardiac output (CO)
  - e.g. tension pneumothorax, cardiac tamponade, pulmonary embolism

c) cardiogenic shock
  - myocardial dysfunction
  - increased JVP, distended neck veins, increased systemic vascular resistance, decreased CO
  - e.g. dysrhythmias, ischemia/infarct, cardiomyopathy, acute valvular dysfunction

d) septic shock
  - see Infectious Diseases, ID22
  - bacterial, viral, fungal, endotoxins/mediators cause vasodilation and capillary leakage
  - associated with contamination of open wounds, intestinal injury or penetrating trauma
  - fever, decreased JVP, wide pulse pressure, increased CO, increased HR, decreased systemic vascular resistance ± pressors
  - initial treatment: antibiotics, volume expansion
e) spinal/neurogenic shock
  - decreased sympathetic tone
  - hypotension without tachycardia or peripheral vasoconstriction (warm skin)
f) anaphylactic shock
  - see Emergency Medicine, ER30
  - acute/subacute generalized allergic reaction due to an inappropriate or excessive immune response (type I hypersensitivity)
treatment of anaphylactic shock:
- moderate reaction: generalized urticaria, angioedema, wheezing, tachycardia
  - epinephrine (1:1000) 0.3-0.5 mg SC
  - antihistamines: diphenhydramine (Benadryl®) 25-50 mg IM
  - salbutamol (Ventolin®) 1 cc via nebulizer
- severe reaction/evolution: severe wheezing, laryngeal/pulmonary edema, shock
  - ABCs, may need ETT due to airway edema
  - epinephrine (1:1000) 0.1-0.3 mg IV (or via ETT if no IV access) to start, repeat as needed
  - antihistamines: diphenhydramine (Benadryl®) 50 mg IV (~1 mg/kg)
  - steroids: hydrocortisone (Solucortef®) 100 mg IV (~1.5 mg/kg) or methylprednisolone (Solumedrol®) 1 mg/kg IV q6h x 24 h
  - large volumes of crystalloid may be required

g) drugs
- vasodilators, high spinal anesthetic interfering with sympathetic outflow
h) other
- transfusion reaction, Addisonian crisis, thyrotoxicosis, hypothyroid, aortocaval syndrome
  - see Hematology, H52 and Endocrinology, E35, E22, E26

Causes of Intraoperative Hypertension
- inadequate anesthesia causing pain and anxiety
- pre-existing HTN, coarctation or preeclampsia
- hypoxemia/hypercarbia
- hypervolemia
- drugs (e.g. ephedrine, epinephrine, cocaine, phenylephrine, ketamine)
- allergic/anaphylactic reaction
- hypermetabolic states: malignant hyperthermia, neuroleptic malignant syndrome
  - see Psychiatry, PS43, thyroid storm, pheochromocytoma (see Endocrinology, E25, E36)

Fluid Balance and Resuscitation
- total requirement = maintenance + deficit + ongoing loss
- in surgical settings this formula must take into account multiple factors including pre-operative fasting/decreased fluid intake, increased losses during or before surgery, fluid shifting during surgery, fluids given with blood products and medications

What is the Maintenance?
- average healthy adult requires approximately 2500 mL water/d
  - 200 mL/d GI losses
  - 800 mL/d insensible losses (respiration, perspiration)
  - 1500 mL/d urine (beware of renal failure)
- increased requirements with fever, sweating, GI losses (vomiting, diarrhea, NG suction), adrenal insufficiency, hyperventilation and polyuric renal disease
- decreased requirements with anuria/oliguria, SIADH, highly humidified atmospheres and CHF
- 4:2:1 rule to calculate maintenance requirements (applies to crystalloids only)
  - 4 mL/kg/h first 10 kg
  - 2 mL/kg/h second 10 kg
  - 1 mL/kg/h for remaining weight >20 kg
- maintenance electrolytes
  - Na+: 3 mEq/kg/d
  - K+: 1 mEq/kg/d
- e.g. 50 kg patient maintenance requirements
  - fluid = 40 + 20 + 30 = 90 mL/h = 2160 mL/d = 2.16 L/d
  - Na⁺ = 150 mEq/d (therefore 150 mEq / 2.16 L/d = 69 mEq/L)
  - K⁺ = 50 mEq/d (therefore 50 mEq / 2.16 L/d = 23 mEq/L)
- above patient's requirements roughly met with 2/3 D5W, 1/3 NS
  - e.g. 2/3 + 1/3 at 100 mL/h with 20 mEq KCl per litre

What is the Deficit?
- patients should be adequately hydrated prior to anesthesia
- total body water (TBW) = 60% or 50% of total body weight for an adult male or female, respectively (e.g. for a 70 kg adult male TBW = 70 x 0.6 = 42 L)
- total Na⁺ content determines ECF volume; [Na⁺] determines ICF volume
- hypovolemia due to volume contraction
  - extra-renal Na⁺ loss
    - GI: vomiting, NG suction, drainage, fistulae, diarrhea
    - skin/resp: insensible losses (fever), sweating, burns
    - vascular: hemorrhage
renal Na+ and H2O loss
- diuretics
- osmotic diuresis
- hypoaldosteronism
- salt-wasting nephropathies
renal H2O loss
- diabetes insipidus (central or nephrogenic)
hypovolemia with normal or expanded ECF volume
- decreased CO
- redistribution
  - hypoalbuminemia: cirrhosis, nephrotic syndrome
  - capillary leakage: acute pancreatitis, rhabdomyolysis, ischemic bowel, sepsis, anaphylaxis

- replace water and electrolytes as determined by patient’s needs
- with chronic hyponatremia, correction must be done gradually over >48 h to avoid central pontine myelinolysis

### Table 6. Signs and Symptoms of Dehydration

<table>
<thead>
<tr>
<th>Percentage of Body Water Loss</th>
<th>Severity</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>3%</td>
<td>Mild</td>
<td>Decreased skin turgor, sunken eyes, dry mucous membranes, dry tongue, reduced sweating</td>
</tr>
<tr>
<td>6%</td>
<td>Moderate</td>
<td>Oliguria, orthostatic hypotension, tachycardia, low volume pulse, cool extremities, reduced filling of peripheral veins and CVP, hemoconcentration, apathy</td>
</tr>
<tr>
<td>9%</td>
<td>Severe</td>
<td>Profound oliguria or anuria and compromised CNS function with or without altered sensorium</td>
</tr>
</tbody>
</table>

### What are the Ongoing Losses?
- tubes
  - Foley catheter, NG, surgical drains
- third spacing (other than ECF, ICF)
  - pleura, GI, retroperitoneal, peritoneal
  - evaporation via exposed viscera, burns
- blood loss
- ongoing loss due to surgical exposure and evaporative losses

### IV Fluids
- replacement fluids include crystalloid and colloid solutions
- IV fluids improve perfusion but NOT O2 carrying capacity of blood

#### Crystalloid Infusion
- salt-containing solutions that distribute within ECF
- maintain euvoelma in patient with blood loss: 3 mL crystalloid infusion per 1 mL of blood loss for volume replacement (i.e. 3:1 replacement). Controversy surrounds this as an initial vs. maximal replacement target
- if large volumes are to be given, use balanced fluids such as Ringer’s lactate or PlasmaLyte®, as too much normal saline (NS) may lead to hyperchloremic metabolic acidosis

#### Colloid Infusion (see Blood Products, A15)
- includes protein colloids (albumin and gelatin solutions) and non-protein colloids (starches, e.g. hydroxyethyl starch (HES) and dextrans)
- distributes within intravascular volume
- 1:1 ratio (infusion:blood loss) only in terms of replacing intravascular volume
- HES colloids remain in intravascular space (metabolized by plasma serum amylase and renally excreted); two available in Canada: Voluven® and Pentaspan®
- beware of coagulopathy with large volume colloid infusions

### Table 7. Colloid HES Solutions

<table>
<thead>
<tr>
<th>Solution</th>
<th>Concentration</th>
<th>Plasma Volume Expansion</th>
<th>Duration (h)</th>
<th>Maximum Daily Dose (mL/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voluven®</td>
<td>6%</td>
<td>1:1</td>
<td>4-6</td>
<td>33-50</td>
</tr>
<tr>
<td>Pentaspan®</td>
<td>10%</td>
<td>1:1.2-1.5</td>
<td>18-24</td>
<td>28</td>
</tr>
</tbody>
</table>

### Initial Distribution of IV Fluids
- H2O follows ions/molecules to their respective compartments
### Anesthesia

#### Table 8. IV Fluid Solutions

<table>
<thead>
<tr>
<th></th>
<th>ECF</th>
<th>Ringer’s Lactate</th>
<th>0.9% NS</th>
<th>0.45% NS in D5W</th>
<th>D5W</th>
<th>2/3 D5W + 1/3 NS</th>
<th>Plasmalyte</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mEq/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na⁺</td>
<td>142</td>
<td>130</td>
<td>154</td>
<td>77</td>
<td>-</td>
<td>51</td>
<td>140</td>
</tr>
<tr>
<td>K⁺</td>
<td>4</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>4</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>103</td>
<td>109</td>
<td>154</td>
<td>77</td>
<td>-</td>
<td>51</td>
<td>98</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>27</td>
<td>28*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td><strong>mOsm/L</strong></td>
<td>280-310</td>
<td>273</td>
<td>308</td>
<td>154</td>
<td>252</td>
<td>269</td>
<td>294</td>
</tr>
<tr>
<td>pH</td>
<td>7.4</td>
<td>6.5</td>
<td>5.0</td>
<td>4.5</td>
<td>4.0</td>
<td>4.3</td>
<td>7.4</td>
</tr>
</tbody>
</table>

*Converted from lactate

### Blood Products

- see Hematology, H50

#### Red Blood Cells (RBCs)
- 1 U RBCs = approx. 300 mL
- 1 U RBCs increases Hb by 10 g/L in a 70 kg patient
- RBCs may be diluted with colloid/crystalloid to decrease viscosity
- decision to transfuse based on initial blood volume, premorbid Hb level, present volume status, expected further blood loss, patient health status, patient consent
- massive transfusion = >1 x blood volume/24 h

#### Autologous RBCs
- replacement of blood volume with one’s own RBCs
- may decrease complications (infectious, febrile, etc.)
- alternative to homologous transfusion in elective procedures, but only if adequate Hb and no infection
- pre-op phlebotomy prior to elective surgery (up to 3U collected 3-5 wk before surgery)
- intraoperative salvage and filtration (cell saver); contraindicated in contaminated (e.g. bowel, abscess) or cancer cases

#### Non-RBC Products
- fresh frozen plasma (FFP)
  - contains all plasma clotting factors and fibrinogen close to normal plasma levels
  - to prevent/treat bleeding due to coagulation factor depletion/deficiencies, liver impairment
- cryoprecipitate
  - contains Factors VIII and XIII, von Willebrand Factor (vWF), fibrinogen
- platelets
  - used in thrombocytopenia, massive transfusions, impaired platelet function
- albumin
  - selective intravascular volume expander
- erythropoietin
  - can be used pre-operatively to stimulate erythropoiesis

#### Complications Due to Transfusion
- infectious risks: HIV, hepatitis B/C, Epstein-Barr virus (EBV), cytomegalovirus (CMV), brucellosis, malaria, salmonellosis, measles, syphilis
- hypervolemia
- electrolyte changes: increased K⁺ in stored blood
- dilutional coagulopathy
- dilutional thrombocytopenia
- hypothermia
- citrate toxicity
- hypocalcemia
- iron overload
- transfusion-related immunosuppression: peri-operative transfusion may be associated with increased risk of post-operative infection, increased short-term mortality and possible cancer recurrence
- see Hematology, H52 for list of transfusion reactions

#### Calculating Acceptable Blood Losses (ABL)
- Blood volume
  - term infant  80 mL/kg
  - adult male  70 mL/kg
  - adult female  60 mL/kg
- Calculate estimated blood volume (EBV) (e.g. in a 70 kg male, approx. 70 mL/kg)
  \[
  \text{EBV} = 70 \text{ kg} \times 70 \text{ mL/kg} = 4800 \text{ mL}
  \]
- Decide on a transfusion trigger, i.e. the Hb level at which you would begin transfusion, (e.g. 70 g/L for a person with Hb(i) = 150 g/L)
  \[
  \text{Hb(f)} = 70 \text{ g/L}
  \]
- Calculate
  \[
  \text{ABL} = \text{Hct(i)} - \text{Hct(f)} \times \frac{\text{EBV}}{\text{Hct(i)}}
  \]
  \[
  = \frac{150 - 70}{150} \times 4800
  = 2613 \text{ mL}
  \]
- Therefore in order to keep the Hb level above 70 g/L, RBCs would have to be given after approximately 2.6 L of blood has been lost.
Table 9. Immune Transfusion Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Risk</th>
<th>Cause</th>
<th>Presentation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hemolytic: Febrile</td>
<td>1 in 100</td>
<td>• Allantibodies to WBC, platelet, or other donor plasma antigens</td>
<td>• Mild fever &lt;38°C with or without rigors; may be &gt;38°C with restlessness and shivering</td>
<td>• Rule out fever due to hemolytic reaction or bacterial contamination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nausea, facial flushing, headache, myalgia, hypotension, chest and back pain</td>
<td>• Occurs quickly; near completion of transfusion or within 2 h</td>
<td>• Mild (&lt;38°C): decrease infusion rate and give antipyretics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Occurs at time of transfusion is too low to be detected or to cause hemolysis</td>
<td>• Stop transfusion, give antipyretics, antihistamines and symptomatic treatment</td>
<td></td>
</tr>
<tr>
<td>Non-Hemolytic: Allergic</td>
<td>1 in 100</td>
<td>• Mild allergic reaction due to IgE antibodies to substances in donor plasma</td>
<td>• Often have history of similar reactions</td>
<td>• Moderate to severe: stop transfusion, IV antihistamines, subcutaneous epinephrine, hydrocortisone, IV fluids, bronchodilators</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mast cells activated with histamine release</td>
<td>• Abrupt onset of pruritic erythema/urticaria on arms and trunk, occasionally with fever</td>
<td>• Pharyngitis: antihistamines 15-60 min prior to transfusion, washed or deglycerolized frozen RBC donor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Usually occurs in pre-exposed (e.g. multiple transfusions, multiparous patients)</td>
<td>• Less common: involvement of face, larynx and bronchioles</td>
<td>• Circulatory support with fluids, catecholamines (epinephrine), bronchodilators</td>
</tr>
<tr>
<td>Non-Hemolytic: Anaphylactoid</td>
<td>&lt;1 in 100</td>
<td>• In IgA deficient patients with anti-IgA antibodies receiving IgA-containing blood</td>
<td>• Rare, potentially lethal</td>
<td>• Respiratory assistance as indicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Immune complexes activate mast cells, basophils, eosinophils and complement system</td>
<td>• Apprehension, urticarial eruptions, dyspnea, hypotension, laryngeal and airway edema, wheezing, chest pain, shock, sudden death</td>
<td>• Evaluate for IgA deficiency and anti-IgA antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Severe symptoms after transfusion of RBC, plasma, platelets, or other components with IgA</td>
<td></td>
<td>• Future transfusions must be free of IgA: washed or deglycerolized RBCs, free of IgA, blood from IgA deficient donor</td>
</tr>
<tr>
<td>Transfusion Related Acute Lung Injury (TRALI)</td>
<td>1 in 5000</td>
<td>• Form of noncardiogenic pulmonary edema</td>
<td>• Occurs 2-4 h post transfusion</td>
<td>• Usually resolves within 48 h with O2, mechanical ventilation, supportive treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Immunologic cause; not due to fluid overload or cardiac failure</td>
<td>• Respiratory distress: mild dyspnea to severe hypoxia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Binding of donor Ab against recipient WBC causing cytokine release leading to increased capillary permeability</td>
<td>• Chest x-ray: consistent with acute pulmonary edema, but pulmonary artery and wedge pressures are not elevated</td>
<td></td>
</tr>
<tr>
<td>Hemolytic: Acute (intravascular hemolysis)</td>
<td>&lt;1 in 40,000</td>
<td>• Caused by donor incompatibility with recipient’s blood</td>
<td>• Fever, chills, chest or back pain, hypotension, tachycardia, nausea, flushing, dyspnea, wheezing, hypoxemia, hemoglobinuria, diffuse bleeding due to DIC, acute renal failure</td>
<td>• Stop transfusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Often due to clerical error</td>
<td>• Notify blood bank, confirm or rule out diagnosis – clerical check, direct Coombs, repeat grouping, RH screen and crossmatch, serum haptoglobin</td>
<td>• Manage hypotension with fluids, isotopes, other blood products</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Antibody coated RBC is destroyed by activation of complement system</td>
<td>• Maintain urine output with crystalloids, furosidine, dopamine, alkalinize urine</td>
<td>• Component treatment if DIC, repeat grouping, RH screen and crossmatch, serum haptoglobin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ABO incompatibility is a common cause; other RBC Ag-Ab systems can be involved</td>
<td>• Component treatment with fluids, isotopes, other blood products</td>
<td>• Manage hypotension with fluids, isotopes, other blood products</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fever, chills, chest or back pain, hypotension, tachycardia, nausea, flushing, dyspnea, wheezing, hypoxemia, hemoglobinuria, diffuse bleeding due to DIC, acute renal failure</td>
<td>• Component treatment (e.g. FFP, cryoprecipitate)</td>
<td></td>
</tr>
<tr>
<td>Hemolytic: Delayed (extravascular hemolysis)</td>
<td>&lt;1 in 7500</td>
<td>• Caused by donor incompatibility with recipient’s blood</td>
<td>• Occurs in recipients sensitized to RBC antigens by previous blood transfusion or pregnancy</td>
<td>• Supportive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Generally mild, caused by antibodies to Rh, Kell, Duffy, or Kidd antigens</td>
<td>• Anemia, mild jaundice, fever 1-21 d post-transfusion</td>
<td>• Direct Coombs, re-examination of pretransfusion specimens from the patient and donor for diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• The level of antibody at the time of transfusion is too low to be detected or to cause hemolysis; later the level of antibody is increased due to secondary stimulus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Transfusion Infection Risks

<table>
<thead>
<tr>
<th>Virus</th>
<th>Risk per 1 unit pRBCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1 in 8-12 million</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>1 in 5-7 million</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>1 in 1-1.7 million</td>
</tr>
<tr>
<td>HTLV</td>
<td>1 in 1-3.3 million</td>
</tr>
<tr>
<td>Syphilis</td>
<td>&lt; 1 in 100 million</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>No cases since 2003</td>
</tr>
</tbody>
</table>

Transfusion and risk of infection in Canada: Update 2012. Paediatr Child Health 2012;17:e102-e111

A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care

In 1999, 340:409-417

Purpose: To determine whether a restrictive strategy of RBC transfusion and a liberal strategy produce equivalent results in critically ill patients.

Study: Randomized controlled trial with 60 d follow-up.

Patients: 838 critically ill patients with evidence of acute hypovolemia after initial transfusion who had Hb concentrations of <80 g/L within 72 h after admission to the ICU. Median age 57.5 yr, 62.5% male.

Intervention: Patients were randomly assigned to either a restrictive strategy of transfusion, in which RBCs were transfused if the Hb dropped <100 g/L, and Hb concentrations were maintained between 70-90 g/L, or a liberal strategy, in which transfusions were given when the Hb dropped <100 g/L and Hb concentrations were maintained between 100-120 g/L.

Main Outcomes: All cause mortality rates at 30 d and 60 d, mortality rates during the stay in ICU and hospitalization, survival times during the first 30 d and rates of organ failure and dysfunction.

Results: Overall, 30 d mortality was similar in the two groups. However, the rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill (8.7% vs. 16.1%) and who were less than 55 yr of age (5.7% vs. 13%), but not among patients with clinically significant cardiac disease.

The mortality rate during hospitalization was significantly lower in the restrictive strategy group (22.2% vs. 28.1%).

Conclusions: With the possible exception of patients with acute MI and unstable angina, a restrictive strategy of RBC transfusion is as effective as, and possibly superior to, a liberal transfusion strategy in critically ill patients.
Extubation

- performed by trained, experienced personnel because reintubation may be required
- criteria:
  - patient must no longer have intubation requirements (see Table 3, Tracheal Intubation, A8)
  - patency: airway must be patent
  - protection: airway reflexes intact
  - patient must be oxygenating and ventilating spontaneously
- laryngospasm more likely in semiconscious patient; must ensure adequate LOC
- general guidelines:
  - ensure patient has normal neuromuscular function (peripheral nerve stimulator monitoring) and hemodynamic status
  - ensure patient is breathing spontaneously with adequate rate and tidal volume
  - suction secretions from pharynx
  - deflate cuff, remove ETT on inspiration (vocal cords abducted)

Complications of Extubation

- early extubation
  - aspiration
  - laryngospasm
- late extubation
  - transient vocal cord incompetence
  - edema (glottic, subglottic)
  - pharyngitis, tracheitis

Laryngospasm

- defined as forceful involuntary spasm of laryngeal muscles caused by stimulation of superior laryngeal nerve (e.g. by oropharyngeal secretions, blood, extubation)
- causes partial or total airway obstruction
- prevention: extubate while patient is still deeply under anesthesia or fully awake
- treatment: bag-mask ventilation with 100% oxygen, low-dose propofol (0.5-1.0 mg/kg) optional, low-dose succinylcholine (0.25-1 mg/kg) and reintubation if hypoxia develops

Post-Operative Care

- pain management should be continuous from OR to post-anesthetic care unit (PACU) to hospital ward and home
- pain service may assist with management of post-operative inpatients

Post-Operative Nausea and Vomiting (PONV)

- hypotension and bradycardia must be ruled out
- pain and surgical manipulation also cause nausea
- often treated with dimenhydrinate (Gravol®), metoclopramide (Maxeran®) (not with bowel obstruction), prochlorperazine (Stemetil®), ondansetron (Zofran®), granisetron (Kytril®)

Post-Operative Confusion and Agitation

- ABCs first – confusion or agitation can be caused by airway obstruction, hypercapnea, hypoxemia
- neurologic status (Glasgow Coma Scale, pupils), residual paralysis from anesthetic
- pain, distended bowel/bladder
- fear/anxiety/separation from caregivers, language barriers
- metabolic disturbance (hypoglycemia, hypercalcemia, hyponatremia – especially post-TURP)
- intracranial cause (stroke, raised intracranial pressure)
- drug effect (ketamine, anticholinergics)
- elderly patients are more susceptible to post-operative delirium

Risk Factors for Post-Operative Nausea and Vomiting (PONV)

- Young age
- Female
- History of PONV
- Non-smoker
- Type of surgery: ophtho, ENT, abdo/pelvic, plastics
- Type of anesthetic: N2O, opioids, volatile agents

Drugs for Preventing Post-Operative Nausea and Vomiting

Cochrane Database Syst Rev 2006;3:CD004125
Purpose: To evaluate the efficacy of antiemetics in preventing PONV.
Methods: A meta-analysis was performed looking at randomized controlled trials comparing an antiemetic to either a second antiemetic or placebo. Trials looking at dosing and/or timing of medication administration were also included. PONV was used as the primary outcome.
Results: 727 studies involving 103,237 patients. Eight drugs significantly reduced the occurrence of PONV, namely: droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and granisetron. Relative risk (RR) versus placebo varied between 0.60 and 0.80. Side effects included a significant increase in drowsiness for droperidol (RR 1.32) and headache for ondansetron (RR 1.16). The cumulative number needed to treat was 3.57.
Conclusion: Antiemetic medication is effective for reducing the occurrence of PONV. However, further investigation needs to be done to determine whether antiemetics can cause more severe (and likely rare) side effects, which could alter how liberally they are used.
Pain Management

Definitions
- nociception: detection, transduction and transmission of noxious stimuli
- pain: perception of nociception which occurs in the brain

Acute Pain
- pain of short duration (<6 wk) usually associated with surgery, trauma or acute illness; often associated with inflammation
- usually limited to the area of damage/trauma and resolves with healing

Pharmacological Management of Acute Pain
- ask the patient to rate the pain out of 10, or use visual analog scale, to determine severity
- 

Table 10. Commonly Used Analgesics

<table>
<thead>
<tr>
<th>Acetaminophen</th>
<th>NSAIDs</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tylenol®</td>
<td>Aspirin®, ibuprofen, naproxen</td>
<td>Oral: codeine, oxycodone, morphine, hydromorphone</td>
</tr>
<tr>
<td></td>
<td>ketorolac (IV)</td>
<td>Parenteral: morphine, hydromorphone, fentanyl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Opioid-sparing</td>
</tr>
</tbody>
</table>

Opioid Equivalency
- 10 mg morphine
- 100 mg codeine
- 5 mg oxycodone
- 2 mg hydromorphone

Figure 8. WHO analgesia ladder

Use NSAIDs with Caution in Patients with:
- Asthma
- Coagulopathy
- GI ulcers
- Renal insufficiency
- Pregnancy, 3rd trimester

Common Side Effects of Opioids
- Nausea and vomiting
- Constipation
- Sedation
- Pruritus
- Abdominal pain
- Urinary retention
- Respiratory depression

When prescribing opioids, consider:
- Breakthrough dose
- Anti-emetics
- Laxative

PCA Parameters
- Loading dose
- Bolus dose
- Lockout interval
- Continuous infusion (optional)
- Maximum 4 h dose (limit)

Advantages of PCA
- Improved patient satisfaction
- Fewer side effects
- Accommodates patient variability
- Accommodates changes in opioid requirements

Figure 9. Acute pain mechanism

Figure 9. Acute pain mechanism

Pharmacological Management of Acute Pain
- ask the patient to rate the pain out of 10, or use visual analog scale, to determine severity

Table 10. Commonly Used Analgesics

<table>
<thead>
<tr>
<th>Acetaminophen</th>
<th>NSAIDs</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tylenol®</td>
<td>Aspirin®, ibuprofen, naproxen</td>
<td>Oral: codeine, oxycodone, morphine, hydromorphone</td>
</tr>
<tr>
<td></td>
<td>ketorolac (IV)</td>
<td>Parenteral: morphine, hydromorphone, fentanyl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Opioid-sparing</td>
</tr>
</tbody>
</table>

Opioid Equivalency
- 10 mg morphine
- 100 mg codeine
- 5 mg oxycodone
- 2 mg hydromorphone

Figure 8. WHO analgesia ladder

Use NSAIDs with Caution in Patients with:
- Asthma
- Coagulopathy
- GI ulcers
- Renal insufficiency
- Pregnancy, 3rd trimester

Common Side Effects of Opioids
- Nausea and vomiting
- Constipation
- Sedation
- Pruritus
- Abdominal pain
- Urinary retention
- Respiratory depression

When prescribing opioids, consider:
- Breakthrough dose
- Anti-emetics
- Laxative

PCA Parameters
- Loading dose
- Bolus dose
- Lockout interval
- Continuous infusion (optional)
- Maximum 4 h dose (limit)

Advantages of PCA
- Improved patient satisfaction
- Fewer side effects
- Accommodates patient variability
- Accommodates changes in opioid requirements
• patient controlled analgesia (PCA)
  • involves the use of computerized pumps that can deliver a constant infusion as well as bolus breakthrough doses of parenterally-administered opioid analgesics
  • limited by lockout intervals
  • most commonly used agents: morphine and hydromorphone
  • refer to Table 14, A26 for suggested infusion rate, PCA dose and lockout intervals

Opioid Antagonists (naloxone, naltrexone)
• opioid overdose manifests primarily at CNS (e.g. respiratory depression) – manage ABCs
• opioid antagonists competitively inhibit opioid receptors, predominantly µ receptors
• naloxone is short-acting (t1/2 = 1 h); effects of narcotic may return when naloxone wears off; therefore, the patient must be observed closely following its administration
• naltrexone is longer-acting (t1/2 = 10 h); less likely to see return of opioid effects
• relative overdose of naloxone may cause nausea, agitation, sweating, tachycardia, hypertension, re-emergence of pain, pulmonary edema, seizures (essentially opioid withdrawal)

Neuropathic Pain
• pain caused by peripheral or central nervous system injury, often described as burning, lancinating, shooting, or tingling
• results in allodynia (pain in response to normally painless stimuli) or hyperalgesia (increased sensitivity to painful stimuli)
• consider adding anticonvulsants (gabapentin, pregabalin) or low-dose tricyclic antidepressant as opioids are ineffective

Chronic Pain
• pain of duration or intensity that persists beyond normal tissue healing and adversely affects functioning
• may have nociceptive and neuropathic components; dysregulation of analgesic pathways implicated
• in the peri-operative period, consider continuing regular long-acting analgesics, and augmenting with regional techniques, adjuvants, additional opioid analgesia, and non-pharmacological techniques

Regional Anesthesia

Definition of Regional Anesthesia
• local anesthetic agent (LA) applied around a peripheral nerve at any point along the length of the nerve (from spinal cord up to, but not including, the nerve endings) for the purpose of reducing or preventing impulse transmission
• no CNS depression (unless overdose of local anesthetic); patient remains conscious
• regional anesthetic techniques categorized as follows:
  ▪ epidural and spinal anesthesia (neuraxial anesthesia)
  ▪ peripheral nerve blocks
  ▪ IV regional anesthesia (e.g. Bier block)

Preparation for Regional Anesthesia

Patient Preparation
• thorough pre-operative evaluation and assessment of patient
• technique explained to patient
• sedation may be indicated before block
• monitoring should be as extensive as for general anesthesia

Relative Indications for Regional Anesthesia
• avoids some of the dangers of general anesthesia (e.g. known difficult intubation, severe respiratory failure, etc.)
• patient specifically requests regional anesthesia
• high quality post-operative pain relief
• general anesthesia not available/contraindicated
• titration of LA dosage for differential blockade (e.g. can block pain but preserve motor function)

Complications of Regional Anesthesia
• failure of technique/inadequate anesthesia
• unintentional total spinal anesthesia
• systemic drug toxicity due to overdose or intravascular injection (leading to CNS and CVS complications)
• injury to nerve root/spinal cord (nerve deficit), to epidural vein (hematoma), to peripheral nerve (intraneural injection)
• infection (e.g. osteitis, epidural abscess, meningitis)
• spinal and epidural: sympathetic blockade causing hypotension and bradycardia (occurs early, followed by sensory then motor blockade)
• post-dural puncture headache

Benefits of Regional Anesthesia
• Reduced peri-op pulmonary complications
• Reduced peri-op analgesia requirements
• Decreased POIV
• Reduced peri-op blood loss
• Ability to monitor CNS status during procedure
• Improved perfusion
• Lower incidence of VTE

Patient Controlled Opioid Analgesia versus Conventional Opioid Analgesia for Postoperative Pain
Cochrane DB Syst Rev 2006;4:CD003348

Purpose: To evaluate the efficacy of patient controlled analgesia (PCA) as compared to conventional ‘as-needed’ analgesia administration providing pain relief in post-operative patients.

Methods: Meta-analyses of randomized controlled trials comparing PCA vs. conventional administration of opioid analgesia. Assessment employed a visual analog scale (VAS) for pain intensity along with overall analgesic consumption, patient satisfaction, length of stay and adverse side effects.

Results: 55 studies with a total of 2023 patients receiving PCA and 1638 patients with standard as-needed opioid administration. PCA provided significantly better pain control through 72 h post-operatively, but patients consumed significantly more opioids (>7 mg morphine/24 h, P < 0.05).

Significantly more patients reported pruritus in the PCA group compared to control with a number needed to harm of 13. No significant difference in overall length of stay in hospital, sedation level, nausea/vomiting or urinary retention.

Conclusions: PCA is more effective than standard as-needed administration for reducing post-operative pain. However, patients using PCA consume more opioids overall and have more pruritus.

To ronto Notes 2014
Epidural and Spinal Anesthesia

Anatomy of Spinal/Epidural Area
- spinal cord extends to L2, dural sac to S2 in adults
- nerve roots (cauda equina) from L2 to S2
- needle inserted below L2 should not encounter cord, thus L3-L4, L4-L5 interspace commonly used
- structures penetrated
  - skin
  - subcutaneous fat
  - supraspinous ligament
  - interspinous ligament
  - ligamentum flavum (last layer before epidural space)
  - dura + arachnoid for spinal anesthesia

Table 11. Epidural versus Spinal Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Epidural</th>
<th>Spinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deposition Site</td>
<td>LA injected in epidural space (space between ligamentum flavum and dura)</td>
<td>LA injected into subarachnoid space in the dural sac surrounding the spinal cord and nerve roots</td>
</tr>
<tr>
<td></td>
<td>Initial blockade is at the spinal roots followed by some degree of spinal cord anesthesia as LA diffuses into the subarachnoid space through the dura</td>
<td></td>
</tr>
<tr>
<td>Onset</td>
<td>Significant blockade requires 10-15 min</td>
<td>Rapid blockade (onset in 2-5 min)</td>
</tr>
<tr>
<td></td>
<td>Slower onset of side effects</td>
<td></td>
</tr>
<tr>
<td>Effectiveness</td>
<td>Effectiveness of blockade can be variable</td>
<td>Very effective blockade</td>
</tr>
<tr>
<td>Difficulty</td>
<td>Technically more difficult; greater failure rate</td>
<td>Easier to perform due to visual confirmation of CSF flow</td>
</tr>
<tr>
<td>Patient Positioning</td>
<td>Position of patient not as important; specific gravity not an issue</td>
<td>Hyperbaric LA solution – position of patient important</td>
</tr>
<tr>
<td>Specific Gravity/Spread</td>
<td>Solutions injected here spread throughout the potential space; specific gravity of solution does not affect spread</td>
<td>LA solution may be made hyperbaric (of greater specific gravity than the cerebrospinal fluid by mixing with 10% dextrose, thus increasing spread of LA to the dependent (low) areas of the subarachnoid space)</td>
</tr>
<tr>
<td>Dosage</td>
<td>Larger volume/dose of LA (usually &gt; toxic IV dose)</td>
<td>Smaller dose of LA required (usually &lt; toxic IV dose)</td>
</tr>
<tr>
<td>Continuous Infusion</td>
<td>Use of catheter allows for continuous infusion or repeat injections</td>
<td>None</td>
</tr>
<tr>
<td>Complications</td>
<td>Failure of technique</td>
<td>Failure of technique</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Bradycardia if cardiac sympathetics blocked (only if ~T2-4 block), i.e. “high spinal”</td>
<td>Bradycardia if cardiac sympathetics blocked (only if ~T2-4 block), i.e. “high spinal”</td>
</tr>
<tr>
<td></td>
<td>Epidural or subarachnoid hematoma</td>
<td>Epidural or subarachnoid hematoma</td>
</tr>
<tr>
<td></td>
<td>Accidental subarachnoid injection can produce spinal anesthesia (and any of the above complications)</td>
<td>Post-spinal headache (CSF leak)</td>
</tr>
<tr>
<td></td>
<td>Systemic toxicity of LA (accidental intravenous)</td>
<td>Transient paresthesias</td>
</tr>
<tr>
<td></td>
<td>Catheter complications (shearing, kinking, vascular or subarachnoid placement)</td>
<td>Spinal cord trauma, infection</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dural puncture</td>
<td></td>
</tr>
<tr>
<td>Combined Spinal-Epidural</td>
<td>Combines the benefits of rapid, reliable, intense blockade of spinal anesthesia together with the flexibility of an epidural catheter</td>
<td></td>
</tr>
</tbody>
</table>

Contraindications to Spinal/Epidural Anesthesia
- absolute contraindications
  - lack of proper equipment or trained personnel
  - lack of IV access
  - allergy to LA
  - infection at puncture site or underlying tissues
  - coagulopathies/anti-coagulation
  - raised ICP
  - sepsis/bacteremia
  - hemodynamic instability/uncorrected hypovolemia

Landmarking Epidural/Spinal Anesthesia
- Spinal processes should be maximally flexed
- L4 spinous processes found between iliac crests
- Common sites of insertion are L3-L4 and L4-L5

Figure 10. Landmarks for placement of epidural/spinal

Classic Presentation of Dural Puncture Headache
- Onset 6 h-3 d after dural puncture
- Postural component (worse sitting)
- Occipital or frontal localization
- ± tinnitus, diplopia
• relative contraindications
  ▪ pre-existing neurological disease
  ▪ aortic/mitral valve stenosis (i.e. fixed cardiac output states)
  ▪ previous spinal surgery, severe kyphoscoliosis
  ▪ severe/unstable psychiatric disease or emotional instability

**Peripheral Nerve Blocks**

• utilizes ultrasound guidance and electrical stimulation (needle will stimulate target nerve/plexus), may be used to guide deposition of local anesthetic around nerve while avoiding neural trauma or intraneural injection
• approximately 2-4 per 10,000 risk of late neurologic injury
• most major nerves or nerve plexi can be targeted (e.g. brachial plexus block, femoral nerve block, sciatic nerve block, etc.)

**Contraindications to Peripheral Nerve Blockade**

• allergy to LA
• patient refusal, lack of cooperation
• lack of resuscitation equipment
• lack of IV access
• certain types of pre-existing neurological dysfunction (e.g. ALS, MS, diabetic neuropathy)
• local infection at block site
• bleeding disorder

**Local Anesthesia**

**Local Anesthetic Agents (LA)**

• see Table 19 for list of LA agents, A28

**Definition and Mode of Action**

• LA are drugs that block the generation and propagation of impulses in excitable tissues: nerves, skeletal muscle, cardiac muscle, brain
• LA bind to receptors on the cytosolic side of the Na⁺ channel, inhibiting Na⁺ flux and thus blocking impulse conduction
• different types of nerve fibres undergo blockade at different rates

**Absorption, Distribution, Metabolism**

• LA readily crosses the blood-brain barrier (BBB) once absorbed into the bloodstream
• ester-type LA (procaine, tetracaine) are broken down by plasma and hepatic esterases; metabolites excreted via kidneys
• amide-type LA (lidocaine, bupivacaine) are broken down by hepatic mixed-function oxidases (P450 system); metabolites excreted via kidneys

**Selection of LA**

• choice of LA depends on
  ▪ onset of action: influenced by pKa (the lower the pKa, the higher the concentration of the base form of the LA and the faster the onset of action)
  ▪ duration of desired effects: influenced by protein binding (longer duration of action when protein binding of LA is strong)
  ▪ potency: influenced by lipid solubility (agents with high lipid solubility penetrate the nerve membrane more easily)
  ▪ unique needs (e.g. sensory blockade with relative preservation of motor function by bupivacaine at low doses)
  ▪ potential for toxicity

**Systemic Toxicity**

• see Table 19, A28 for maximum doses, potency and duration of action for common LA agents
• occurs by accidental intravascular injection, LA overdose, or unexpectedly rapid absorption
• CNS effects first appear to be excitatory due to initial block of inhibitory fibres; then subsequent block of excitatory fibres
• CNS effects (in order of appearance)
  ▪ numbness of tongue, perioral tingling, metallic taste
  ▪ disorientation, drowsiness
  ▪ tinnitus

![Figure 11. Local anesthetic systemic toxicity](image-url)
• visual disturbances
• muscle twitching, tremors
• unconsciousness
• convulsions, seizures
• generalized CNS depression, coma, respiratory arrest

• CVS effects
  • vasodilation, hypotension
  • decreased myocardial contractility
  • dose-dependent delay in cardiac impulse transmission
    * prolonged PR, QRS intervals
    * sinus bradycardia
  • CVS collapse

• treatment of systemic toxicity
  • early recognition of signs, get help
  • 100% O₂, manage ABCs
  • diazepam or sodium thiopental may be used to increase seizure threshold
  • manage arrhythmias (see ACLS Guidelines, A28)
  • Intralipid® 20% to bind local anesthetic in circulation

### Local Infiltration and Hematoma Blocks

#### Local Infiltration
- injection of tissue with LA, producing a lack of sensation in the infiltrated area due to LA acting on nerve endings
- suitable for small incisions, suturing, excising small lesions
- can use fairly large volumes of dilute LA to infiltrate a large area
- low concentrations of epinephrine (1:100,000-1:200,000) cause vasoconstriction, thus reducing bleeding and prolonging the effects of LA by reducing systemic absorption

#### Fracture Hematoma Block
- special type of local infiltration for pain control during manipulation of certain fractures
- hematoma created by fracture is infiltrated with LA to anesthetize surrounding tissues
- sensory blockade may only be partial
- no muscle relaxation

### Topical Anesthetics
- various preparations of local anesthetics available for topical use, may be a mixture of agents, e.g. EMLA cream is a combination of 2.5% lidocaine and prilocaine
- must be able to penetrate the skin or mucous membrane

### Obstetrical Anesthesia

#### Physiologic Changes in Pregnancy
- **airway**
  - possible difficult airway as tissues becomes edematous and friable especially in labour
- **respiratory**
  - decreased FRC and increased O₂ consumption → desaturation occurs more quickly during apnea
- **cardiovascular system**
  - increased blood volume > increased RBC mass → mild anemia
  - decreased SVR proportionately greater than increased CO → decreased BP
  - prone to decreased BP due to aortocaval compression – therefore for surgery, a pregnant patient is positioned in left uterine displacement using a wedge under her right flank
- **central nervous system**
  - decreased MAC due to hormonal effects
  - increased block height due to engorged epidural veins
- **gastrointestinal system**
  - delayed gastric emptying
  - increased volume and acidity of gastric fluid
  - decreased LES tone
  - increased abdominal pressure
  - combined, these lead to an increased risk of aspiration – therefore for surgery, a pregnant patient is given sodium citrate 30 cc PO immediately before surgery to neutralize gastric acidity

#### Where Not to Use LA with Epinephrine
“Ears, Fingers, Toes, Penis, Nose”

#### The Effect of Epidural Analgesia on Labour, Maternal, and Neonatal Outcomes: A Systematic Review

**Am J Obstet Gynecol** 2002;186:S69-77

**Study:** Meta-analysis of 14 studies with 4324 women.

**Selection Criteria:** RCTs and prospective cohort studies between 1980-2001 comparing epidural analgesia to parenteral opioid administration during labour.

**Types of Participants:** Healthy women with uneventful pregnancies.

**Intervention:** Participants were randomized to either epidural analgesia or parenteral opioid administration during labour.

**Outcomes and Results:**
- **Maternal**
  - there were no differences between the 2 groups in first-stage labour length, incidence of Caesarean delivery, incidence of instrumented vaginal delivery for dystocia, nausea, or mid-to-low back pain post-partum. However, second-stage labour length was longer (mean=15 min) and there were greater reports of fever and hypotension in the epidural group. Also, lower pain scores and greater satisfaction with analgesia were reported among the epidural group. There was no difference in lactation success at 6 wk and urinary incontinence was more frequent in the epidural group immediately post-partum, but not at 3 mo or 1 yr (evidence from PC studies only). Neonates – there were no differences between the 2 groups for incidence of fetal heart rate abnormalities, intrapartum meconium, poor 5-min Apgar score, or low umbilical artery pH. However, the incidence of poor 1-min Apgar scores and need for neonatal naloxone were higher in the parenteral opioid group.
- **Conclusions:** Epidural analgesia is a safe intrapartum method for labour pain relief and women should not avoid epidural analgesia for fear of neonatal harm, Caesarean delivery, breastfeeding difficulties, long-term back pain or long-term urinary incontinence.
Options for Analgesia during Labour
- psychoprophylaxis – Lamaze method
- patterns of breathing and focused attention on fixed object
- systemic medication
  - easy to administer, but risk of maternal or neonatal depression
  - opioids most commonly used if delivery is not expected within 4 h
- inhalational analgesia
  - easy to administer, makes uterine contractions more tolerable, but does not relieve pain completely
  - 50% nitrous oxide
- neuraxial analgesia
  - provides excellent analgesia with minimal depressant effects
  - hypotension is the most common complication
  - maternal BP monitored q2-5 min for 15-20 min after initiation and regularly thereafter
  - epidural usually given as it preferentially blocks sensation, leaving motor function intact

Options for Caesarean Section
- neuraxial: spinal or epidural
- general: used if contraindications or time precludes regional blockade

Pediatric Anesthesia

Respiratory System
- in comparison to adults, anatomical differences in infants include
  - large head, short trachea/neck, large tongue, adenoids and tonsils
  - narrow nasal passages (obligate nasal breathers until 5 mo)
  - narrowest part of airway at the level of the cricoid vs. glottis in adults
  - epiglottis is longer, U shaped and angled at 45 degrees; carina is wider and is at the level of T2 (T4 in adults)
- physiologic differences include
  - faster RR, immature respiratory centres which are depressed by hypoxia/hypercapnea (airway closure occurs in the neonate at the end of expiration)
  - less oxygen reserve during apnea – decreased total lung volume, vital and functional reserve capacity together with higher metabolic needs
  - greater V/Q mismatch – lower lung compliance due to immature alveoli (mature at 8 yr)
  - greater work of breathing – greater chest wall compliance, weaker intercostals/diaphragm and higher resistance to airflow

Cardiovascular System
- blood volume at birth is approximately 80 mL/kg; transfusion should be started if >10% of blood volume lost
- children have a high HR and low BP
- CO is dependent on HR, not stroke volume because of low heart wall compliance; therefore, bradycardia → severe compromise in CO

Temperature Regulation
- vulnerable to hypothermia
- minimize heat loss by use of warming blankets, covering the infant's head, humidification of inspired gases and warming of infused solutions

Central Nervous System
- MAC of halothane is increased compared to the adult (i.e. 0.75% adult, 0.87% neonates, 1.2% infant)
- NMJ is immature for the first 4 wk of life and thus there is an increased sensitivity to non-depolarizing relaxants
- parasympathetics mature at birth, sympathectics mature at 4-6 mo → autonomic imbalance
- infant brain is 12% of body weight and receives 34% of CO (adult: 2% body weight and 14% CO)

Glucose Maintenance
- infants less than 1 yr old can become seriously hypoglycemic during pre-operative fasting and post-operatively if feeding is not recommenced as soon as possible
- after 1 yr, children are able to maintain normal glucose homeostasis in excess of 8 h

Pharmacology
- higher dose requirements because of higher TBW (75% vs. 60% in adults) and greater volume of distribution
- barbiturates/opioids more potent due to greater permeability of BBB

Nociceptive Pathways in Labour and Delivery
Labour
- Cervical dilation and effacement stimulates visceral nerve fibres entering the spinal cord at T10-L1

Delivery
- Distention of lower vagina and perineum causes somatic nociceptive impulses via the pudendal nerve entering the spinal cord at S2-S4

To increase alveolar minute ventilation in neonates, increase respiratory rate, not tidal volume.

Neonate: 30-40 breaths/min
Age 1-13: \( 24 - \frac{\text{age}}{2} \) breaths/min

To calculate diameter (mm) of tracheal tube in children after 1 year:

Ages 1-3 years: \( \text{age} + 4 \)
Ages 4-8 years: \( \text{age} + 6 \)
Ages 9-12 years: \( \text{age} + 8 \)
Ages 13-15 years: \( \text{age} + 10 \)

Length (cm) of tracheal tube:

Ages 0-4 years: \( \frac{\text{age}}{2} + 12 \)
Ages 5-9 years: \( \frac{\text{age}}{2} + 15 \)
Ages 10-15 years: \( \frac{\text{age}}{2} + 18 \)
• muscle relaxants
  ▪ non-depolarizing
    ▪ immature NMJ, variable response
  ▪ depolarizing
    ▪ must pre-treat with atropine or may experience profound bradycardia and/or sinus node arrest due to PNS > SNS (also dries oral secretions)
    ▪ more susceptible to arrhythmias, hyperkalemia, rhabdomyolysis, myoglobinemia, masseter spasm and malignant hyperthermia

Uncommon Complications

Malignant Hyperthermia (MH)

• hypermetabolic disorder of skeletal muscle
• due to an uncontrolled increase in intracellular Ca\(^{2+}\) (because of an anomaly of the ryanodine receptor which regulates the Ca\(^{2+}\) channel in the sarcoplasmic reticulum of skeletal muscle)
• autosomal dominant inheritance
• incidence of 1-5 in 100,000, may be associated with skeletal muscle abnormalities such as dystrophy or myopathy
• anesthetic drugs triggering MH include
  ▪ all inhalational agents except nitrous oxide
  ▪ depolarizing muscle relaxants: SCh

Clinical Picture

• onset: immediate or hours after contact with trigger agent
  ▪ increased oxygen consumption
  ▪ increased ET\(_{CO_2}\) on capnograph
  ▪ tachycardia/dysrhythmia
  ▪ tachypnea/cyanosis
  ▪ diaphoresis
  ▪ hypertension
  ▪ increased temperature (late sign)
• muscular symptoms
  ▪ trismus (masseter spasm) common but not specific for MH (occurs in 1% of children given SCh with halothane anesthesia)
  ▪ tender, swollen muscles due to rhabdomyolysis
  ▪ trunk or total body rigidity

Complications

• coma
• DIC
• rhabdomyolysis
• myoglobinuric renal failure/hepatic dysfunction
• electrolyte abnormalities (e.g. hyperkalemia) and secondary arrhythmias
• ARDS
• pulmonary edema
• can be fatal if untreated

Prevention

• suspect MH in patients with a family history of problems/death with anesthetic
• avoid all trigger medications (use regional if possible) and use vapour free equipment
• central body temp and ET\(_{CO_2}\) monitoring

Malignant Hyperthermia Management [Based on Malignant Hyperthermia Association of the U.S. (MHAUS) Guidelines, 2008]

1. notify surgeon, discontinue volatile agents and succinylcholine, hyperventilate with 100% oxygen at flows of 10 L/min or more; halt the procedure as soon as possible
2. dantrolene 2.5 mg/kg IV, through large-bore IV if possible
  ▪ repeat until there is control of signs of MH; sometimes up to 30 mg/kg is necessary
3. bicarbonate 1-2 mEq/kg if blood gas values are not available for metabolic acidosis
4. cool patients with core temperature >39°C
  ▪ lavage open body cavities, stomach, bladder, rectum; apply ice to surface; infuse cold saline IV
  ▪ stop cooling if temperature is <38°C to prevent drift to <36°C
5. dysrhythmias usually respond to treatment of acidosis and hyperkalemia
  ▪ use standard drug therapy except Ca\(^{2+}\) channel blockers as they may cause hyperkalemia and cardiac arrest in presence of dantrolene
6. hyperkalemia
   - treat with hyperventilation, bicarbonate, glucose/insulin, calcium
   - bicarbonate 1-2 mEq/kg IV, calcium chloride 10 mg/kg or calcium gluconate 10-50 mg/kg
   for life-threatening hyperkalemia and check glucose levels hourly

7. follow ET, electrolytes, blood gases, creatine kinase (CK), core temperature, urine output/colour with Foley-catheter, coagulation studies
   - if CK and/or potassium rises persistently or urine output falls to <0.5 mL/kg/h, induce diuresis to >1 mL/kg/h urine to avoid myoglobinuric renal failure
8. maintain anesthesia with benzodiazepines, opioids and propofol
9. transfer to ICU bed

### Abnormal Pseudocholinesterase

- pseudocholinesterase hydrolyzes SCh and mivacurium
- 1 in 50 people will be heterozygous for an abnormal pseudocholinesterase allele
- heterozygotes will experience a prolonged duration of muscular blockade (2-3x normal)
- homozygotes will have a greatly increased duration of blockade (4-8 h) following administration of SCh
- SCh and mivacurium are contraindicated in those with abnormal pseudocholinesterase
- if SCh or mivacurium are given accidentally, treat with mechanical ventilation until function returns to normal (do not use cholinesterase inhibitors)

### Common Medications

#### Table 12. Intravenous Induction Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Action</th>
<th>Indications</th>
<th>Caution</th>
<th>Dosing</th>
<th>Special Considerations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylphenol – hypnotic</td>
<td>Ultra-short acting thiobarbiturate – hypnotic</td>
<td>Induction</td>
<td>Allergy (egg, soy)</td>
<td>IV induction: 2.5-3.0 mg/kg (less with opioids)</td>
<td>0-30% decreased BP due to vasodilation, Reduce burning at IV site by mixing with lidocaine</td>
<td></td>
</tr>
<tr>
<td>Inhibitory at GABA synapse</td>
<td>Decreased time Cl⁻ channels open, facilitating GABA and suppressing glutamic acid</td>
<td>Control of convulsive states</td>
<td>Pts who cannot tolerate sudden decreased BP (i.e. fixed cardiac output or shock)</td>
<td>IV induction: 3-5 mg/kg</td>
<td>Combining with rocuronium causes precipitates to form</td>
<td></td>
</tr>
<tr>
<td>Decreased cerebral metabolic rate and blood flow, decreased ICP, decreased SV, decreased BP and decreased SV</td>
<td>Decreased cerebral metabolism and blood flow, decreased CPP, decreased CO, decreased BP, decreased reflex tachycardia, decreased respiration</td>
<td>Major trauma, hypovolemia, severe asthma because sympathomimetic</td>
<td>Ketamine allergy</td>
<td>IV induction 1-2 mg/kg</td>
<td>High incidence of emergence reactions (vivid dreaming, out-of-body sensation, illusions)</td>
<td></td>
</tr>
<tr>
<td>May act on NMDA, opiate and other receptors</td>
<td>Increased HR, increased BP, increased SV, increased coronary flow, increased myocardial O₂ uptake, CNS and respiratory depression, bronchial smooth muscle relaxation</td>
<td>Used for sedation, amnesia and anxiolysis</td>
<td>History of psychosis</td>
<td>Dissociation in 15 s, analgesia, amnesia and unconsciousness in 45-60 s</td>
<td>Antagonist: flumazenil (Anexate®) competitive inhibitor, 0.2 mg IV over 15 s, repeat with 0.1 mg/min (max of 2 mg), t₁/₂ of 60 min</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines – anxiolytic</td>
<td>Causes increased glycine inhibitory neurotransmitter, facilitates GABA</td>
<td>Marked respiratory depression</td>
<td>Pts who cannot tolerate HTN (e.g. CHE, increased ICP, aneurysm)</td>
<td>Unconscious for 10-15 min, analgesia for 40 min, amnesia for 1-2 h</td>
<td>Midozolam also has anesthetic (antegrade) effect and decreased risk of thrombophlebitis</td>
<td></td>
</tr>
<tr>
<td>Ketamine allergy</td>
<td>Produces antianxiety and skeletal muscle relaxant effects</td>
<td></td>
<td></td>
<td>t₁/₂ = ~3 h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Toronto Notes 2014
### Table 13. Opioids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Relative Dose to 10 mg</th>
<th>Moderate Dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>200 mg PO</td>
<td>15-30 mg PO</td>
<td>Late (30-60 min)</td>
<td>Moderate (4-6 h)</td>
<td>Primarily post-operative use, not for IV use</td>
</tr>
<tr>
<td>Meperidine (Demerol)</td>
<td>75 mg IV</td>
<td>2-3 mg/kg IV</td>
<td>Moderate (10 min)</td>
<td>Moderate (2-4 h)</td>
<td>Anticholinergic, hallucinations, less pupillary constriction than morphine, metabolite build up may cause seizures</td>
</tr>
<tr>
<td>Morphine</td>
<td>10 mg IV</td>
<td>0.2-0.3 mg/kg IV</td>
<td>Moderate (5-10 min)</td>
<td>Moderate (4-5 h)</td>
<td>Histamine release leading to decrease in BP</td>
</tr>
<tr>
<td>Meperidine (Demerol)</td>
<td>20 mg PO</td>
<td>0.4-0.6 mg/kg PO</td>
<td>Moderate (5-10 min)</td>
<td>Moderate (4-5 h)</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15 mg PO</td>
<td>10-20 mg PO (no IV)</td>
<td>Late (30-45 min)</td>
<td>Long (8-12 h)</td>
<td>Do not split, crush or chew tablet</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid)</td>
<td>2 mg IV</td>
<td>40-60 µg/kg IV</td>
<td>Moderate (15 min)</td>
<td>Moderate (4-5 h)</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>100 µg IV</td>
<td>2-3 µg/kg IV</td>
<td>Rapid (&lt;5 min)</td>
<td>Short (0.5-1 h)</td>
<td>Transient muscle rigidity in very high doses</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>100 µg IV</td>
<td>0.5-1.5 µg/kg IV</td>
<td>Rapid (1-3 min)</td>
<td>Ultra short (&lt;10 min)</td>
<td>Only use during induction and maintenance of anesthesia</td>
</tr>
</tbody>
</table>

In general, parenteral route is 2-3 times more potent than oral

### Table 14. Opioid PCA Doses

<table>
<thead>
<tr>
<th>Agent</th>
<th>PCA Dose</th>
<th>PCA Lockout Interval</th>
<th>PCA 4 h Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1 mg</td>
<td>5 min</td>
<td>30 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>25-50 µg</td>
<td>5 min</td>
<td>400 µg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.2 mg</td>
<td>5 min</td>
<td>6 mg</td>
</tr>
</tbody>
</table>

### Table 15. Volatile Inhalational Agents

<table>
<thead>
<tr>
<th>MAC (% gas in O₂)</th>
<th>Sevoflurane</th>
<th>Desflurane</th>
<th>Isoflurane</th>
<th>Enflurane</th>
<th>Halothane</th>
<th>Nitrous oxide (N₂O)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>6.0</td>
<td>1.2</td>
<td>1.7</td>
<td>0.8</td>
<td>104</td>
<td></td>
</tr>
</tbody>
</table>

| CNS                | Increased ICP | Increased ICP | Decreased cerebral metabolic rate | Increased ICP | ECG seizure-like activity | Increased ICP | Increased cerebral blood flow | — |
| Resp               | Respiratory depression (severely decreased TV, increased RRI), decreased response to respiratory CO₂ reflexes, bronchodilation | — |
| CVS                | Less decrease of contractility, stable HR | Tachycardia with rapid increase in concentration | Decreased BP and CO, increased HR, theoretical chance of coronary steal** | Stable HR, decreased contractility | Decreased BP, CO, HR and conduction sensitizes myocardium to epinephrine-induced arrhythmias | Can cause decreased HR in pediatric cases in those with existing heart disease |
| MSK                | Muscle relaxation, potentiation of other muscle relaxants, uterine relaxation | — |

*Properties and Adverse Effects of N₂O

Due to its high MAC, nitrous oxide is combined with other anesthetic gases to attain surgical anesthesia. A MAC of 104% is possible in a pressurized chamber only.

Second Gas Effect: see Determinants of Speed of Onset of Volatile Anesthetics sidebar, A6

Expansion of closed spaces: closed spaces such as a pneumothorax, the middle ear, bowel lumen and ETT cuff will markedly enlarge if N₂O is administered.

Diffusion hypoxia: during anesthesia, the washout of N₂O from body stores into alveoli can dilute the alveolar O₂, creating a hypoxic mixture if the original O₂ is low.

**Coronary steal: isoflurane causes small vessel dilation which may compromise blood flow to areas of the heart with fixed perfusion [e.g. stents, atherosclerosis].
### Table 16. Depolarizing Muscle Relaxants (Non-Competitive): Succinylcholine (SCh)

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Mimics ACh and binds to ACh receptors causing prolonged depolarization; initial fasciculation may be seen, followed by temporary paralysis secondary to blocked ACh receptors by SCh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubating Dose</td>
<td>1-1.5 mg/kg</td>
</tr>
<tr>
<td>Onset</td>
<td>30-60 s – RAPID (fastest of all muscle relaxants)</td>
</tr>
<tr>
<td>Duration</td>
<td>3-5 min – SHORT (no reversing agent for SCh)</td>
</tr>
<tr>
<td>Metabolism</td>
<td>SCh is hydrolyzed by plasma cholinesterase (pseudocholinesterase), found only in plasma and not at the NMJ</td>
</tr>
<tr>
<td>Indications</td>
<td>• Assist intubation</td>
</tr>
<tr>
<td></td>
<td>• Increased risk of aspiration (need rapid paralysis and airway control)</td>
</tr>
<tr>
<td></td>
<td>• Short procedures (e.g. full stomach), hiatus hernia, obesity, pregnancy, trauma</td>
</tr>
<tr>
<td></td>
<td>• Electroconvulsive therapy (ECT)</td>
</tr>
<tr>
<td></td>
<td>• Laryngospasm</td>
</tr>
<tr>
<td>Side Effects</td>
<td>1. SCh also stimulates muscarinic cholinergic autonomic receptors (in addition to nicotinic receptors)</td>
</tr>
<tr>
<td></td>
<td>• May cause bradycardia, dysrhythmias, sinus arrest, increased secretions of salivary glands (especially in children)</td>
</tr>
<tr>
<td></td>
<td>2. Hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>• Disruption of motor nerve activity causes proliferation of extrajunctional (outside NMJ) cholinergic receptors</td>
</tr>
<tr>
<td></td>
<td>• Depolarization of an increased number of receptors by SCh may lead to massive release of potassium out of muscle cells</td>
</tr>
<tr>
<td></td>
<td>• Patients at risk:</td>
</tr>
<tr>
<td></td>
<td>• 3rd degree burns 24 h-6 mo after injury</td>
</tr>
<tr>
<td></td>
<td>• Traumatic paralysis or neuromuscular diseases (e.g. muscular dystrophy)</td>
</tr>
<tr>
<td></td>
<td>• Severe intra-abdominal infections</td>
</tr>
<tr>
<td></td>
<td>• Severe closed head injury</td>
</tr>
<tr>
<td></td>
<td>• Upper motor neuron lesions</td>
</tr>
<tr>
<td></td>
<td>3. Can trigger MH</td>
</tr>
<tr>
<td></td>
<td>4. Increased ICP/intracocular pressure/intragastric pressure (no increased risk of aspiration if competent lower esophageal sphincter)</td>
</tr>
<tr>
<td></td>
<td>5. Fasciculations, post-op myalgia – may be minimized if small dose of non-depolarizing agent given before SCh administration</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Absolute</td>
</tr>
<tr>
<td></td>
<td>Relative</td>
</tr>
</tbody>
</table>

### Table 17. Non-Depolarizing Muscle Relaxants (Competitive)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Competitive blockade of postsynaptic ACh receptors preventing depolarization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubating Dose (mg/kg)</td>
<td>Mivacuronium</td>
</tr>
<tr>
<td>Onset (min)</td>
<td>0.2</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>15-25</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Plasma cholinesterase</td>
</tr>
<tr>
<td>Indications</td>
<td>Assist intubation, assist mechanical ventilation in some ICU patients, reduce fasciculations and post-op myalgias secondary to SCh</td>
</tr>
<tr>
<td>Side Effects:</td>
<td>Histamine Release</td>
</tr>
<tr>
<td>Considerations</td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>Increased duration of action in renal or liver failure</td>
</tr>
<tr>
<td></td>
<td>Considerations</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Histamine Release</td>
</tr>
<tr>
<td>Other</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Considerations</td>
<td>Pancuronium if increased HR and BP desired</td>
</tr>
</tbody>
</table>
### Table 18. Reversal Agents for Non-Depolarizing Relaxants

<table>
<thead>
<tr>
<th>Cholinesterase Inhibitor</th>
<th>Neostigmine</th>
<th>Pyridostigmine</th>
<th>Edrophonium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset and Duration</td>
<td>Intermediate</td>
<td>Longest</td>
<td>Shortest</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Inhibits enzymatic degradation of ACh, increases ACh at nicotinic and muscarinic receptors, displaces non-depolarizing muscle relaxants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscarinic effects of reversing agents include unwanted bradycardia, salivation and increased bowel peristalsis*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Dose | 0.04-0.08 mg/kg | 0.1-0.4 mg/kg | 0.5-1 mg/kg |

*Atropine and glycopyrrolate are anticholinergic agents administered during the administration of reversal agents to minimize muscarinic effects

### Table 19. Local Anesthetic Agents

<table>
<thead>
<tr>
<th>Maximum Dose</th>
<th>Maximum Dose with</th>
<th>Potency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>chloroprocaine</td>
<td>11 mg/kg</td>
<td>14 mg/kg</td>
<td>Low</td>
</tr>
<tr>
<td>lidocaine</td>
<td>5 mg/kg</td>
<td>7 mg/kg</td>
<td>Medium</td>
</tr>
<tr>
<td>bupivacaine</td>
<td>2.5 mg/kg</td>
<td>3 mg/kg</td>
<td>High</td>
</tr>
<tr>
<td>ropivacaine</td>
<td>2.5 mg/kg</td>
<td>3 mg/kg</td>
<td>High</td>
</tr>
</tbody>
</table>

---

### Advanced Cardiac Life Support (ACLS) Guidelines

**Figure 13. Adult cardiac arrest algorithm**

**Figure 14. Adult tachycardia algorithm**


**Figure 15. Adult bradycardia algorithm**

Acronyms ................................................. 2
Basic Anatomy Review ............................ 2
Cardiomyopathy
Coronary Circulation
Cardiac Anatomy

Differential Diagnoses of Common Presentations ................................. 4
Chest Pain
Loss of Consciousness
Local Edema
Generalized Edema
Palpitations
Dyspnea

Cardiac Diagnostic Tests ............................ 5
Electrocardiography Basics
Approach to ECGs
Rate
Rhythm
Axis
Intraventricular Conduction Abnormalities
Hypertrophy and Chamber Enlargement
Ischemia/Infarction
Miscellaneous ECG Changes
Cardiac Biomarkers
Ambulatory ECG
Echocardiography
Stress Testing
Exercise Testing
Nuclear Cardiology
Stress Echocardiography
Indications for Stress Testing
Cardiac Catheterization and Angiography
Contrast-Enhanced CT Coronary Angiography
Magnetic Resonance Imaging

CARDIAC DISEASE
Arrhythmias ............................................. 12
Mechanisms of Arrhythmias
Bradyarrhythmias
AV Conduction Blocks
Supraventricular Tachyarrhythmias
Pre-Excitation Syndromes
Ventricular Tachyarrhythmias
Electrophysiology Studies
Electrical Pacing
Implantable Cardioverter Defibrillators
Catheter Ablation

Ischemic Heart Disease ............................... 22
Chronic Stable Angina
Variant Angina
Syndrome X
Acute Coronary Syndromes
Management of Acute Coronary Syndromes
Treatment Algorithm for Chest Pain
Sudden Cardiac Arrest

Coronary Revascularization
Percutaneous Coronary Intervention
Coronary Artery Bypass Graft Surgery
Off Pump Coronary Artery Bypass Surgery

Heart Failure ........................................... 30
Congestive Heart Failure
Sleep-Disordered Breathing

Cardiac Transplantation ............................. 34
Ventricular Assist Devices

Myocardial Disease ................................... 35
Myocarditis
Dilated Cardiomyopathy
Hypertrophic Cardiomyopathy
Restrictive Cardiomyopathy

Valvular Heart Disease ............................... 38
Infective Endocarditis
Rheumatic Fever
Choice of Valve Prosthesis
Summary of Valvular Disease

Pericardial Disease .................................... 42
Acute Pericarditis
Pericardial Effusion
Cardiac Tamponade
Constrictive Pericarditis

VASCULAR DISEASE
Peripheral Arterial Disease ....................... 44
Peripheral Vascular Anatomy
Acute Arterial Occlusion/Insufficiency
Chronic Arterial Occlusion/Insufficiency

Hypertension .......................................... FM37
Pulmonary Hypertension .......................... R16

Aortic Disease ......................................... 47
Aortic Anatomy
Aortic Dissection
Aortic Aneurysm

Peripheral Venous Disease ........................ 50
Deep Venous Thromboembolism
Superficial Venous Thrombosis
Varicose Veins
Chronic Venous Insufficiency
Lymphedema

Common Medications .............................. 53
Antiarrhythmics

Landmark Cardiac Trials ........................... 56

References .......................................... 58
Acronyms

AAA abdominal aortic aneurysm
ABI ankle-brachial index
ACEI angiotensin converting enzyme inhibitor
ACS acute coronary syndrome
AFib atrial fibrillation
AR aortic regurgitation
ARB angiotensin receptor blocker
ARDS acute respiratory distress syndrome
AS aortic stenosis
ASA acetylsalicylic acid (Aspirin®)
AV atrioventricular
AVM arteriovenous malformation
AVNRT atrioventricular nodal re-entrant tachycardia
AVRT atrioventricular re-entrant tachycardia
BBB bundle branch block
BP blood pressure
CABG coronary artery bypass graft
CXR chest x-ray
CAD coronary artery disease
CO cardiac output
CCB calcium channel blocker
CHF congestive heart failure
CPD chronic obstructive pulmonary disease
CTA CT angiography

Basic Anatomy Review

Coronary Circulation

- conventional arterial supply to the heart arises from the right and left coronary arteries, which originate from the root of the aorta (see Figure 1)
  - right coronary artery (RCA)
    - acute marginal branches
    - atrioventricular (AV) nodal artery
    - posterior interventricular artery (PIV) = posterior descending artery (PD)
  - left main coronary artery (LCA): two major branches
    - left anterior descending artery (LAD)
      - septal branches
      - diagonal branches
    - left circumflex artery (LC)
      - obtuse marginal branches
  - dominance of circulation
    - right-dominant circulation: PIV and at least one posterolateral branch arise from RCA (80%)
    - left-dominant circulation: PIV and at least one posterolateral branch arise from LC (15%)
    - balanced circulation: dual supply of posteroinferior LV from RCA and LC (5%)
  - the sinoatrial (SA) node is supplied by the SA nodal artery, which may arise from the RCA (60%) or LCA (40%)
  - most venous blood from the heart drains into the RA through the coronary sinus, although a small amount drains through the Thebesian veins into all four chambers, contributing to the physiologic R-L shunt

![Figure 1. Anatomy of the coronary arteries (right anterior oblique projection)](image-url)
Cardiac Anatomy

- layers of the heart
  - endocardium
  - myocardium
  - epicardium
  - visceral pericardium
  - pericardial cavity
  - parietal pericardium

- valves
  - semilunar valves: no subvalvular apparatus present
    - aortic valve, 3 valve leaflets: separates LV and ascending aorta
    - pulmonic valve, 3 valve leaflets: separates RV and main pulmonary artery (PA)
  - atrioventricular valves: subvalvular apparatus present in the form of chordae tendinae and papillary muscles
    - tricuspid valve, 3 valve leaflets: separates RA and RV
    - mitral valve, 2 valve leaflets: separates LA and LV

- conduction system (see Figure 3)
  - SA node governs pacemaking control
  - anterior-, middle- and posterior-internal nodal tracts carry impulses in the right atrium and along Bachmann's bundle in the left atrium
  - atrial impulses converge at the AV node
    - the AV node is the only conducting tract from the atria to the ventricles because of electrical isolation by the annulus fibrosis (except when accessory pathways are present)
    - the bundle of His bifurcates into left and right bundle branches (LBB and RBB)
    - LBB further splits into anterior and posterior fascicles
    - RBB and fascicles of LBB give off Purkinje fibres which conduct impulses into the ventricular myocardium
cardiovascular innervation
• sympathetic nerves
  • innervate the SA node, AV node, ventricular myocardium and vasculature
  • SA node (β1) fibres increase pacemaking activity (chronotropy)
  • cardiac muscle (β1) fibres increase contractility (inotropy) to help increase cardiac output
  • stimulation of β1- and β2-receptors in the skeletal and coronary circulation causes vasodilatation
• parasympathetic nerves
  • innervate the SA node, AV node, atrial myocardium but few vascular beds
  • basal vagal tone dominates the tonic sympathetic stimulation of the SA node and AV node resulting in slowing of pacemaker activity and conduction (i.e. reduced dromotropy – if only affecting AV node conduction)
  • parasympathetics have very little impact on total peripheral vascular resistance

Differential Diagnoses of Common Presentations

Note: bold text indicates most common, underlined text indicates life threatening

Chest Pain
• cardiac
  • MI/angina
  • myocarditis
  • pericarditis/Dressler’s syndrome
  • cardiac tamponade
• pulmonary
  • pneumonia
  • pulmonary embolism (PE)
  • pneumothorax/hemorthorax
    • tension pneumothorax
  • empyema
  • pulmonary neoplasm
  • bronchiectasis
  • TB
• gastrointestinal
  • esophageal: spasm, GERD, esophagitis, ulceration, achalasia, neoplasm, Mallory-Weiss syndrome, esophageal rupture
  • gastrointestinal
    • PUD
    • gastritis
    • pancreatitis
    • biliary colic
    • mediastinal
      • lymphoma
      • thymoma
    • vascular
      • dissecting aortic aneurysm
      • aortic rupture
    • surface structures
      • costochondritis
      • rib fracture
      • skin (bruising, herpes zoster)
      • breast
      • anxiety/psychosomatic

Loss of Consciousness
• hypovolemia
• cardiac
  • structural or obstructive causes
    • acute coronary syndrome
    • aortic stenosis
    • hypertrophic cardiomyopathy (HCM)
  • cardiac tamponade, constrictive pericarditis
  • arrhythmias (see Arrhythmias, C12)
• respiratory
  • massive pulmonary embolism
  • pulmonary hypertension
  • hypoxia
  • hypercapnia
• neurologic
  • stroke/TIA (esp. vertebrobasilar insufficiency)
  • migraine
  • seizure
  • metabolic
    • anemia
    • hypoglycemia
  • drugs
    • antihypertensives
    • antiarrhythmics
    • diuretics
  • vasovagal
    • autonomic dysfunction
    • diabetic neuropathy
    • psychiatric
    • panic attack

Local Edema
• inflammation/infection
• venous or lymphatic obstruction
  • thrombophlebitis/deep vein thrombosis
• venous insufficiency
• chronic lymphangitis
• lymphatic tumour infiltration
• filariasis
• increased hydrostatic pressure/fluid overload
  • heart failure
  • pregnancy
  • drugs (e.g. CCBs)
  •iatrogenic(e.g. IV fluids)
• decreased oncotic pressure/hypoalbuminemia
• nephrotic syndrome
• liver cirrhosis
• malnutrition
• increased capillary permeability
  • severe sepsis
• hormonal
• hypothyroidism
• exogenous steroids
• pregnancy
• estrogens
Palpitations

- cardiac
  - arrhythmias (PAC, PVC, SVT, VT)
  - valvular heart disease
  - hypertrophic cardiomyopathy (HCM)
- endocrine
  - thyrotoxicosis
  - pheochromocytoma
  - hypoglycemia
- systemic
  - fever
  - anemia
- drugs
  - stimulants and anticholinergics
  - psychiatric
  - panic attack

Dyspnea

- cardiovascular
  - acute MI
  - CHF/LV failure
  - aortic/mitral stenosis
  - aortic/mitral regurgitation
  - arrhythmia
  - cardiac tamponade
  - constrictive pericarditis
  - left-sided obstructive lesions (e.g. left atrial myxoma)
  - elevated pulmonary venous pressure
- respiratory
  - airway disease
    - asthma
    - COPD exacerbation
    - upper airway obstruction (anaphylaxis, foreign body, mucus plugging)
  - parenchymal lung disease
    - ARDS
- non-cardiovascular
  - pneumonia
  - interstitial lung disease
  - pulmonary vascular disease
  - pulmonary embolism
  - pulmonary HTN
  - pulmonary vasculitis
  - pleural disease
    - pneumothorax
    - pleural effusion
  - neurovascular and chest wall disorders
    - C-spine injury
    - polymyositis, myasthenia gravis, Guillain-Barré syndrome
    - kyphoscoliosis
    - anxiety/psychosomatic
    - hematological/metabolic
    - anemia, acidosis, hypercapnia

Cardiac Diagnostic Tests

Electrocardiography (ECG) Basics

- the electrocardiogram (ECG) is a graphic representation of the electrical activity of the heart recorded from the surface of the body
- on the ECG graph
  - the horizontal axis represents time
    - 1 mm (1 small square) = 40 msec
    - 5 mm (1 large square) = 200 msec (at paper speed 25 mm/s)
  - the vertical axis represents voltage
    - 1 mm (1 small square) = 0.1 mV
    - 10 mm (2 large squares) = 1 mV (at standard gain setting)
- leads
  - standard 12-lead ECG
    - limb leads: I, II, III, aVL, aVR, aVF
    - precordial leads: V1-V6 (V1-V2 septal, V3-V4 anterior, V5-V6 lateral)
  - additional leads
    - right-sided leads: V3R-V6R (useful in RV infarction and dextrocardia)
    - lateral = I, aVL, V5, V6; inferior = II, III, aVF; anterior = V1-V4

Approach to ECGs

RATE

- normal = 60-100 bpm (atrial rate: 150-250 bpm = paroxysmal tachycardia, 250-350 bpm = atrial flutter, >350 bpm = AFib)
- regular rhythm
  - to calculate the rate, divide 300 by number of large squares between 2 QRS complexes (there are 300 large squares in 1 min: 300 x 200 msec = 60 s)
  - or remember 300-150-100-75-60-50-43 (rate falls in this sequence with the number of large squares between 2 QRS complexes)
- irregular rhythm
  - rate = 6 x number of R-R intervals in 10 s (the “rhythm strips” are 10 s recordings)
  - types: wandering pacemaker, multifocal atrial tachycardia, AFib
  - atrial escape = 60-80 bpm; junctional escape = 40-60 bpm; ventricular escape = 20-40 bpm

For more examples and practice visit www.ecgmadesimple.com.
RHYTHM

- regular: R-R interval is the same across the tracing
- irregular: R-R interval varies across the tracing
- regularly-irregular: repeating pattern of varying R-R intervals
- irregularly irregular: R-R intervals vary erratically
- normal sinus rhythm (NSR)
  - P wave precedes each QRS; QRS follows each P wave
  - P wave axis is normal (positive in leads I, aVF)
  - rate between 60-100 bpm

AXIS

- mean axis indicates the direction of the mean vector
- can be determined for any waveform (P, QRS, T)
- the standard ECG reported QRS axis usually refers to the mean axis of the anterior plane; it indicates the mean direction of ventricular depolarization forces
- QRS axis in the frontal plane (see Figure 7)
  - normal axis: -30º to 90º (i.e. positive QRS in leads I and II)
  - left axis deviation (LAD): axis < -30º
  - right axis deviation (RAD): axis > 90º
- QRS axis in the horizontal plane is not routinely calculated; it is directed posteriorly and to the left
  - transition from negative to positive is usually in lead V3

INTRAVENTRICULAR CONDUCTION ABNORMALITIES

Left Bundle Branch Block (LBBB)

- Complete LBBB
  - QRS duration > 120 msec
  - Broad notched or slurred R waves in leads I, aVL and usually V5 and V6
  - Deep broad S waves in leads V1-2
  - Secondary ST-T changes (–ve in leads with broad R waves, +ve in V1-2) are usually present
  - LBBB can mask ECG signs of MI

Right Bundle Branch Block (RBBB)

- Complete RBBB
  - QRS duration > 120 msec
  - Positive QRS in lead V1 (VSR’ or occasionally broad R wave)
  - Broad S waves in leads I, V5-6 (> 40 msec)
  - Usually secondary T wave inversion in leads V1-2

Left Anterior Fascicular Block (LAFB)

- Left axis deviation (-30º to -90º)
  - Small q and prominent R in leads I and aVL
  - Small r and prominent S in leads II, III, and aVF

Left Posterior Fascicular Block (LPFB)

- Right axis deviation (110º to 180º)
  - Small r and prominent S in leads I and aVL
  - Small q and prominent R in leads II, III, and aVF

Bifascicular Block

- Left axis deviation (-30º to -90º)
  - Small q and prominent R
  - The first 60 msec (1.5 small squares) of the QRS shows the pattern of LAFB or LPFB
  - Bifascicular block refers to impaired conduction in two of the three fascicles, most commonly a RBBB and left anterior hemiblock; the appearance on an ECG meets the criteria for both types of blocks

Nonspecific Intraventricular Block

- QRS duration > 120 msec
- absence of criteria for LBBB or RBBB

Intervals

<table>
<thead>
<tr>
<th>PR</th>
<th>Increased (&gt; 200 msec):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart block</td>
</tr>
<tr>
<td></td>
<td>Atrial flutter</td>
</tr>
<tr>
<td></td>
<td>Sinus bradycardia</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Decreased (&lt; 120 msec):</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-excitation syndrome (WPW)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QRS</th>
<th>Increased (&gt; 120 msec):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bundle branch block</td>
</tr>
<tr>
<td></td>
<td>Ventricular Tachycardia</td>
</tr>
<tr>
<td></td>
<td>Ventricular hypertrophy</td>
</tr>
<tr>
<td></td>
<td>WPW</td>
</tr>
<tr>
<td></td>
<td>Ectopic ventricular beat</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
</tr>
<tr>
<td></td>
<td>Drugs (e.g. TCAs, antiarrhythmics)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QT</th>
<th>Increased (QTc* &gt; 440 msec):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Genetic long QT syndrome</td>
</tr>
<tr>
<td></td>
<td>Drugs (e.g. antibiotics, SSRIs, anti-psychotics, antiarrhythmics)</td>
</tr>
<tr>
<td></td>
<td>Electrolyte disturbances (e.g. hypocalcemia, hypomagnesium, hypokalemia)</td>
</tr>
<tr>
<td></td>
<td>Hypothyroid</td>
</tr>
</tbody>
</table>

| QTc* = QT interval – √RR interval |

QTc* = QT interval – √RR interval

Figure 7. Axial reference system
Each lead contains a (+) area displayed by the bold arrows. Impulses traveling toward the positive region of the lead results in an upward deflection in that lead. Normal QRS axis is between -30º and +90º.

Figure 8. Complete LBBB, RBBB, LVH and RVH (please see online examples for the full range of waveforms and the text for additional characteristics)
HYPERTROPHY AND CHAMBER ENLARGEMENT

Left Ventricular Hypertrophy (LVH)  
- S in V1 + R in V5 or V6 > 35 mm above age 40, (>40 mm for age 31-40, >45 mm for age 21-30)  
- R in aVL > 11 mm  
- R in I + S in III > 25 mm  
- Additional criteria:  
  - LV strain pattern (ST depression and T wave inversion in leads I, aVL, V4-V6)  
  - Left atrial enlargement  

Right Ventricular Hypertrophy (RVH)  
- Right axis deviation  
- R/S ratio > 1 or QR in lead V1  
- RV strain pattern: ST segment depression and T wave inversion in leads V1-2

Left Atrial Enlargement (LAE)  
- Biphasic P wave with the negative terminal component of the P wave in lead V1 ≥ 1 mm wide and ≥ 1 mm deep  
- P wave > 120 msec, notched in lead II (“P mitrale”)  

Right Atrial Enlargement (RAE)  
- P wave > 2.5 mm in height in leads II, III, or aVF (“P pulmonale”)  

ISCHEMIA/INFARCTION  
- look for the anatomic distribution of the following ECG abnormalities (see Table 1)  
- ischemia  
  - ST segment depression  
  - T wave inversion (most commonly in V1-V6)  
- injury  
  - transmural (involving the epicardium): ST elevation in the leads facing the area injured/infarced; transient ST elevation may occur in patients with coronary artery spasm (e.g. Prinzmetal angina) which can be slight or prominent (>10 mm)  
  - subendocardial: marked ST depression in the leads facing the affected area; may be accompanied by enzyme changes and other signs of MI, may also occur with angina

- evolving infarction (ST elevation in contiguous leads = acute MI)  
- “typical” sequential changes of evolving MI  
  1. hyperacute T waves (tall, symmetric T waves) in the leads facing the infarcted area, with or without ST elevation  
  2. ST elevation (injury pattern) in the leads facing the infarcted area  
    - usually in the first hours post infarct  
    - in acute posterior infarction, there is ST depression in V1-V3 (reciprocal to ST elevation in the posterior leads, that are not recorded in the standard 12-lead ECG)  
  3. significant Q waves: >40 msec or >1/3 of the total QRS (hours to days post-infarct)  
- this classical sequence does not always occur  
- Q waves of infarction may appear in the very early stages, with or without ST changes  
- non-Q wave infarction: there may be only ST or T changes despite clinical evidence of infarction  
- completed infarction  
- abnormal Q waves (wide Q waves may be found in III and aVL in normal individuals)  
  - duration >40 msec (>30 msec in aVF for inferior infarction)  
  - Q/QRS voltage ratio is >33%  
- abnormal R waves (R/S ratio > 1, duration >40 msec) in V1 and more frequently in V2 are found in posterior infarction (usually in association with signs of inferior and/or lateral infarction)  

Figure 10. Typical ECG changes with infarction  
- evolving infarction (ST elevation in contiguous leads = acute MI)  
- “typical” sequential changes of evolving MI  
- significant Q waves: >40 msec or >1/3 of the total QRS (hours to days post-infarct)  
- completed infarction  
- abnormal Q waves (wide Q waves may be found in III and aVL in normal individuals)  
- duration >40 msec (>30 msec in aVF for inferior infarction)  
- Q/QRS voltage ratio is >33%  
- abnormal R waves (R/S ratio > 1, duration >40 msec) in V1 and more frequently in V2 are found in posterior infarction (usually in association with signs of inferior and/or lateral infarction)  

ISCHEMIA/INFARCTION  
- look for the anatomic distribution of the following ECG abnormalities (see Table 1)  
- ischemia  
  - ST segment depression  
  - T wave inversion (most commonly in V1-V6)  
- injury  
  - transmural (involving the epicardium): ST elevation in the leads facing the area injured/infarced; transient ST elevation may occur in patients with coronary artery spasm (e.g. Prinzmetal angina) which can be slight or prominent (>10 mm)  
  - subendocardial: marked ST depression in the leads facing the affected area; may be accompanied by enzyme changes and other signs of MI, may also occur with angina

- evolving infarction (ST elevation in contiguous leads = acute MI)  
- “typical” sequential changes of evolving MI  
  1. hyperacute T waves (tall, symmetric T waves) in the leads facing the infarcted area, with or without ST elevation  
  2. ST elevation (injury pattern) in the leads facing the infarcted area  
    - usually in the first hours post infarct  
    - in acute posterior infarction, there is ST depression in V1-V3 (reciprocal to ST elevation in the posterior leads, that are not recorded in the standard 12-lead ECG)  
  3. significant Q waves: >40 msec or >1/3 of the total QRS (hours to days post-infarct)  
- this classical sequence does not always occur  
- Q waves of infarction may appear in the very early stages, with or without ST changes  
- non-Q wave infarction: there may be only ST or T changes despite clinical evidence of infarction  
- completed infarction  
- abnormal Q waves (wide Q waves may be found in III and aVL in normal individuals)  
  - duration >40 msec (>30 msec in aVF for inferior infarction)  
  - Q/QRS voltage ratio is >33%  
- abnormal R waves (R/S ratio > 1, duration >40 msec) in V1 and more frequently in V2 are found in posterior infarction (usually in association with signs of inferior and/or lateral infarction)  

Figure 9. LAE, RAE (please see online examples and text above for characteristics)

Significant Q wave  
- Septal depolarization by the left bundle  
- Seen in leads I, II, III, aVL, V5, V6  
- < 40 msec

Insignificant Q wave  
- Septal depolarization by the left bundle  
- Seen in leads I, II, III, aVL, V5, V6  
- < 40 msec

Differential of ST Segment Changes  
ST Elevation “I HELP A PAL”  
- Ischemia with reciprocal changes  
- Hypothermia (Osborne waves)  
- Early repolarization (normal variant; need old ECGs)  
- LBBB  
- Post-MI  
- Acute STEMI  
- Prinzmetal’s (Vasospastic) angina  
- Acute pericarditis (diffuse changes)  
- Left/right ventricular aneurysm

ST Depression “WAR SHIP”  
- WPW syndrome  
- Acute NSTEMI  
- RBBB/LBBB  
- STEMI with reciprocal changes  
- Hypertrophy (LVH or RVH) with strain  
- Ischemia  
- Post-MI
Table 1. Areas of Infarction (Q wave)/Ischemia (in right dominant anatomy)

<table>
<thead>
<tr>
<th>Vessel Usually Involved</th>
<th>Infarct Area (LAD and LC)</th>
<th>Leads (LAD and LC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left anterior descending (LAD)</td>
<td>Anteroseptal</td>
<td>V1, V2</td>
</tr>
<tr>
<td></td>
<td>Anterior</td>
<td>V3, V4</td>
</tr>
<tr>
<td></td>
<td>Anterolateral</td>
<td>I, aVL, V3-6</td>
</tr>
<tr>
<td></td>
<td>Extensive anterior</td>
<td>I, aVL, V1-6</td>
</tr>
<tr>
<td>Right coronary artery (RCA)</td>
<td>Inferior</td>
<td>II, III, aVF</td>
</tr>
<tr>
<td></td>
<td>Right ventricle</td>
<td>V3R, V4R (right sided chest leads)</td>
</tr>
<tr>
<td></td>
<td>Posterior MI (assoc. with inf. MI)</td>
<td>V1, V2 (prominent R waves)</td>
</tr>
<tr>
<td>Circumflex</td>
<td>Lateral</td>
<td>I, aVL, V5-6</td>
</tr>
<tr>
<td></td>
<td>Isolated posterior MI</td>
<td>V1, V2 (prominent R waves)</td>
</tr>
</tbody>
</table>

MISCELLANEOUS ECG CHANGES

Electrolyte Disturbances
- hyperkalemia (see Figure 11)
  - mild to moderate (K⁺ 5-7 mmol/L): tall peaked T waves
  - severe (K⁺ >7 mmol/L): progressive changes whereby P waves flatten and disappear, QRS widens and may show bizarre patterns, axis shifts left or right, ST shift with tall T waves
- hypokalemia (see Figure 12)
  - ST segment depression, prolonged QT interval, low T waves, prominent U waves (U>T)
  - enhances the toxic effects of digitalis
- hypercalcemia: shortened QT interval
- hypocalcemia: prolonged QT interval

Hypothermia
- sinus bradycardia
- when severe, prolonged QRS and QT intervals
- AFib with slow ventricular response and other atrial/ventricular dysrhythmias
- Osborne J waves (see Figure 13): "hump-like" waves at the junction of the J point and the ST segment

Pericarditis
- early: diffuse ST segment elevation ± PR segment depression, upright T waves
- later: isoelectric ST segment, flat or inverted T waves
- low voltage if chronic constrictive pericarditis
- tachycardia

Drug Effects
- digitalis
  - therapeutic levels may be associated with "digitalis effect" (see Figure 14):
    - ST downsloping or "scooping"
    - T wave depression or inversion
    - QT shortening ± U waves
    - slowing of ventricular rate in AFib
  - toxic levels associated with:
    - arrhythmias: paroxysmal atrial tachycardia (PAT) with conduction block, severe bradyarhythmia in AFib, accelerated junctional rhythms, PVCs, ventricular tachycardia (see Arrhythmias, C12)
    - "regularization" of ventricular rate in AFib due to a junctional rhythm and AV dissociation
  - amiodarone, quinidine, phenothiazines, tricyclic antidepressants, antipsychotics, some antihistamines, some antibiotics: prolonged QT interval, U waves

Figure 11. Hyperkalemia

Figure 12. Hypokalemia

Figure 13. Osborne J waves of a hypothermic patient

Low Voltage
- Definition: total QRS height in precordial leads <10 mm and limb leads <5 mm

Differential diagnosis
- Myocardial disease
  - Ischemia
  - Cardiomyopathy (usually infiltrative type), myocarditis
- Pericardial effusion
- Thick chest wall/barrel chest: COPD, obesity
- Generalized edema
- Hypothyroidism/myxedema
- Inappropriate voltage standardization

High Voltage
- Definition: total QRS height in precordial leads >17 mm and limb leads >11 mm

Differential diagnosis
- Myocardial disease
  - Hypertrophy
  - Valvular disease
  - Pericarditis

Digitalis Side Effects
- Palpitations, fatigue, visual changes (yellow vision), decreased appetite, hallucinations, confusion and depression.

Quinidine
- Wide P wave
- Wide QRS
- Prolonged QT
- ± ST depression
- ± U wave
Pulmonary Disorders
- cor pulmonale (often secondary to COPD)
  - low voltage, RAD, poor R wave progression
  - RAE and RVH with strain
  - multifocal atrial tachycardia (MAT)
- massive PE
  - sinus tachycardia and AFib/atrial flutter are the most common arrhythmias
  - RAD, RVH with strain – most specific sign is S1Q3T3 (S in I, Q and inverted T wave in III)

Cardiac Biomarkers
- provide diagnostic and prognostic information in acute coronary syndromes and in heart failure

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Peak Duration Elevated</th>
<th>DDX of Elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin I, Troponin T</td>
<td>1-2 d, Up to 2 wk</td>
<td>MI, CHF, AFib, acute PE, myocarditis, chronic renal insufficiency, sepsis, hypovolemia</td>
</tr>
<tr>
<td>CK-MB</td>
<td>1 d, 3 d</td>
<td>MI, myocarditis, pericarditis, muscular dystrophy, cardiac defibrillation, etc.</td>
</tr>
</tbody>
</table>

- check troponin I at presentation and 8 h later ± creatine kinase-MB (CK-MB; depends on local laboratory protocol)
- new CK-MB elevation can be used to diagnose reinfarction
- other biomarkers of cardiac disease:
  - AST and LDH also increased in MI (low specificity)
  - BNP and NT-proBNP: secreted by ventricles in response to increased end-diastolic pressure and volume
    - DDx of elevated BNP: CHF, AFib, PE, COPD exacerbation, pulmonary HTN

Ambulatory ECG
- indications for outpatient testing: palpitations, syncope, antiarrhythmic drug monitoring, arrhythmia surveillance in patients with documented or potentially abnormal rhythms, and surveillance of non-sustained arrhythmias that can lead to prophylactic intervention
- available technologies
  - Holter monitor
    - battery operated, continually records up to 3 leads for 24-48 h
    - symptoms recorded by patient on Holter clock for correlation with ECG findings
  - continuous loop recorder (diagnostic yield 66-83%)
    - worn continuously and can record data before and after patient activation for symptomatic episodes (usually worn for 2 wk)
  - external and implantable devices
    - external devices can be transtelephonically downloaded
  - implantable loop recorder (ILR): cannot be transtelephonically downloaded; left in place for 14 to 18 mo

Echocardiography

Transthoracic Echocardiography (TTE)
- ultrasound beams are directed across the chest wall to obtain images of the heart
- indications: evaluation of left ventricular ejection fraction (LVEF), wall motion abnormalities, myocardial ischemia and complications of MI, chamber size, wall thickness, valve morphology, proximal great vessel morphology, pericardial effusion, unexplained hypotension, murmurs, syncope, congenital heart disease
- use with Doppler to quantify degree of valvular stenosis or regurgitation
Transoesophageal Echocardiography (TEE)
- ultrasound probe inserted into the esophagus to allow for better resolution of the heart and structures
- better visualization of posterior structures, including left atrium, mitral and aortic valves, interatrial septum
- invasive procedure used to complement transthoracic echocardiography
- indications: intracardiac thrombi, tumours, valvular vegetations (infective endocarditis), aortic dissection, aortic atheromas, prosthetic valve function, shunt, technically inadequate transthoracic study
- use with Doppler to quantify degree of valvular stenosis or regurgitation

Stress Echocardiography
- echocardiography in combination with either physiologic (exercise treadmill or bike testing) or pharmacologic (dobutamine infusion) stress
- validated in demonstrating myocardial ischemia and assessing viability
- provides information on the global left ventricular response to exercise
- used for valvular heart disease evaluation

Contrast Echocardiography
- contrast agents injected into the bloodstream to improve imaging of the heart
- conventional agent: agitated saline (contains microbubbles of air)
- allows visualization of right heart and intracardiac shunts, most commonly patent foramen ovale (PFO) and sometimes intrapulmonary shunt
- newer contrast agents are capable of crossing the pulmonary bed and achieving left heart opacification following intravenous injection; these contrast agents improve visualization of endocardial borders and enhance evaluation of LV ejection fraction, wall motion abnormalities, and intracardiac mass

Stress Testing

EXERCISE TESTING
- cardiovascular stress test that uses treadmill or bicycle exercise with electrocardiographic and blood pressure monitoring
- guidelines for use:
  - patients with intermediate (10-90%) pretest probability of CAD based on age, gender and symptoms
  - exercise test results stratify patients into risk groups:
    - low risk patients can be treated medically without invasive testing
    - intermediate risk patients may need additional testing in the form of exercise imaging studies or cardiac catheterization
    - high risk patients should be referred for cardiac catheterization

Indications for Terminating Exercise Stress Test
- drop in systolic blood pressure of >10 mmHg from baseline despite an increase in workload, when accompanied by other evidence of ischemia
- moderate to severe angina
- ST elevation (>1 mm) in leads without diagnostic Q-waves (other than V1 or aVR)
- increasing nervous system symptoms (e.g. ataxia, dizziness, or near syncope)
- signs of poor perfusion (cyanosis or pallor)
- technical difficulties in monitoring ECG or systolic blood pressure
- patient’s desire to stop
- sustained ventricular tachycardia

Interpretation
- the most commonly used ECG criteria for a positive exercise test: ≥1 mm of horizontal or downsloping ST-segment depression or elevation (at least 60 to 80 msec after the end of the QRS complex)
- ST depression <1 mm at rest, no left bundle branch block, no digoxin or estrogen use

NUCLEAR CARDIOLOGY
- myocardial perfusion imaging (MPI) with ECG-gated single photon emission computed tomography (SPECT), using radiolabelled tracer
- evaluates myocardial viability, detects ischemia, and assesses perfusion and LV function simultaneously
- predicts the likelihood of further cardiac event rates independent of the patient’s history, examination, resting ECG, and stress ECG
- often denoted as MIBI scan with reference to radiolabelled tracer (sestamibi)
- stress with either treadmill or IV vasodilator stress [dipyridamole (Persantine®), adenosine]
- images of the heart obtained during stress and at rest 3-4 h later
  - fixed defect: impaired perfusion at rest and during stress (infarcted/hibernating)
  - reversible defect: impaired perfusion only during stress (ischemic)

Most Commonly Used Treadmill Stress Test Protocols
- The Bruce Protocol: 7 stage test with each stage lasting 3 min. With each successive stage, the treadmill increases in both speed and gradient
- The Modified Bruce, Modified Naughton Protocol: for older individuals or those with limited exercise capacity

Important Contraindications to Exercise Testing
- Acute MI, aortic dissection, pericarditis, myocarditis, PE
- Severe AS, arterial HTN
- Inability to exercise adequately

Important Prognostic Factor

Duke Treadmill Score (DTS)
- Duke Treadmill Score (DTS)
- Important Prognostic Factor

Weighted Index Score:
- Weighted Index Score:
- Treadmill exercise time using standard Bruce protocol
- Maximum net ST segment deviation (depression or elevation)
- Exercise-induced angina provides diagnostic and prognostic information (such as 1-yr mortality)
- DTS = exercise time – (5 x MaxST) – (4 x angina index)

Am J Cardiol 1987;60:793-800

Patients with normal imaging (nuclear perfusion or stress echo) studies at peak stress have a <1% yr incidence of death or nonfatal MI and are thus often spared further invasive evaluation.
Cardiac Diagnostic Tests

- tracers
  - thallium-201 ($^{201}$Tl, a K$^+$ analogue)
  - technetium-99 ($^{99}$Tc)-labelled tracer (sestamibi/Cardiolite® or hexamibi/Myoview®)

**STRESS ECHOCARDIOGRAPHY**
- see Stress Echocardiography, C10

**INDICATIONS FOR STRESS TESTING**
- exercise ECG
  - initial evaluation in patients who are able to exercise
- exercise stress echo
  - when ECG is uninterpretable
  - intermediate pre-test probability with normal/equivocal exercise ECG
  - post-ACS when used to decide on potential efficacy of revascularization
  - to evaluate the clinical significance of valvular heart disease
- dobutamine stress echo (DSE)
  - among patients unable to exercise; same indications as exercise stress echo
  - low dose DSE can be used to assess myocardial viability and for assessing aortic stenosis with LV systolic dysfunction
- exercise MPI
  - when ECG is uninterpretable
  - intermediate pre-test probability with normal/equivocal exercise ECG
  - in patients with previous imaging whose symptoms have changed
  - to diagnose ischemia
- dipyridamole/adenosine MPI
  - to diagnose CAD in possible ACS patients with non-diagnostic ECG and negative serum biomarkers
  - when ECG is uninterpretable due to LBBB or V-paced rhythm
  - among patients unable to exercise, with the same indications as exercise MPI

---

**Cardiac Catheterization and Angiography**

- risks of procedure related complications: vascular injury, renal failure, stroke, MI
- mortality rate 0.1-0.2%
- invasive: catheters are introduced percutaneously into arterial and venous circulation under conscious sedation and contrast is injected
- arterial access most commonly through the femoral artery; radial approach gaining favour especially for obese patients and outpatients dependent on driving and ambulation
- venous access through the femoral vein or internal jugular vein
- same day procedure as outpatient
- indications for prehospitalization: anticoagulation, renal failure, diabetes, contrast allergy
- catheterization permits direct measurement of intracardiac pressures, transvalvular and mean peak pressure gradients, valve areas, cardiac output, shunt data, oxygen saturations, and visualization of coronary arteries, cardiac chambers and great vessels
- angiography may provide valuable information regarding lesion severity, complexity, location and prognosis

**Right Heart Catheterization (Swan-Ganz Catheter)**
- right atrial, right ventricular, and pulmonary artery pressures are recorded
- pulmonary capillary wedge pressure (PCWP)
  - obtained by advancing the catheter to wedge in the distal pulmonary artery
  - records pressure measured from the pulmonary venous system
  - in the absence of pulmonary venous disease reflects left atrial pressure

**Left Heart Catheterization**
- systolic and end-diastolic pressure tracings recorded; LV size, wall motion and ejection fraction can be assessed by injecting contrast into the LV (left ventriculography) via femoral/radial artery catheterization
- cardiac output (measured by the Fick oxygen method or the indicator dilution method)

---

ACC/AHA 2009 Guidelines for Use of Nuclear Testing
Stable angina, baseline ECG abnormalities, post-revascularization assessment, heart failure, patients unable to exercise, preoperative risk assessment for patients undergoing noncardiac surgery.

**Sensitivity and Specificity of Various Stress Testing**
- Exercise ECG (Sn 88; Sp 77)
- Stress Echocardiography (Sn 76; Sp 88)
- PET scanning (Sn 91; Sp 82)
- MIBI scanning (Sn 88; Sp 77)
Coronary Angiography
- coronary vasculature accessed via the coronary ostia
- contraindicated in severe renal failure (due to contrast agent toxicity) must check renal status

Diagnostic Catheterization
- complications for diagnostic catheterization <1%
- inadequate diagnostic procedures occur in fewer than 1% of cases
- provocative pharmacological agents can be used to unmask pathology
  - fluid loading may unmask latent pericardial constriction
  - afterload reduction or inotropic stimulation may be used to increase the outflow tract gradient in HCM
  - coronary vasoreactive agents (e.g. methylergonovine, acetylcholine)
  - a variety of pulmonary vasoreactive agents in primary pulmonary HTN (e.g. oxygen, calcium channel blockers, adenosine, nitric oxide, or prostacyclin)

Contrast-Enhanced CT Coronary Angiography
- fast ECG-synchronized multi-slice CT image acquisition in the heart has enabled non-invasive imaging of the coronary arterial tree
- often used to assess coronary artery and previous graft stenosis/viability that could not be seen during coronary angiography
- sensitivity = 85%, specificity = 90% for the diagnosis of obstructive coronary disease with >50% stenosis

Magnetic Resonance Imaging (MRI)
- offers high spatial resolution, eliminates the need for iodinated contrast, and does not involve exposure to ionizing radiation
- valuable in assessment of congenital cardiac anomalies, abnormalities of the aorta, and assessment of viable myocardium

CARDIAC DISEASE

Arrhythmias

Mechanisms of Arrhythmias

(I) Alterations in Impulse Formation
A. Abnormal Automaticity
- automaticity is a property of certain cardiomyocytes to depolarize to their threshold voltage to spontaneously generate action potentials in a rhythmical fashion
- under normal circumstances only cells in the specialized conduction system (SA node, AV node and ventricular conduction system) exhibit natural automaticity. These cells are pacemaking cells. The automaticity of these cells can become abnormally increased or decreased
in disease (e.g. post-MI ventricular ischemia) cells in the myocardium outside the conduction system may inappropriately acquire the property of automaticity and contribute to abnormal depolarization. If these ectopic generators depolarize at a rate that is greater than the SA node, they assume pacemaking control and become the source of abnormal rhythm.

Automaticity can be influenced by:
- neurohormonal tone (sympathetic and parasympathetic stimulation)
- abnormal metabolic conditions (hypoxia, acidosis, hypothermia)
- electrolyte abnormalities
- drugs (e.g. digitalis)
- local ischemia/infarction
- other cardiac pathology

This mechanism is responsible for the accelerated idioventricular rhythm and ventricular tachycardia that often occurs 24 to 72 h post MI.

B. Triggered Activity due to Afterdepolarizations
1. Early Afterdepolarizations
   - occur in the context of action potential prolongation
   - consequence of the membrane potential becoming more positive during repolarization
   - result in self-maintaining depolarizing oscillations of action potential, generating a tachyarrhythmia
   - basis for the degeneration of QT prolongation, either congenital or acquired, into Torsades de Pointes

2. Delayed Afterdepolarizations
   - occur after the action potential has fully repolarized, but before the next usual action potential, thus called a delayed afterdepolarization
   - commonly occurs in situations of high intracellular calcium (digitalis intoxication, ischemia) or during enhanced catecholamine stimulation

II) Alterations in Impulse Conduction
A. Re-Entry Circuits
   - the presence of self-sustaining re-entry circuit causes rapid repeated depolarizations in a region of myocardium
   - e.g. myocardium that is infarcted/ischemic will consist of non-excitable and partially excitable zones which will promote the formation of re-entry circuits

B. Conduction Block
   - ischemia, fibrosis, trauma, and drugs can cause transient, permanent, unidirectional or bidirectional block
   - most common cause of block is due to refractory myocardium (cardiomyocytes are in refractory period or zone of myocardium unexcitable due to fibrosis)
   - if block occurs along the specialized conduction system distal zones of the conduction system can assume pacemaking control
   - conduction block can lead to bradycardia or tachycardia when impaired conduction leads to re-entry phenomenon

C. Bypass Tracts
   - normally the only conducting tract from the atria to the ventricles is the AV node
   - congenital/acquired accessory conducting tracts bypass the AV node and facilitate premature ventricular activation before normal AV node conduction
   - see Pre-Excitation Syndromes, C18

---

**Figure 17. Clinical approach to arrhythmias**

- **Bradycardiacs (<60 bpm)**
  - Sinus bradycardia
  - Sinoatrial block
  - Sinus arrest
  - AV block (2nd and 3rd degree)
  - Junctional rhythm
  - Idioventricular rhythm

- **Tachyarrhythmias (>100 bpm)**

  **Regular**
  - Narrow QRS (SVTs)
    - Sinus tachycardia
    - Atrial tachycardia
    - Junctional tachycardia
    - AVNRT
    - AVRT (orthodromic)
    - Atrial flutter
  - Wide QRS
    - SVT with aberrancy/BBB
    - Atrial flutter with variable block
  - Atrial fibrillation

  **Irregular**
  - Narrow QRS (SVTs)
    - Atrial fibrillation
    - Ventricular tachycardia
    - AVRT (antidromic)
    - Premature atrial contraction
    - Polymorphic VT (torsades)
    - Premature ventricular contraction
  - Wide QRS
    - Atrial fibrillation with BBB
    - A. flutter with BBB and variable block
Bradyarrhythmias

SA NODAL DYSFUNCTION

Sinus Bradycardia
- P axis normal (P waves positive in I and aVF)
- rate <60 bpm
- marked sinus bradycardia (<50 bpm) may be seen in normal adults, particularly athletes, and in elderly individuals
- caused by
  - increased vagal tone or vagal stimulation
  - vomiting
  - episodes of myocardial ischemia or infarction (inferior MI)
  - sick sinus syndrome
  - increased intracranial pressure
  - hypothyroidism
  - hypothermia
  - drugs (β-blockers, calcium channel blockers, etc.)
- treatment: if symptomatic, atropine during acute episodes; pacing for sick sinus syndrome; if drug-induced, reduction or withdrawal of drugs

Sinus Block, Pause, and Arrest
- three disorders involving the SA node; the sinus pacemaker fires but the impulse fails to depolarize the atrial myocardium resulting in no initial P wave (and consequently no QRS complex, ST segment, or T wave)
- sinus block (SA block), a complete block or failure of the sinus node to depolarize the atria; the block can last one or more cardiac cycles and is a multiple of the normal P-P interval
- sinus pause: a delay in the formation of a sinus impulse in the SA node resulting in a temporary pause (usually >3 s)
- sinus arrest: a longer delay in the formation of a sinus impulse in the SA node
  - there is no clear cut-off between sinus pause vs. arrest – if the pause lasts greater than 3x the normal P-P interval then it may be called an arrest
  - the P-P prolongation is not phasic or gradual (unlike sinus arrhythmia) and is not a multiple of the normal P-P interval (unlike sino-atrial block)
- escape beats or rhythm may occur:
  - atrial escape: P waves with abnormal morphology
  - junctional escape: P waves not seen, or follow the QRS (retrograde P), rate 40-60 bpm
  - ventricular escape: no P wave; wide, abnormal QRS; slow rate 20-40 bpm

Sick Sinus Syndrome
- characterized by sinus node dysfunction (marked bradycardia, sinus pause/arrest, sinoatrial block)
  - when symptomatic, electronic pacemaker is indicated
  - frequently associated with episodes of atrial tachyarrhythmias ("tachy-brady syndrome")
  - usually require a combination of a pacemaker for bradycardia and medications (β-blocker, calcium channel blocker, and/or digoxin, initiated after pacemaker insertion) for tachycardia

AV Conduction Blocks

First Degree AV Block
- prolonged PR interval (>200 msec)
- frequently found among otherwise healthy adults
- no treatment required

Second Degree AV Block
- some of the atrial impulses are not conducted to the ventricles
- can describe block by ratio of number of P waves to number of QRS (e.g. 2:1, 3:1, 4:1 increases in severity)
- second degree AV block is further subdivided into Type I and Type II block:
  - Type I (Mobitz I) second degree AV block
    - a gradual prolongation of the PR interval precedes the failure of conduction of a P wave (Wenckebach phenomenon)
    - AV block is usually in AV node (proximal)
      - triggers (usually reversible): increased vagal tone (e.g. following surgery), RCA-mediated ischemia
      - not an indication for temporary or permanent pacing
Type II (Mobitz II) second degree AV block
- the PR interval is constant; there is an abrupt failure of conduction of a P wave
- AV block is usually distal to the AV node (i.e. His bundle)
- increased risk of high grade or 3rd degree AV block

2:1 AV Block
- often not possible to determine whether the block is type I or type II
- prolonged or repeated recordings may clarify the diagnosis

Third Degree AV Block
- complete failure of conduction of the supraventricular impulses to the ventricles
- ventricular depolarization initiated by an escape pacemaker distal to the block
- QRS can be narrow or wide (junctional vs. ventricular escape rhythm)
- P-P and R-R intervals are constant, variable PR intervals
- no relationship between P waves and QRS complexes (P waves “marching through”)
- management (see Electrical Pacing, C21)

Supraventricular Tachyarrhythmias

Presentation for SVT (and pre-excitation syndromes)
- presentation can include: palpitations, dizziness, dyspnea, chest discomfort, presyncope/syncope
- may precipitate congestive heart failure (CHF), hypotension or ischemia in patients with underlying disease
- untreated tachycardias can cause cardiomyopathy (rare, potentially reversible with treatment of SVTs)
- includes supraventricular and ventricular rhythms

Supraventricular Tachyarrhythmias (SVT)
- tachyarrhythmias that originate in the atria or AV junction
- this term is used when a more specific diagnosis of mechanism and site of origin cannot be made
- characterized by narrow QRS, unless there is pre-existing bundle branch block or aberrant ventricular conduction (abnormal conduction due to a change in cycle length)

Sinus Tachycardia
- sinus rhythm with rate >100 bpm
- occurs in normal subjects with increased sympathetic tone (exercise, emotions, pain), alcohol use, caffeinated beverages, drugs (e.g. β-adrenergic agonists, anticholinergic drugs, etc.)
- etiology: fever, hypotension, hypovolemia, anemia, thyrotoxicosis, CHF, MI, shock, PE, etc.
- treatment: treat underlying disease; consider β-blocker if symptomatic, calcium channel blocker if β-blockers contraindicated
Atrial Fibrillation (AFib)
- irregular rhythm caused by presence of 3 or more atrial foci (may mimic AFib)
- atrial rate 100-200 bpm, at least 3 distinct P wave morphologies and PR intervals vary, some P waves may not be conducted
- occurs more commonly in patients with COPD, and hypoxemia; less commonly in patients with hypokalemia, hypomagnesemia, sepsis, theophylline or digitalis toxicity
- treatment: treat the underlying cause; calcium channel blockers may be used (e.g. diltiazem, verapamil), β-blockers may be contraindicated because of severe pulmonary disease
- no role for electrical cardioversion, antiarrhythmics or ablation

Multifocal Atrial Tachycardia (MAT)
- irregular rhythm caused by presence of 3 or more atrial foci
- atrial rate 100-200 bpm, at least 3 distinct P wave morphologies and PR intervals vary, some P waves may not be conducted
- occurs more commonly in patients with COPD, and hypoxemia; less commonly in patients with hypokalemia, hypomagnesemia, sepsis, theophylline or digitalis toxicity
- treatment: treat the underlying cause; calcium channel blockers may be used (e.g. diltiazem, verapamil), β-blockers may be contraindicated because of severe pulmonary disease
- no role for electrical cardioversion, antiarrhythmics or ablation

Atrial Flutter
- rapid, regular atrial depolarization from a macro re-entry circuit within the atrium (most commonly the right atrium)
- atrial rate 250-350 bpm, usually 300 bpm
- AV block usually occurs; it may be fixed (2:1, 3:1, 4:1, etc.) or variable
- etiology: CAD, thyrotoxicosis, mitral valve disease, cardiac surgery, COPD, PE, pericarditis
- ECG: sawtooth flutter waves (most common type of flutter) in inferior leads (II, III, aVF); narrow QRS (unless aberrancy) (see Figure 22)
- in atrial flutter with 2:1 block, carotid sinus massage (first check for bruits), Valsalva maneuver, or adenosine may decrease AV conduction and bring out flutter waves
- treatment
  - acute: if unstable (e.g. hypotension, CHF, angina): electrical cardioversion
  - if stable
    1) rate control: β-blocker, diltiazem, verapamil, or digoxin
    2) chemical cardioversion: sotalol, amiodarone, type I antiarrhythmics, or electrical cardioversion
  - anticoagulation guidelines same as for patients with AFib (see Atrial Fibrillation, below)
  - long-term: antiarrhythmics, catheter radiofrequency (RF) ablation (success rate dependent on site of origin of atrial flutter)

Atrial Fibrillation (AFib)
- see CCS Atrial Fibrillation Guidelines 2012 for details (free mobile apps available on iOS, Android and Blackberry)
- most common sustained arrhythmia
- incidence increases with age (10% of population >80 yr old)
- symptoms: palpitations, fatigue, syncope, may precipitate or worsen heart failure
- classification:
  - chronic/permanent: continuous atrial fibrillation that is unresponsive to cardioversion; cardioversion will not be attempted
  - lone: occurs in persons younger than 60 yr and in whom no clinical or echocardiographic causes are found
  - nonvalvular: not caused by valvular disease, prosthetic heart valves, or valve repair
  - paroxysmal: episodes that terminate spontaneously
  - persistent: atrial fibrillation sustained for more than 7 d or atrial fibrillation that terminates only with cardioversion
  - recurrent: two or more episodes of atrial fibrillation
  - secondary: caused by a separate underlying condition or event (e.g. myocardial infarction, cardiac surgery, pulmonary disease, hyperthyroidism)
  - may be associated with thromboembolic events (4%/yr in nonvalvular AFib)

- initiation
  - single circuit re-entry and/or ectopic foci act as aberrant generators producing atrial tachycardia (350-600 bpm)
  - impulses conduct irregularly across the atrial myocardium to give rise to fibrillation
  - in some cases, ectopic foci have also been mapped to the pulmonary vein ostia and can be ablated

- maintenance
  - the tachycardia causes atrial structural and electrophysiological remodelling changes that further promote AFib; the longer the patient is in AFib the more difficult it is to convert back to sinus rhythm

- consequences
  - the AV node irregularly filters incoming atrial impulses producing an irregular ventricular response of <200 bpm and the tachycardia leads to suboptimal cardiac output
  - fibrillatory conduction of the atria promotes blood stasis increasing the risk of thrombus formation – AFib is an important risk factor for stroke

Premature Beats
- premature atrial contraction (PAC) (Figure 27)
  - ectopic supraventricular beat originating in the atria
  - P wave morphology of the PAC usually differs from that of a normal sinus beat
  - junctional premature beat
  - ectopic supraventricular beat that originates in the vicinity of the AV node
  - P wave is usually not seen or an inverted P wave is seen and may be before or closely follow the QRS complex
  - treatment usually not required

Multifocal Atrial Tachycardia (MAT)
- occurs more commonly in patients with COPD, and hypoxemia; less commonly in patients with hypokalemia, hypomagnesemia, sepsis, theophylline or digitalis toxicity
- treatment: treat the underlying cause; calcium channel blockers may be used (e.g. diltiazem, verapamil), β-blockers may be contraindicated because of severe pulmonary disease
- no role for electrical cardioversion, antiarrhythmics or ablation

Atrial Flutter
- rapid, regular atrial depolarization from a macro re-entry circuit within the atrium (most commonly the right atrium)
- atrial rate 250-350 bpm, usually 300 bpm
- AV block usually occurs; it may be fixed (2:1, 3:1, 4:1, etc.) or variable
- etiology: CAD, thyrotoxicosis, mitral valve disease, cardiac surgery, COPD, PE, pericarditis
- ECG: sawtooth flutter waves (most common type of flutter) in inferior leads (II, III, aVF); narrow QRS (unless aberrancy) (see Figure 22)
- in atrial flutter with 2:1 block, carotid sinus massage (first check for bruits), Valsalva maneuver, or adenosine may decrease AV conduction and bring out flutter waves
- treatment
  - acute: if unstable (e.g. hypotension, CHF, angina): electrical cardioversion
  - if stable
    1) rate control: β-blocker, diltiazem, verapamil, or digoxin
    2) chemical cardioversion: sotalol, amiodarone, type I antiarrhythmics, or electrical cardioversion
  - anticoagulation guidelines same as for patients with AFib (see Atrial Fibrillation, below)
  - long-term: antiarrhythmics, catheter radiofrequency (RF) ablation (success rate dependent on site of origin of atrial flutter)

Atrial Fibrillation (AFib)
- see CCS Atrial Fibrillation Guidelines 2012 for details (free mobile apps available on iOS, Android and Blackberry)
- most common sustained arrhythmia
- incidence increases with age (10% of population >80 yr old)
- symptoms: palpitations, fatigue, syncope, may precipitate or worsen heart failure
- classification:
  - chronic/permanent: continuous atrial fibrillation that is unresponsive to cardioversion; cardioversion will not be attempted
  - lone: occurs in persons younger than 60 yr and in whom no clinical or echocardiographic causes are found
  - nonvalvular: not caused by valvular disease, prosthetic heart valves, or valve repair
  - paroxysmal: episodes that terminate spontaneously
  - persistent: atrial fibrillation sustained for more than 7 d or atrial fibrillation that terminates only with cardioversion
  - recurrent: two or more episodes of atrial fibrillation
  - secondary: caused by a separate underlying condition or event (e.g. myocardial infarction, cardiac surgery, pulmonary disease, hyperthyroidism)
  - may be associated with thromboembolic events (4%/yr in nonvalvular AFib)

- initiation
  - single circuit re-entry and/or ectopic foci act as aberrant generators producing atrial tachycardia (350-600 bpm)
  - impulses conduct irregularly across the atrial myocardium to give rise to fibrillation
  - in some cases, ectopic foci have also been mapped to the pulmonary vein ostia and can be ablated

- maintenance
  - the tachycardia causes atrial structural and electrophysiological remodelling changes that further promote AFib; the longer the patient is in AFib the more difficult it is to convert back to sinus rhythm

- consequences
  - the AV node irregularly filters incoming atrial impulses producing an irregular ventricular response of <200 bpm and the tachycardia leads to suboptimal cardiac output
  - fibrillatory conduction of the atria promotes blood stasis increasing the risk of thrombus formation – AFib is an important risk factor for stroke
Table 3. CHADS2 Risk Prediction for Non-Valvular AFib

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>CHADS2 Score</th>
<th>Stroke Risk (%/Yr)</th>
<th>Anticoagulation Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
<td>0</td>
<td>1.9 (low)</td>
<td>ASA 81-325 mg OD</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
<td>2.8 (low-mod)</td>
<td>oral anticoagulants*</td>
</tr>
<tr>
<td>Age &gt;75</td>
<td>1</td>
<td>2-3</td>
<td>4.0-5.9 (mod)</td>
<td>oral anticoagulants*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>4-6</td>
<td>8.5-18.2 (high)</td>
<td>oral anticoagulants*</td>
</tr>
<tr>
<td>Stroke/TIA (prior)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AFib on ECG
- no organized P waves due to rapid atrial activity (350-600 bpm) causing a chaotic fibrillatory baseline
- irregularly irregular ventricular response (typically 100-180 bpm), narrow QRS (unless aberrancy or previous BBB)
- wide QRS complexes due to aberrancy may occur following a long-short cycle sequence ("Ashman phenomenon")
- loss of atrial contraction, thus no "a" wave seen in JVP, no S4 on auscultation

Management (adapted from CCS Atrial Fibrillation Guidelines 2012)
**Major objectives (RACE):** all patients with AF (paroxysmal, persistent, or permanent), should be stratified using a predictive index for stroke risk and for the risk of bleeding, and most patients should receive either an oral anticoagulant or ASA (see Table 3)

1. Rate control: β-blockers, diltiazem, verapamil (in patients with heart failure: digoxin, amiodarone)
2. Anticoagulation: use either warfarin, dabigatran, rivaroxaban, apixaban to prevent thromboembolism
3. Cardioversion (electrical)
   - if AFib <24-48 h, can usually cardiovert without anticoagulation
   - if AFib >24-48 h, anticoagulate for 3 wk prior and 4 wk after cardioversion
   - if patient unstable (hypotensive, active angina due to tachycardia, uncontrolled heart failure) should cardiovert immediately
4. Etiology
   - HTN, CAD, valvular disease, pericarditis, cardiomyopathy, myocarditis, ASD, post-operative, PE, COPD, thyrotoxicosis, sick sinus syndrome, alcohol ("holiday heart")
   - may present in young patients without demonstrable disease ("lone AFib") and in the elderly without underlying heart disease

Additional Management Points Regarding AFib
- studies of patients with AFib suggest that there is no difference in long-term survival when treating patients with a rhythm-control versus rate-control strategy
- however, many patients with a significant underlying structural heart lesion (e.g. valve disease, cardiomyopathy) will not tolerate AFib well (since may be dependent on atrial kick) and these patients should be cardioverted (chemical or electrical) as soon as possible

Newly Discovered AFib
- anticoagulants may be beneficial if high risk for stroke
- if the episode is self-limited and not associated with severe symptoms, no need for antiarrhythmic drugs
- if AFib persists, 2 options:
  1. rate control and anticoagulation (as indicated above)
  2. cardioversion (as above)

Recurrent AFib/Permanent AFib
- if episodes are brief or minimally symptomatic, antiarrhythmic drugs may be avoided; rate control and anticoagulation are appropriate
- patients who have undergone at least one attempt to restore sinus rhythm may remain in AFib after recurrence: permanent AFib may be accepted (with rate control and antithrombotics as indicated by CHADS2 score) in certain clinical situations
• if symptoms are bothersome or episodes are prolonged, antiarrhythmic drugs should be used
  ▪ no or minimal heart disease: flecainide, propafenone or sotalol
  ▪ LV dysfunction: amiodarone
  ▪ CAD: β-blockers, amiodarone

**AV Nodal Re-Entrant Tachycardia (AVNRT)**
- re-entrant circuit using dual pathways (fast conducting β-fibres and slow conducting α-fibres) within or near the AV node; often found in the absence of structural heart disease – cause is commonly idiopathic, although familial AVNRT has been reported
- sudden onset and offset
- fast regular rhythm: rate 150-250 bpm
- usually initiated by a supraventricular or ventricular premature beat
- AVNRT accounts for 60-70% of all paroxysmal SVTs
- retrograde P waves may be seen but are usually lost in the QRS complex (see Figure 24)
- treatment
  ▪ acute: Valsalva or carotid massage, adenosine is first choice if unresponsive to vagal maneuvers; if no response, try metoprolol, digoxin, diltiazem, electrical cardioversion if patient hemodynamically unstable (hypotension, angina or CHF)
  ▪ long-term: 1st line – β-blocker, diltiazem, digoxin; 2nd line – flecainide, propafenone; 3rd line – catheter ablation

**Pre-Excitation Syndromes**
- refers to a subset of SVTs mediated by an accessory pathway which can lead to ventricular pre-excitation

**Wolff-Parkinson-White (WPW) Syndrome**
- congenital defect present in 1.5-2/1000 of the general population
- an accessory conduction tract (Bundle of Kent; can be in right or left atrium) abnormally allows early electrical activation of part of one ventricle
- impulses travel at a greater conduction velocity across the Bundle of Kent thereby effectively ‘bypassing’ AV node
- since the ventricles are activated earlier, the ECG shows early ventricular depolarization in the form of initial slurring of the QRS complex – the so-called “delta wave”
- atrial impulses that conduct to the ventricles through both the Bundle of Kent and the normal AV node/His-Purkinje system generate a broad “fusion complex”
- ECG features of WPW
  ▪ PR interval <120 msec
  ▪ delta wave: slurred upstroke of the QRS (the leads with the delta wave vary with site of bypass)
  ▪ widening of the QRS complex due to premature activation
  ▪ secondary ST segment and T wave changes
  ▪ tachyarrhythmias may occur – most often AVRT and AFib

© Laura E. Smith 2012
Figure 24. AVNRT

© Young M. Kim 2011
Figure 25. Mechanism for AVNRT

© Young M. Kim 2011
Figure 26. Accessory pathway conduction in WPW causes early ventricular activation leading to the appearance of a delta wave (slurred upstroke of the QRS) on the ECG before usual conduction occurs across the AV node.
AFib in WPW Patients
- AFib is the index arrhythmia in up to 20% of patients with WPW syndrome
  - it is usually intermittent rather than persistent or permanent
- rapid atrial depolarizations in AFib are conducted through the bypass tract which is not able to filter impulses like the AV node can
- consequently the ventricular rate becomes extremely rapid (>200 bpm) and the QRS complex widens
- treatment: electrical cardioversion, IV procainamide or IV amiodarone
  - do not use drugs that slow AV node conduction (digoxin, β-blockers) as this may cause preferential conduction through the bypass tract and precipitate VF
- long-term: ablation of bypass tract if possible

AV Re-Entrant Tachycardia (AVRT)
- re-entrant loop via accessory pathway and normal conduction system
- initiated by a premature atrial or ventricular complex
- orthodromic AVRT: stimulus from a premature complex travels up the bypass tract (V to A) and down the AV node (A to V) with narrow QRS complex (no delta wave because stimulus travels through normal conduction system) (see Figure 28)
  - comprises 95% of the reentrant tachycardias associated with WPW syndrome
- antidromic AVRT: more rarely the stimulus goes up the AV node (V to A) and down the bypass tract (A to V); wide and abnormal QRS as ventricular activation is only via the bypass tract
- treatment
  - acute: similar to AVNRT except avoid long-acting AV nodal blockers, e.g. digoxin and verapamil
  - long-term: for recurrent arrhythmias ablation of the bypass tract is recommended
  - drugs such as flecainide and procainamide can be used

Ventricular Tachyarrhythmias

Premature Ventricular Contraction (PVC) or Ventricular Premature Beat (VPB)
- QRS width >120 msec, no preceding P wave, bizarre QRS morphology
- origin: LBBB morphology of VT = RV origin; RBBB morphology of VT = LV origin
- PVCs may be benign but are usually significant in the following situations:
  - consecutive (≥3 = VT) or multiform (varied origin)
  - PVC falling on the T wave of the previous beat (“R on T phenomenon”): may precipitate ventricular tachycardia or VF

Accelerated Idioventricular Rhythm
- ectopic ventricular rhythm with rate 50-100 bpm
- more frequently occurs in the presence of sinus bradycardia and is easily overdriven by a faster supraventricular rhythm
- frequently occurs in patients with acute MI or other types of heart disease (cardiomyopathy, hypertensive, valvular) but it does not affect prognosis and does not usually require treatment

Ventricular Tachycardia (VT)
- 3 or more consecutive ectopic ventricular complexes (Figure 29)
  - rate >100 bpm (usually 140-200)
  - ventricular flutter: if rate >200 bpm and complexes resemble a sinusoidal pattern
  - “sustained VT” if it lasts longer than 30 s
  - ECG characteristics: wide regular QRS tachycardia (QRS usually >140 msec);
  - AV dissociation; bizarre QRS pattern. Also favour Dx of VT: left axis or right axis deviation, nonspecific intraventricular block pattern, monophasic or biphasic QRS in V1 with RBBB, QRS concordance in V1-V6
  - occasionally during VT supraventricular impulses may be conducted to the ventricles generating QRS complexes with normal or aberrant supraventricular morphology (“ventricular capture”) or summation pattern (“fusion complexes”)
- monomorphic VT
  - identical complexes with uniform morphology
  - more common than polymorphic VT
  - typically result from intraventricular re-entry circuit
  - potential causes: chronic infarct scarring, acute MI/ischemia, cardiomyopathies, myocarditis, arrhythmogenic right ventricular dysplasia, idiopathic, drugs (e.g. cocaine), electrolyte disturbances
- polymorphic VT
  - complexes with constantly changing morphology, amplitude, and polarity
  - more frequently associated with hemodynamic instability due to faster rates (typically 200-250 bpm) vs. monomorphic VT
  - potential causes: acute MI, severe or silent ischemia, and predisposing factors for QT prolongation (see Torsades de Pointes, C20)
• treatment
  ▪ sustained VT (>30 s) is an emergency, requiring immediate treatment
  ▪ hemodynamic compromise: electrical cardioversion
  ▪ no hemodynamic compromise: electrical cardioversion, lidocaine, amiodarone, type 1a agents (procainamide, quinidine)

Figure 29. Ventricular tachycardia (monomorphic)

Table 4. Wide Complex Tachycardia: Clues for Differentiating VT vs. SVT with Aberrancy*

<table>
<thead>
<tr>
<th>Clinical Clues</th>
<th>ECG Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting symptoms</td>
<td>Not helpful</td>
</tr>
<tr>
<td>History of CAD and previous MI</td>
<td>AV dissociation VT</td>
</tr>
<tr>
<td>Physical exam</td>
<td>Capture or fusion beats VT</td>
</tr>
<tr>
<td>Cannon “a” waves</td>
<td>QRS width &gt; 140 msec VT</td>
</tr>
<tr>
<td>Variable S1</td>
<td>Extreme axis deviation VT</td>
</tr>
<tr>
<td>Carotid sinus massage/adenosine terminates arrhythmia</td>
<td>Positive QRS concordance (R wave across chest leads) VT</td>
</tr>
<tr>
<td>Carotid sinus massage/adenosine terminates arrhythmia</td>
<td>Negative QRS concordance (S wave across chest leads) May suggest VT</td>
</tr>
<tr>
<td>Carotid sinus massage/adenosine terminates arrhythmia</td>
<td>Axis shift during arrhythmia VT (polymorphic)</td>
</tr>
</tbody>
</table>

*If patient >65 and previous MI or structural heart disease, then chance of VT >95%
**May terminate VT in some patients with no structural heart disease

Torsades de Pointes
• a variant of polymorphic VT that occurs in patients with baseline QT prolongation – “twisting of the points” (Figure 30)
• looks like usual VT except that QRS complexes “rotate around the baseline” changing their axis and amplitude
• ventricular rate >100 bpm, usually 150-300 bpm
• etiology: predisposition in patients with prolonged QT intervals
  ▪ congenital long QT syndromes
  ▪ drugs: e.g. class IA (quinidine), class III (sotalol), phenothiazines (TCAs), erythromycin, quinolones, antihistamines
  ▪ electrolyte disturbances: hypokalemia, hypomagnesemia
  ▪ nutritional deficiencies causing above electrolyte abnormalities
• treatment: IV magnesium, temporary pacing, isoproterenol and correct underlying cause of prolonged QT, electrical cardioversion if hemodynamic compromise

Figure 30. Torsades de pointes

Ventricular Fibrillation (VFib)
• chaotic ventricular arrhythmia, with very rapid irregular ventricular fibrillatory waves of varying morphology (Figure 31)
• terminal event, unless advanced cardiac life-support (ACLS) procedures are promptly initiated to maintain ventilation and cardiac output, and electrical defibrillation is carried out
• most frequent cause of sudden death
• refer to ACLS algorithm for complete therapeutic guidelines

Figure 31. Ventricular fibrillation
**Electrophysiology (EPS) Studies**

- invasive test for the investigation and treatment of cardiac rhythm disorders using intracardiac catheters
- provide detailed analysis of the arrhythmia mechanism and precise site of origin when ECG data are nondiagnostic or unobtainable
- bradyarrhythmias: define the mechanisms of SA node dysfunction and localize site of AV conduction block
- tachyarrhythmias: map for possible ablation or to assess inducibility of ventricular tachycardia

**Electrical Pacing**

- the decision to implant a pacemaker usually is based on symptoms of a bradyarrhythmia or tachyarrhythmia in the setting of heart disease

**Pacemaker Indications**

- SA node dysfunction (most common): symptomatic bradycardia ± hemodynamic instability
- common manifestations include: syncope, presyncope, or severe fatigue
- SA node dysfunction is commonly caused by: intrinsic disease within the SA node (e.g. idiopathic degeneration, fibrosis, ischemia, or surgical trauma), abnormalities in autonomic nervous system function, and drug effects
- AV nodal-infranodal block: Mobitz II, complete heart block

**Pacemaker Complications**

- complications related to surgical implantation include venous access (pneumothorax, hemothorax, air embolism), pacemaker leads (perforation, malposition), pocket hematomas and infection
- complications specific to the pacemaker include a failure to pace, failure to sense, pulse generator failure, pacemaker syndrome and pacemaker mediated tachycardia

**Pacing Techniques**

- temporary: transvenous (jugular, subclavian, femoral) or external pacing
- permanent: transvenous into RA, apex of RV or both
- can sense and pace atrium, ventricle or both
- new generation: rate responsive, able to respond to physiologic demand
- biventricular

**Implantable Cardioverter Defibrillators (ICDs)**

- sudden cardiac death (SCD) usually results from ventricular fibrillation (VFib), sometimes preceded by monomorphic or polymorphic ventricular tachycardia (VT)
- ICDs detect ventricular tachyarrhythmias and are highly effective in terminating VT/VFib and in aborting SCD
- mortality benefit vs. antiarrhythmics in secondary prevention
- benefit seen in patients with ischemic and non-ischemic cardiomyopathy, depressed left ventricular ejection fraction (LVEF), prolonged QRS
- see Heart Failure, C30 for current treatment recommendations

**Catheter Ablation**

**Techniques**

- radiofrequency (RF) energy: a low-voltage high-frequency form of electrical energy (similar to cautery). RF energy produces small, homogeneous, necrotic lesions approximately 5-7 mm in diameter and 3-5 mm in depth

**Indications**

- paroxysmal SVT
  - AVNRT: accounts for more than half of all cases
- accessory pathway (orthodromic reciprocating tachycardia): 30% of SVT
  - re-entrant rhythm, with an accessory AV connection as the retrograde limb
  - corrected by targeting the accessory pathway
- atrial flutter: flutter focus in RA
- AFib: potential role for pulmonary vein ablation
- ventricular tachycardia: focus arises from the right ventricular outflow tract and less commonly originates in the inferoseptal left ventricle near the apex (note: majority of cases of VT are due to scarring from previous MI and cannot be ablated)
Major Complications

- 1% of patients
- death: 0.1-0.2%
- cardiac: high grade AV block requiring permanent pacemaker, tamponade, pericarditis
- vascular: hematoma, vascular injury, thromboembolism, TIA/stroke
- pulmonary: PE

Ischemic Heart Disease

Epidemiology

- most common cause of cardiovascular morbidity and mortality
- atherosclerosis and thrombosis are the most important pathogenetic mechanisms
- male:female ratio = 2:1 with all age groups included (Framingham study), 8:1 for age <40, 1:1 for age >70
- peak incidence of symptomatic IHD is age 50-60 (men) and 60-70 (women)
- for primary prevention of ischemic heart disease please see Family Medicine, FM19

Table 5. Risk Factors and Markers for Atherosclerotic Heart Disease

<table>
<thead>
<tr>
<th>Non-modifiable Risk Factors</th>
<th>Modifiable Risk Factors</th>
<th>Markers of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Hyperlipidemia*</td>
<td>Elevated lipoprotein(a)</td>
</tr>
<tr>
<td>Male, postmenopausal female</td>
<td>Hypertension (HTN)*</td>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td>Family history (FHx) of MI*</td>
<td>Diabetes mellitus (DMI)*</td>
<td>Elevated high-sensitivity C-reactive protein (hsCRP)</td>
</tr>
<tr>
<td>First degree male relative &lt;55</td>
<td>Cigarette smoking*</td>
<td>Coronary artery calcification</td>
</tr>
<tr>
<td>First degree female relative &lt;65</td>
<td>Metabolic syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sedentary lifestyle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heavy alcohol intake</td>
<td></td>
</tr>
</tbody>
</table>

* Major risk factor

Figure 32. Pathophysiology of atherosclerosis

Chronic Stable Angina

Definition

- symptom complex resulting from an imbalance between oxygen supply and demand in the myocardium

Etiology and Pathophysiology

- factors that decrease myocardial oxygen supply
  - decreased luminal diameter: atherosclerosis, vasospasm
  - decreased duration of diastole: tachycardia (decreased duration of diastolic coronary perfusion)
  - decreased hemoglobin: anemia
  - decreased $\text{SaO}_2$: hypoxemia
  - congenital anomalies

Chronic stable angina is most often due to a fixed stenosis caused by an atheroma.

Acute coronary syndromes are the result of plaque rupture.
• factors that increase myocardial oxygen demand
  • increased heart rate: hyperthyroidism
  • increased contractility: hyperthyroidism
  • increased wall stress: myocardial hypertrophy, aortic stenosis

**Signs and Symptoms**
• typical: retrosternal chest pain, tightness or discomfort radiating to left (± right) shoulder/arm/neck/jaw, associated with diaphoresis, nausea, anxiety
• predictably precipitated by the “3 Es”: exertion, emotion, eating
• brief duration, lasting <10-15 min and typically relieved by rest and nitrates
• Levine's sign: clenching fist over sternum when describing chest pain
• anginal equivalents: dyspnea, acute LV failure, flash pulmonary edema

**Clinical Assessment**
• history including directed risk factor assessment and physical exam
• labs: HB, fasting glucose, fasting lipid profile
• ECG (at rest and during episode of chest pain if possible)
• CXR (suspected heart failure, valvular disease, pericardial disease, aortic dissection/aneurysm, or signs or symptoms of pulmonary disease)
• stress testing (see Cardiac Diagnostic Tests, C5) or angiography
  ▪ to assess systolic murmur suggestive of aortic stenosis, mitral regurgitation and/or HCM
  ▪ to assess LV function in patients with Hx of prior MI, pathological Q waves, signs or symptoms of congestive heart failure (CHF)

**Differential Diagnosis**
• see Differential Diagnosis of Common Presentations, C4

**Treatment of Chronic Stable Angina**
1. **General measures**
   • goals: to reduce myocardial oxygen demand and/or increase oxygen supply
   • lifestyle modification (diet, exercise)
   • treatment of risk factors: statins (see Endocrinology, E5, Family Medicine, FM9 for target lipid guidelines), antihypertensives, etc.
2. **Antiplatelet therapy** (first-line therapy)
   • ASA
3. **β-blockers** (first-line therapy – decrease overall mortality)
   • increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
   • cardioselective agents preferred (e.g. metoprolol, atenolol) to avoid peripheral effects (inhibition of vasodilation and bronchodilation via β2 receptors)
   • avoid intrinsic sympathomimetics (e.g. acebutolol) which increase demand
4. **Nitrates** (symptomatic control, no clear impact on survival)
   • decrease preload (venous dilatation) and afterload (arteriolar dilatation), and increase coronary perfusion
   • maintain daily nitrate-free intervals to prevent tolerance (tachyphylaxis)
5. **Calcium channel blockers** (CCBs, second-line or combination)
   • increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
   • caution: verapamil/diltiazem combined with β-blockers may cause symptomatic sinus bradycardia or AV block
6. **ACE inhibitors** (ACEI, not used to treat symptomatic angina)
   • angina patients tend to have risk factors for CV disease which warrant use of an ACEI (e.g. hypertension, diabetes, proteinuric renal disease, previous MI with LV dysfunction)
   • benefit in all patients at high risk for CV disease (concomitant DM, renal dysfunction or LV systolic dysfunction)
   • angiotensin II receptor blockers (ARBs) can be used when ACEI contraindicated (e.g. hypersensitivity, angioedema)
7. **Invasive strategies**
   • revascularization (see Coronary Revascularization, C28 and COURAGE trial sidebar)

**VARIANT ANGINA** (Prinzmetal’s Angina)
• myocardial ischemia secondary to coronary artery vasospasm, with or without atherosclerosis
• uncommonly associated with infarction or LV dysfunction
• typically occurs between midnight and 8 AM, unrelated to exercise, relieved by nitrates
• typically ST elevation on ECG
• diagnosed by provocative testing with ergot vasoconstrictors (rarely done)
• treat with nitrates and CCBs

**SYNDROME X**
• typical symptoms of angina but normal angiogram
• may show definite signs of ischemia with exercise testing
• thought to be due to inadequate vasodilator reserve of coronary resistance vessels
• better prognosis than overt epicardial atherosclerosis

**Optimal Medical Therapy with or without PCI for Stable Coronary Disease. COURAGE Trial**
*Randomized, controlled trial with median follow-up of 4.6 yr.*
*Population: 2287 patients who had objective evidence of myocardial ischemia and significant stable coronary artery disease.*
*Intervention: Patients were randomized to receive intensive pharmacologic therapy and lifestyle intervention with or without percutaneous coronary intervention (PCI).*
*Outcome: Primary outcome was all-cause mortality and non-fatal myocardial infarction (MI). Secondary outcome had additional events of stroke, all MI, and hospitalization for unstable angina with negative biomarkers.*
*Results: There was no significant difference in primary (unadjusted hazard ratio: 1.05; p=0.62) or secondary outcomes (hazard ratio: 1.05; p=0.62) between the PCI and non-PCI intervention groups. The PCI group had significantly lower rates of subsequent revascularization at 4 yr of follow-up (hazard ratio 0.63, p<0.001) and was more angina-free in the first 4 yr of follow-up.*
*Conclusions: PCI is an adjunct in initial management in patients with significant stable coronary artery disease does not reduce mortality, MI, stroke or hospitalization for ACS, but does provide angina relief and reduced risk of revascularization.*
Acute Coronary Syndromes (ACS)

Definition
- ACS includes the spectrum of UA, NSTEMI and STEMI. This distinction aids in providing the appropriate therapeutic intervention
  - MI is defined by evidence of myocardial necrosis. It is diagnosed by a rise/fall of serum markers plus any one of:
    - symptoms of ischemia (chest/upper extremity/mandibular/epigastric discomfort; dyspnea)
    - ECG changes (ST-T changes, new BBB or pathological Q waves)
    - imaging evidence (myocardial loss of viability, wall motion abnormality or intracoronary thrombus)
  - if biomarker changes are unattainable, cardiac symptoms combined with new ECG changes is sufficient
  - NSTEMI meets criteria for myocardial infarction without ST elevation or BBB
  - STEMI meets criteria for myocardial infarction characterized by ST elevation or new BBB
- UA is clinically defined by any of the following:
  - accelerating pattern of pain: increased frequency, increased duration, decreased threshold of exertion, decreased response to treatment
  - angina at rest
  - new-onset angina
  - angina post-MI or post-procedure (e.g. percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG])

Investigations
- history and physical
  - note that up to 30% of MIs are unrecognized or “silent” due to atypical symptoms – more common in women, DM, elderly, post-heart transplant (because of denervation)
- ECG
- CXR
- labs
  - serum cardiac biomarkers for myocardial damage (repeat 8 h later) (see Cardiac Biomarkers, C9)
  - CBC, INR/PTT, electrolytes and magnesium, creatinine, urea, glucose, serum lipids
  - draw serum lipids within 24-48 h because values are unreliable from 2-48 d post-MI

MANAGEMENT OF ACUTE CORONARY SYNDROMES

1. General measures
   - ABCs: assess and correct hemodynamic status first
   - bed rest, cardiac monitoring, oxygen
   - nitroglycerin SL followed by IV
   - morphine IV

2. Anti-platelet and anticoagulation therapy
   - ASA 162-325 mg chewed
   - NSTEMI
     - clopidogrel 300 mg loading dose, then 75 mg QD in addition to ASA or if ASA contraindicated, subcutaneous low molecular weight heparin or IV unfractionated heparin (UFH) (LMWH preferred, except in renal failure or if CABG is planned within 24 h)
     - if PCI is planned: clopidogrel 300 mg loading dose and IV GP IIb/IIIa inhibitor (e.g. abciximab)
     - anticoagulation options depend on reperfusion strategy:
       - primary PCI: UFH during procedure; bivalirudin is a possible alternative
       - thrombolysis: LMWH (enoxaparin) until discharge from hospital; can use UFH as alternative because of possible rescue PCI
       - no reperfusion: LMWH (enoxaparin) until discharge from hospital
     - continue LMWH or UFH followed by oral anticoagulation at discharge if at high risk for thromboembolic event (large anterior MI, AFib, severe LV dysfunction, CHF, previous DVT or PE, or echo evidence of mural thrombus)
   - STEMI
     - clopidogrel 300 mg loading dose, then 75 mg QD in addition to ASA or if ASA contraindicated, subcutaneous low molecular weight heparin or IV unfractionated heparin (UFH) (LMWH preferred, except in renal failure or if CABG is planned within 24 h)
     - if PCI is planned: clopidogrel 300 mg loading dose and IV GP IIb/IIIa inhibitor (e.g. abciximab)
     - anticoagulation options depend on reperfusion strategy:
       - primary PCI: UFH during procedure; bivalirudin is a possible alternative
       - thrombolysis: LMWH (enoxaparin) until discharge from hospital; can use UFH as alternative because of possible rescue PCI
       - no reperfusion: LMWH (enoxaparin) until discharge from hospital
     - continue LMWH or UFH followed by oral anticoagulation at discharge if at high risk for thromboembolic event (large anterior MI, AFib, severe LV dysfunction, CHF, previous DVT or PE, or echo evidence of mural thrombus)

3. β-blockers
   - first dose IV followed by oral administration
   - STEMI: contraindications include signs of heart failure, low output states, risk of cardiogenic shock, heart block, asthma or airway disease; initiate orally within 24 h of diagnosis when indicated
   - if β-blockers are contraindicated or if β-blockers/nitrates fail to relieve ischemia, non-dihydropyridine calcium channel blockers (e.g. diltiazem, verapamil) may be used as second-line therapy in the absence of severe LV dysfunction or pulmonary vascular congestion (calcium channel blockers do not prevent MI or decrease mortality)
4. Invasive strategies and reperfusion options

- **UA/NSTEMI**: early coronary angiography ± revascularization if possible is recommended with any of the following high-risk indicators:
  - recurrent angina/ischemia at rest despite intensive anti-ischemic therapy
  - CHF or LV dysfunction
  - hemodynamic instability
  - high (≥3) TIMI risk score (tool used to estimate mortality following an ACS)
  - sustained ventricular tachycardia
  - dynamic ECG changes
  - high-risk findings on non-invasive stress testing
  - PCI within the previous 6 mo
  - repeated presentations for ACS despite treatment and without evidence of ongoing ischemia or high risk features
  - note: thrombolysis is NOT administered for UA/NSTEMI

- **STEMI**
  - after diagnosis of STEMI is made, do not wait for results of further investigations before implementing reperfusion therapy
  - goal is to re-perfuse artery: thrombolysis (“EMS-to-needle”) within 30 min or primary PCI (“EMS-to-balloon”) within 90 min (depending on capabilities of hospital and access to hospital with PCI facility)
  - thrombolysis
    - preferred if patient presents ≤12 h of symptom onset, and <30 min after presentation to hospital, has contraindications to PCI, or PCI cannot be administered within 90 min
  - **PCI**
    - early PCI (≤12 h after symptom onset and <90 min after presentation) improves mortality vs. thrombolysis with fewer intra-cranial hemorrhages and recurrent MIs
    - rescue PCI: following failed thrombolytic therapy (diagnosed when following thrombolysis, ST segment elevation fails to resolve below half its initial magnitude and patient still having chest pain)

**Enoxaparin versus Unfractionated Heparin with Fibrinolysis for ST-elevation Myocardial Infarction**

*NEJM* 2006;354:1477-88

**Study:** Prospective multicenter RCT.

**Patients:** 20,479 patients (median age 60 yr. 77% male) with STEMI who were scheduled to undergo fibrinolysis.

**Intervention:** Patients were randomized to receive either enoxaparin or weight-based unfractionated heparin in addition to thrombolysis and standard therapies.

**Primary Outcome:** Death or recurrent nonfatal MI 30 d post-event.

**Results:** The composite primary outcome occurred less often in the enoxaparin group compared with those who received unfractionated heparin (9.9% vs. 12.0%, p < 0.001, NNT = 47). Taken separately, there was a trend toward reduced mortality (6.9% vs. 7.5%, p = 0.11) and a significant reduction in nonfatal reinfarction (3.0% vs. 4.5%, p < 0.001) in the enoxaparin group. The risk of major bleeding was significantly increased in the enoxaparin group (2.1% vs. 1.4%, p < 0.001, NNH = 142).

**Conclusion:** In patients with STEMI receiving thrombolysis, enoxaparin is superior to unfractionated heparin in preventing recurrent nonfatal MI and may lead to a small reduction in mortality.

### Figure 33. Reperfusion strategy in STEMI

### Table 6. Contraindications for Thrombolysis in STEMI

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior intracranial hemorrhage</td>
<td>Chronic, severe, poorly controlled HTN</td>
</tr>
<tr>
<td>Known structural cerebral vascular lesion</td>
<td>Uncontrolled HTN (sBP &gt; 180, dBP &gt; 110)</td>
</tr>
<tr>
<td>Known malignant intracranial neoplasm</td>
<td>Current anticoagulation</td>
</tr>
<tr>
<td>Significant closed-head or facial trauma ≤3 mo</td>
<td>Noncompressible vascular punctures</td>
</tr>
<tr>
<td>Ischemic stroke ≤3 mo</td>
<td>Ischemic stroke ≥3 mo</td>
</tr>
<tr>
<td>Active bleeding</td>
<td>Recent internal bleeding ≤2-4 wk</td>
</tr>
<tr>
<td>Suspected aortic dissection</td>
<td>Prolonged CPR or major surgery ≥3 wk</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Active peptic ulcer disease</td>
</tr>
</tbody>
</table>
Long-Term Management of ACS

• risk of progression to MI or recurrence of MI or death is highest within 1 mo
• at 1-3 mo after the acute phase, most patients resume a clinical course similar to that in patients with chronic stable coronary disease
• pre-discharge work-up: ECG and echo to assess residual LV systolic function
• drugs required in hospital to control ischemia should be continued after discharge in all patients
• other medications for long-term management of ACS are summarized below

1. General Measures
   • education
   • risk factor modification

2. Antiplatelet and Anticoagulation Therapy
   • ECASA 75-162 mg daily
   • clopidogrel 75 mg daily (at least 1 mo, up to 9-12 mo, if stent placed at least 12 mo)
   • prasugrel 10 mg daily or ticagrelor 90 mg twice daily can be used as alternatives to clopidogrel when indicated
   • ± warfarin x 3 mo if high risk (large anterior MI, LV thrombus, LVEF <30%, history of VTE, chronic AFib)

3. β-Blockers (e.g. metoprolol 25-50 mg bid or atenolol 50-100 mg daily)

4. Nitrates
   • alleviate ischemia but do not improve outcome
   • use with caution in right-sided MI patients who have become preload dependent

5. Calcium Channel Blockers (NOT recommended as first line treatment, consider as alternative to β-blockers)

6. Angiotensin-Converting Enzyme Inhibitors (ACEI)
   • prevent adverse ventricular remodelling
   • recommended for asymptomatic high-risk patients (e.g. diabetics), even if LVEF >40%
   • recommended for symptomatic CHF, reduced LVEF (<40%), anterior MI
   • use ARBs in patients who are intolerant of ACEI

7. ± Aldosterone Antagonists
   • if on ACEI and β-blockers and LVEF <40% and CHF or DM
   • significant mortality benefit shown with eplerenone by 30 d

8. Statins (early, intensive, irrespective of cholesterol level; e.g. atorvastatin 80 mg daily)

9. Invasive Cardiac Catheterization if indicated (risk stratification, see Figure 34)

Figure 34. Post-MI risk stratification

Prognosis following STEMI

• 5-15% of hospitalized patients will die
  • risk factors
    • infarct size/severity
    • age
    • co-morbid conditions
    • development of heart failure or hypotension
• post-discharge mortality rates
  • 6-8% within first year, half of these within first 3 months
  • 4% per year following first year
  • risk factors
    • LV dysfunction
    • residual myocardial ischemia
    • ventricular arrhythmias
    • history of prior MI
### Table 7. Complications of Myocardial Infarction

<table>
<thead>
<tr>
<th>Complication</th>
<th>Etiology</th>
<th>Presentation</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arrhythmia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Tachycardia</td>
<td>Sinus, AFib, VT, VFib</td>
<td>First 48 h</td>
<td>See Arrhythmias, C12</td>
</tr>
<tr>
<td>2. Bradycardia</td>
<td>Sinus, AV block</td>
<td>First 48 h</td>
<td></td>
</tr>
<tr>
<td><strong>Myocardial Rupture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. LV free wall</td>
<td>Transmural infarction</td>
<td>1-7 d</td>
<td>Surgery</td>
</tr>
<tr>
<td>2. Papillary muscle (→ MR)</td>
<td>Inferior infarction</td>
<td>1-7 d</td>
<td>Surgery</td>
</tr>
<tr>
<td>3. Ventricular septum (→ VSD)</td>
<td>Septal infarction</td>
<td>1-7 d</td>
<td>Surgery</td>
</tr>
<tr>
<td><strong>Shock/CHF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infarction or aneurysm</td>
<td>Within 48 h</td>
<td>Inotropes, intra-aortic balloon pump</td>
</tr>
<tr>
<td><strong>Post-Infarct Angina</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persistent coronary stenosis</td>
<td>Anytime</td>
<td>Aggressive medical therapy</td>
</tr>
<tr>
<td></td>
<td>Multivessel disease</td>
<td></td>
<td>PCI or CABG</td>
</tr>
<tr>
<td><strong>Recurrent MI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reocclusion</td>
<td>Anytime</td>
<td>Aggressive medical therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PCI or CABG</td>
</tr>
<tr>
<td><strong>Thromboembolism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mural/apical thrombus</td>
<td>7-10 d</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td></td>
<td>DVT</td>
<td>up to 6 mo</td>
<td></td>
</tr>
<tr>
<td><strong>Pericarditis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inflammatory</td>
<td>1-7 d</td>
<td>ASA</td>
</tr>
<tr>
<td><strong>Dressler’s syndrome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autoimmune</td>
<td>2-8 wk</td>
<td></td>
</tr>
</tbody>
</table>

### Treatment Algorithm for Chest Pain

**Symptoms suggestive of an acute coronary syndrome**
- 1. 12-lead electrocardiogram
- 2. Aspirin
- 3. Supplemental oxygen
- 4. Sublingual nitroglycerin
- 5. Morphine PRN
- 6. Cardiac enzymes

**No ST-segment changes**
- Initial enzymes normal
- Observe:
  - 1. Nitroglycerin PRN
  - 2. Analgesia
  - 3. Serial ECG and cardiac enzymes

**No current chest pain**, **serial studies negative**
- Provocative stress testing
- Negative results
- Search for other causes of chest pain

**Provocative stress testing**
- Negative results
- Positive results

**Positive results**
- 1. GP IIb/IIIa inhibitor
- 2. Coronary angiography
- 3. Coronary revascularization

**Negative results**
- 1. Clopidogrel
- 2. LMWH

**ST segment depression**
- Consistent with unstable angina or NSTEMI
- 1. Clopidogrel
- 2. LMWH

**No high-risk markers**
- No recurrent chest pain
- Provocative stress testing
- Negative results

**Positive results**
- 1. GP IIb/IIIa inhibitor
- 2. Coronary angiography
- 3. Coronary revascularization

**High-risk markers present**
- Elevated troponin
- Persistent/recurrent chest pain
- Persistent ST depression
- Associated heart failure
- Hemodynamic instability
- LVEF <40%
- PCI in preceding 6 months
- Thrombolytic therapy
- Primary PCI

**PredischARGE stress testing**
- Negative results
- Aggressive risk factor modification
- Long-term anti-anginal therapy

**Echocardiogram**
- LMWH: low-molecular-weight heparin; NSTEMI: non-ST-segment elevation myocardial infarction

**Figure 35. Treatment algorithm for chest pain**
Sudden Cardiac Arrest

Definition
• unanticipated, non-traumatic cardiac death in a stable patient which occurs within 1 h of symptom onset; VFib is most common cause

Etiology
• primary cardiac pathology
  ▪ ischemia/MI
  ▪ LV dysfunction
  ▪ severe ventricular hypertrophy
    ▪ HCM
    ▪ AS
  ▪ long QT syndrome
  ▪ congenital heart disease
  ▪ mutations in cardiac ion channels

Management
• acute: resuscitate with prompt CPR and defibrillation
• investigate underlying cause (cardiac catheterization, electrophysiologic studies, echo)
• treat underlying cause
• antiarrhythmic drug therapy: amiodarone, β-blockers
• implantable cardioverter defibrillator (ICD)
• refer to ACLS guidelines (see Anesthesia, A28)

Coronary Revascularization

PERCUTANEOUS CORONARY INTERVENTION (PCI)
• interventional cardiology technique aimed at relieving significant coronary stenosis
• main techniques: balloon angioplasty, stenting
• less common techniques: rotational/directional/extraction atherectomy

Indications
• medically refractory angina
• NSTEMI/UA with high risk features (e.g. high TIMI risk score)
• primary/rescue PCI for STEMI

Balloon Angioplasty and Intracoronary Stenting
• coronary lesions dilated with balloon inflation
• major complication is restenosis (approximately 15% at 6 mo), felt to be due to elastic recoil and neointimal hyperplasia
• majority of patients receive intracoronary stent(s) to prevent restenosis
  ▪ bare metal stent (BMS)
  ▪ drug-eluting stent (DES)
    ▪ coated with antiproliferative drugs (sirolimus, paclitaxel)
    ▪ reduced rate of neointimal hyperplasia and restenosis compared to BMS (5% vs. 20%)
    ▪ complication: late stent thrombosis (5 events per 1000 stents implanted)

Adjunctive Therapies
• ASA and heparin decrease post-procedural complications
• further reduction in ischemic complications has been demonstrated using GPIIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) in coronary angiography and stenting
• following stent implantation
  ▪ dual antiplatelet therapy (ASA and clopidogrel) for 1 mo with BMS or ≥12 mo with DES
  ▪ ASA and prasugrel can be considered for those at increased risk of stent thrombosis

Procedural Complications
• mortality and emergency bypass rates <1%
• nonfatal MI: approximately 2-3%
CORONARY ARTERY BYPASS GRAFT (CABG) SURGERY

- Objective of CABG is complete reperfusion of the myocardium.

**Indications**

- **CABG**
  - ≥50% diameter stenosis in the left main coronary artery
  - ≥70% diameter stenosis in three major coronary arteries
  - ≥70% diameter stenosis in the proximal LAD artery plus one other major coronary artery
  - Survivors of sudden cardiac arrest with presumed ischemia-mediated VT caused by significant (≥70% diameter) stenosis in a major coronary artery

- **Other:**
  - ≥70% diameter stenosis in two major coronary arteries (without proximal LAD disease) and evidence of extensive ischemia
  - ≥70% diameter stenosis in the proximal LAD artery and evidence of extensive ischemia
  - Multivessel CAD in patients with diabetes
  - LV systolic dysfunction (LVEF 35% to 50%) and significant multivessel CAD or proximal LAD stenosis where viable myocardium is present in the region of intended revascularization

- **PCI**
  - UA/NSTEMI if not a CABG candidate
  - STEMI when PCI can be performed more rapidly and safely than CABG

- **CABG or PCI**
  - One or more significant (≥70% diameter) coronary artery stenosis amenable to revascularization and unacceptable angina despite medical therapy

### Table 8. Choice of Revascularization Procedure

<table>
<thead>
<tr>
<th>Procedure</th>
<th>PCI Advantages</th>
<th>CABG Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>Less invasive technique</td>
<td>Greater ability to achieve complete revascularization</td>
</tr>
<tr>
<td></td>
<td>Decreased periprocedural morbidity and mortality</td>
<td>Decreased need for repeated revascularization procedures</td>
</tr>
<tr>
<td></td>
<td>Shorter periprocedural hospitalization</td>
<td></td>
</tr>
<tr>
<td>PCI Indications</td>
<td>Single or double-vessel disease</td>
<td>Triple-vessel or left main disease</td>
</tr>
<tr>
<td></td>
<td>Inability to tolerate surgery</td>
<td>DM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plaque morphology unfavourable for PCI</td>
</tr>
</tbody>
</table>

### Table 9. Conduits for CABG

<table>
<thead>
<tr>
<th>Graft Type</th>
<th>Occlusion/Patency Rate</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saphenous Vein (SVG)</td>
<td>At 10 yr, 50% occluded,</td>
<td>Used when arterial grafts are not available or many grafts are required, such as triple or quadruple bypass</td>
</tr>
<tr>
<td></td>
<td>25% stenotic, 25% angiographically normal</td>
<td></td>
</tr>
<tr>
<td>Left Internal Thoracic/Mammary Artery (LITA/LIMA)</td>
<td>90-95% patency at 15 yr</td>
<td>Most preferred option because of excellent patency</td>
</tr>
<tr>
<td>(LIMA to LAD)</td>
<td></td>
<td>Improved event-free survival (angina, MI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased late cardiac events</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No increase in operative risk</td>
</tr>
<tr>
<td>Right Internal Thoracic/Mammary Artery (RITA/RIMA)</td>
<td>Pedicled RIMA patency comparable to LIMA</td>
<td>Used in bilateral ITA/IMA grafting</td>
</tr>
<tr>
<td></td>
<td>Free RIMA patency less</td>
<td>Patients receiving bilateral ITAs/IMAs have less risk of recurrent angina, late MI, angioplasty</td>
</tr>
<tr>
<td>Radial Artery (free graft)</td>
<td>85-90% patency at 5 yr</td>
<td>Prone to severe vasospasm postoperatively due to muscular wall</td>
</tr>
<tr>
<td>Right Gastroepiploic Artery</td>
<td>80-90% patency at 5 yr</td>
<td>Primarily used as an in situ graft to bypass the RCA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use limited because of the fragile quality of the artery, other technical issues, increased operative time (laparotomy incision) and incisional discomfort with associated ileus</td>
</tr>
<tr>
<td>Complete Arterial Revascularization</td>
<td></td>
<td>For younger patients (&lt; 60 yr of age)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Is preferred due to longer term graft patency</td>
</tr>
<tr>
<td>Redo Bypass Grafting</td>
<td></td>
<td>Operative mortality 2-3 times higher than first operation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10% periprocedural MI rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reoperation undertaken only in symptomatic patients who failed medical therapy and in whom angiography has documented progression of the disease Increased risk with redo-sternotomy secondary to adhesions which may result in laceration to aorta, RV, IMA/ITA and other bypass grafts</td>
</tr>
</tbody>
</table>

### Operative Issues

- Left ventricular (LV) function is an important determinant of outcome of all heart diseases
- Patients with severe LV dysfunction usually have poor prognosis, but surgery can sometimes dramatically improve LV function
- Assess viability of non-functioning myocardial segments in patients with significant LV dysfunction using delayed thallium myocardial imaging, PET scanning or MRI.
Table 10. Risk Factors for CABG Mortality and Morbidity (decreasing order of significance)

<table>
<thead>
<tr>
<th>Risk Factors for CABG Mortality</th>
<th>Risk Factors for CABG Postop Morbidity or Increased Length of Stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency of surgery (emergent or urgent)</td>
<td>Reoperation</td>
</tr>
<tr>
<td>Reoperation</td>
<td>Emergent procedure</td>
</tr>
<tr>
<td>Older age</td>
<td>Preoperative intra-aortic balloon pump (IABP)</td>
</tr>
<tr>
<td>Poor left ventricular function (see below)</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Female gender</td>
<td>CABG + valve surgery</td>
</tr>
<tr>
<td>Left main disease</td>
<td>Older age</td>
</tr>
<tr>
<td>Others include catastrophic conditions (cardiogenic shock, ventricular septal rupture, ongoing CPR), dialysis-dependent renal failure, end-stage COPD, diabetes, cerebrovascular disease, and peripheral vascular disease</td>
<td>Renal dysfunction</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
</tr>
<tr>
<td></td>
<td>DM</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
</tr>
</tbody>
</table>

**Procedural Complications**
- CABG using cardiopulmonary bypass (CPB)
  - stroke and neurocognitive defects (microembolization of gaseous and particulate matter)
  - immunosuppression
  - systemic inflammatory response leading to:
    - myocardial dysfunction
    - renal dysfunction
    - neurological injury
    - respiratory dysfunction
    - coagulopathies

**OFF-PUMP CORONARY ARTERY BYPASS (OPCAB) SURGERY**

**Procedure**
- OPCAB avoids the use of CPB by allowing surgeons to operate on a beating heart
  - stabilization devices (e.g. Genzyme Immobilizer®) hold heart in place allowing operation while positioning devices (Medtronic Octopus® and Starfish® system) allow the surgeon to lift the beating heart to access the lateral and posterior vessels
  - procedure is safe and well tolerated by most patients; however, OPCAB surgery remains technically more demanding

**Indications**
- used in poor candidates for CPB who have: calcified aorta, poor LVEF, severe peripheral vascular disease (PVD), severe COPD, chronic renal failure, coagulopathy, transfusion objections (e.g. Jehovah’s Witness), good target vessels, anterior/lateral wall revascularization, target revascularization in older, sicker patients
- **absolute contraindications**: hemodynamic instability, poor quality target vessels including intramyocardial vessels, diffusely diseased vessels and calcified coronary vessels
- **relative contraindications**: cardiomegaly/CHF, critical left main disease, small distal targets, recent or current acute MI, cardiogenic shock, LVEF <35%

**Outcomes**
- OPCAB decreases in-hospital morbidity (decreased incidence of chest infection, inotropic requirement, supraventricular arrhythmia), blood product transfusion, ICU stay, length of hospitalization, and CK-MB and troponin I levels
- no significant difference in terms of survival at 2 yr, frequency of cardiac events (MI, PCI, CHF, recurrent angina, redo CABG) or medication usage compared to on-pump CABG

**Heart Failure**

### Congestive Heart Failure (CHF)

**Definitions**
- heart failure: a complex clinical syndrome, resulting from almost any cardiac disorder that impairs the ability of the ventricle to fill with or eject blood
- forward heart failure: heart unable to maintain adequate cardiac output to meet demand or is able to do so only by elevating filling pressure
- backward heart failure: heart unable to accommodate venous return resulting in elevated filling pressures and vascular congestion (systemic or pulmonary)
- heart failure can involve left side of heart (left heart failure), right side (right heart failure) or both (biventricular failure) (see Table 11)
- heart failure can also have components of ineffective ventricular filling (diastolic dysfunction) and/or contraction (systolic dysfunction)
- most cases associated with poor cardiac output (low-output heart failure); however, some cases of CHF not due to intrinsic cardiac disease but instead due to increased demand (high-output heart failure)
Pathophysiology

- primary insults (myocyte loss, overload) → pump dysfunction, which leads to:
  - remodeling (dilatation, hypertrophy)
  - neurohumoral activation → necrosis and apoptosis
- both pathways result in further damage (re-starting the cycle), edema, tachycardia, vasoconstriction, congestion
- compensatory response to myocardial stress (perpetuate disease process)
  - increased end-systolic ventricular pressure (pressure overload)
    - e.g. HTN, aortic stenosis → hypertrophy
  - increased end-diastolic ventricular volume (volume overload)
    - e.g. aortic regurgitation → cardiac dilatation
- systemic response to ineffective circulating volume
  - activation of sympathetic nervous and renin-angiotensin-aldosterone systems results in:
    - salt and water retention with intravascular expansion
    - increased heart rate and myocardial contractility
    - increased afterload

Systolic Dysfunction

- impaired myocardial contractile function → decreased LVEF and SV → decreased CO
- findings: apex beat displaced, S3, increased heart size on CXR, decreased LVEF, LV dilatation
- causes:
  - ischemic (e.g. extensive CAD, previous MI)
  - non-ischemic
    - HTN
    - DM
    - alcohol (and other toxins)
    - myocarditis
  - dilated cardiomyopathy (multiple causes – see Dilated Cardiomyopathy, C36)

Heart Failure with Preserved Ejection Fraction (HFPEF)

- previously known as “diastolic dysfunction”
- up to 1/2 of all HF patients have normal systolic function (i.e. normal ejection fraction) and the cause of heart failure is impaired diastolic filling: prevalence higher in older patients
- increased LV filling pressures produce venous congestion upstream (i.e. pulmonary and systemic venous congestion)
- findings: HTN, apex beat sustained, S4, normal-sized heart on CXR, LVH on ECG/echo, normal LVEF
- causes of decreased compliance:
  - transient: ischemia (relaxation of myocardium is active and requires ATP)
  - permanent
    - severe hypertrophy (HTN, aortic stenosis, HCM)
    - restrictive cardiomyopathy (e.g. amyloid)
    - MI

High-Output Heart Failure

- caused by demand for increased cardiac output
- often exacerbates existing heart failure or decompensates a patient with other cardiac pathology
- differential diagnosis: anemia, thiamine deficiency (beriberi), hyperthyroidism, A-V fistula or L-R shunting, Paget's disease, renal disease, hepatic disease

---

**Table 11. Signs and Symptoms of Left vs. Right Heart Failure**

<table>
<thead>
<tr>
<th>Left Failure</th>
<th>Right Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low cardiac output (forward)</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Syncpe</td>
</tr>
<tr>
<td></td>
<td>Systemic hypotension</td>
</tr>
<tr>
<td></td>
<td>Cool extremities</td>
</tr>
<tr>
<td></td>
<td>Slow capillary refill</td>
</tr>
<tr>
<td></td>
<td>Peripheral cyanosis</td>
</tr>
<tr>
<td></td>
<td>Pulsus alternans</td>
</tr>
<tr>
<td></td>
<td>Mitrail regurgitation</td>
</tr>
<tr>
<td>Venous congestion (backward)</td>
<td>Dyspnea, orthopnea, PND</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td>Crackles</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Dichotomies of Heart Failure**

- Forward vs. Backward
- Left-sided vs. Right-sided
- Systolic vs. Diastolic dysfunction
- Low output vs. High output

**Use Ejection Fraction to Grade LV Dysfunction**

- Grade I (EF > 60%) (Normal)
- Grade II (EF = 40-59%)
- Grade III (EF = 21-39%)
- Grade IV (EF < 20%)

**A Validated Clinical and Biochemical Score for the Diagnosis of Acute Heart Failure: the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Acute Heart Failure Score**

Am Heart J 2006;151:48-54

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Possible Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 75 yr</td>
<td>1</td>
</tr>
<tr>
<td>Orthopnea present</td>
<td>2</td>
</tr>
<tr>
<td>Lack of cough</td>
<td>1</td>
</tr>
<tr>
<td>Current loop diuretic use (before presentation)</td>
<td>1</td>
</tr>
<tr>
<td>Rales on lung exam</td>
<td>1</td>
</tr>
<tr>
<td>Lack of fever</td>
<td>2</td>
</tr>
<tr>
<td>Elevated NT-proBNP (&gt; 450 pg/mL if &lt; 50 yr, &gt; 900 pg/mL if &gt; 50 yr)</td>
<td>4</td>
</tr>
<tr>
<td>Intersitial edema on chest x-ray</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
</tr>
</tbody>
</table>

Likelihood of heart failure:

- Law = 0.6
- Intermediate = 6-8
- High = 9-14

---

**New York Heart Association (NYHA) Functional Classification of Heart Failure**

- Class I: ordinary physical activity does not cause symptoms of HF
- Class II: comfortable at rest, ordinary physical activity results in symptoms
- Class III: marked limitation of ordinary activity; less than ordinary physical activity results in symptoms
- Class IV: inability to carry out any physical activity without discomfort; symptoms may be present at rest

---

**Brain natriuretic peptide (BNP) is secreted by ventricles due to LV stretch and wall tension. Cardiomyocytes secrete BNP precursor that is cleaved into proBNP. After secretion into ventricles, proBNP is cleaved into the active C-terminal portion and the inactive NT-proBNP. The above scoring algorithm developed by Bagga et al. is commonly used. A score of <5 has a negative predictive value of 86%, while scores >8 had a sensitivity of 96% and specificity of 84% (P < 0.001) for the diagnosis of acute heart failure.**
Etiologies of Primary Insults
- consider predisposing, precipitating and perpetuating factors

Precipitants of Symptomatic Exacerbations
- consider natural progression of disease vs. new precipitant
- always search for reversible cause
- differential diagnosis can also be organized as follows:
  - new cardiac insult/disease: MI, arrhythmia, valvular disease
  - new demand on CV system: HTN, anemia, thyrotoxicosis, infection, etc.
- failure to take medications as prescribed

Investigations
- identify and assess precipitating factors and treatable causes of CHF
- blood work: CBC, electrolytes (including calcium and magnesium), BUN, creatinine, fasting blood glucose, Hba1c, lipid profile, liver function tests, serum TSH, ± ferritin, BNP, uric acid
- ECG: look for chamber enlargement, arrhythmia, ischemia/infarction
- CXR: cardiomegaly, pleural effusion, redistribution, Kerley B lines, bronchiolar-alveolar cuffing
- echo: LV EF, cardiac dimensions, wall motion abnormalities, valvular disease, pericardial effusion
- radionuclide angiography: LV EF
- myocardial perfusion scintigraphy (thallium or sestamibi SPECT)

Acute Treatment of Pulmonary Edema
- treat acute precipitating factors (e.g. ischemia, arrhythmias)
- L – Lasix® (furosemide) 40-500 mg IV
- M – morphine 2-4 mg IV: decreases anxiety and preload (venodilation)
- N – nitroglycerin: topical/IV/SL
- O – oxygen: in hypoxemic patients
- P – positive airway pressure (CPAP/BiPAP): decreases preload and need for ventilation when appropriate
- P – position: sit patient up with legs hanging down unless patient is hypotensive

in ICU setting or failure of LMNOPP, other interventions may be necessary
- nitroprusside IV
- hydralazine PO
- sympathomimetics
  - dopamine
    - low dose: selective renal vasodilation (high potency D1 agonist)
    - medium dose: inotropic support (medium potency β1 agonist)
    - high dose: increases SVR (low potency β1 agonist), which is undesirable
  - dobutamine
    - selective inotrope (β1 agonist) and arterial vasodilator (β1 antagonist)
  - phosphodiesterase inhibitors (milrinone)
    - inotropic effect and vascular smooth muscle relaxation (decreased SVR), similar to dobutamine
- consider pulmonary artery catheter to monitor pulmonary capillary wedge pressure (PCWP)
  - if patient is unstable or a cardiac etiology is uncertain (PCWP >18 indicates likely cardiac etiology)
- mechanical ventilation as needed
- rarely used, but potentially life-saving measures:
  - intra-aortic balloon pump (IABP)
  - left or right ventricular assist device (LVAD/RVAD)
  - cardiac transplant

Long Term Management
- note that most evidence-based management applies to HFREF
- priorities in HFPEF focus on controlling systolic and diastolic hypertension, as a risk factor
- control measure
- priorities in HFREF focus on controlling systolic and diastolic hypertension, as a risk factor
- control measure

Conservative Measures
- symptomatic measures: oxygen in hospital, bedrest, elevate the head of bed
- lifestyle measures: diet, exercise, DM control, smoking cessation, decrease alcohol consumption, patient education, sodium and fluid restriction
- multidisciplinary heart failure clinics: for management of individuals at higher risk, or with recent hospitalization

Toronto Notes 2014

Five Most Common Causes of CHF
- CAD (60-70%)
- HTN
- Idiopathic (often dilated cardiomyopathy)
- Valvular (e.g. AS, AR and MR)
- Alcohol (dilated cardiomyopathy)

Precipitants of Heart Failure
HEART FAILED
Hypertension (common)
Endocarditis/environment (e.g. heat wave)
Anemia
Rheumatic heart disease and other valvular disease
Thyrotoxicosis
Failure to take meds (very common)
Arrhythmia (common)
Infection/Ischemia/Infarction (common)
Lung problems (PE, pneumonia, COPD)
Endocrine (pheochromocytoma, hyperaldosteronism)
Diabetic indiscritions (common)

Various clinical guidelines, including the Acute Heart Failure Syndromes AHA 2010 Guidelines, and the 2012 Canadian Cardiovascular Society (CCS) Heart Failure Management Guidelines, indicate the current approach of acute heart failure exacerbation may be too homogenous. The CCS guidelines in particular offer several suggestions, including cautious use of oxygen in normoxic patients due to the possible risk of causing increased systemic resistance and reduced cardiac output, reserving the use of non-invasive ventilation for patients not responding to medical therapy, as well as preference for high dose rather than low dose diuretic therapy.

The most common cause of right heart failure is left heart failure.

Measuring NT-pro BNP
BNP is secreted by ventricles due to LV stretch and wall tension.
Cardiomyocytes secrete BNP precursor that is cleaved into proBNP. After secretion into ventricles proBNP is cleaved into the active C-terminal portion and the inactive NT-proBNP portion.

<table>
<thead>
<tr>
<th>Age</th>
<th>NT-proBNP levels (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>&lt; 450</td>
</tr>
<tr>
<td>50-75</td>
<td>&gt; 900</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>&gt; 1800</td>
</tr>
</tbody>
</table>

Limitations: Age, body habitus, renal function, pulmonary embolism
Pharmacological Therapy

1. Vasodilators
   - ACEI: standard of care – slows progression of LV dysfunction and improves survival
     - all symptomatic patients functional class II-IV
     - all asymptomatic patients with LVEF <40%
   - post-MI
   - angiotensin II receptor blockers (ARBs)
     - second-line to ACEI if not tolerated, or as adjunct to ACEI if β-blockers not tolerated
     - – hydralazine and nitrates
     - second-line to ACEI, decrease in mortality not as great as with ACEI
   - may consider in acute renal failure until creatinine stabilizes

2. β-blockers: slow progression and improve survival
   - class I-III with LVEF <40%
   - stable class IV patients
   - note: should be used cautiously, titrate slowly because may initially worsen CHF

3. Diuretics: symptom control, management of fluid overload
   - furosemide (40-500 mg daily) for potent diuresis
   - metolazone may be used with furosemide to increase diuresis
   - furosemide, metolazone, and thiazides oppose the hyperkalemia that can be induced by
     β-blockers, ACEI, ARBs, and aldosterone antagonists

4. Aldosterone antagonists: mortality benefit in severe CHF
   - spironolactone for class IIB and IV CHF already on ACEI and loop diuretic
   - eplerenone may be considered if intolerable endocrine side effects
   - note: potential for life threatening hyperkalemia
     - monitor K⁺ after initiation and avoid if Cr >220 μmol/L or K⁺ >5.2 mmol/L

5. Inotropes: digoxin improves symptoms and decreases hospitalizations, no effect on mortality
   - indications: patient in sinus rhythm and symptomatic on ACEI, or CHF and AFib
   - patients on digitalis glycosides may worsen if these are withdrawn

6. Antiarrhythmic drugs: for use in CHF with arrhythmia
   - can use amiodarone, β-blocker, or digoxin

7. Anticoagulants: warfarin for prevention of thromboembolic events
   - prior thromboembolic event or AFib, presence of LV thrombus on echo
   - possible benefit in other patients with LVEF <30% (controversial)

Procedural Interventions

- resynchronization therapy: symptomatic improvement with biventricular pacemaker
  - consider if QRS >130 msec, LVEF <35%, and severe symptoms despite optimal therapy
  - greatest benefit likely with marked LV enlargement, mitral regurgitation, QRS >150 msec,
    high diuretic requirement
- ICD: mortality benefit in 1st prevention of sudden cardiac death
  - prior MI, optimal medical therapy, LVEF <30%, clinically stable
  - prior MI, non-sustained VT, LVEF 30-40%, EPS inducible VT
- LVAD/RVAD (see Ventricular Assist Devices, C34)
- cardiac transplantation (see Cardiac Transplantation, C34)
- valve repair if patient is surgical candidate and has significant valve disease contributing to CHF
  (see Valvular Heart Disease, C38)
Sleep-Disordered Breathing

- 45-55% of patients with CHF have sleep disturbances, including Cheyne-Stokes breathing and sleep apnea (central or obstructive)
- associated with a worse prognosis and greater LV dysfunction
- nasal continuous positive airway pressure (CPAP) is effective in treating Cheyne-Stokes respiration/sleep apnea with improvement in cardiac function and symptoms

Cardiac Transplantation

- treatment for end-stage heart disease; due to ischemic or non-ischemic cardiomyopathy
- worldwide 1-yr survival is 85-90%, 5-yr survival about 60%, annual mortality rate of 4%
- matching is according to blood type, body size and weight (should be within 25%), and HLA tissue matching (if time allows)

Indications for Surgery

- severe cardiac disability despite maximal medical therapy (recurrent hospitalizations for CHF, NYHA III or IV, peak metabolic oxygen consumption <14 mL/kg/min in absence of β-blocker)
- symptomatic cardiac ischemia refractory to conventional treatment (unstable angina not amenable to CABG or angioplasty with LVEF <30%; recurrent, symptomatic ventricular arrhythmias)
- exclusion of all surgical alternatives to cardiac transplantation

Prerequisites

- emotionally stable with social support
- medically compliant and motivated
- relative contraindications: incurable malignancy, major systemic illness, irreversible major organ disease (e.g. renal, hepatic), active systemic infection (e.g. Hep C, HIV), obesity, irreversible pulmonary HTN (pulmonary vascular resistance [PVR] >6 Wood units), severe COPD (FEV1 ≤1 L) or active drug addiction or alcoholism

Complications

- rejection
  - common, less than 5% have serious hemodynamic compromise
  - gold standard to detect rejection: endomyocardial biopsy
  - no noninvasive tests to detect rejection
- infection
  - leading cause of morbidity and mortality after cardiac transplantation
- allograft CAD
  - approximately 50% develop graft CAD within 5 yr of transplantation
  - most common cause of late death following transplantation
- malignancy
  - develops in 15% of cardiac transplant recipients due to immunosuppressive medication
  - second most common cause of late death following transplantation
- cutaneous neoplasms most common, followed by non-Hodgkin’s lymphoma and lung cancer
- immunosuppressive medication side effects (prednisone, cyclosporine, tacrolimus, sirolimus)

Ventricular Assist Devices (VADs)

- work to unload the ventricle while maintaining output; also results in decreased myocardial oxygen consumption permitting recovery of the myocardium that is not irreversibly injured
- can support the left (LVAD), right (RVAD), or both ventricles (BiVAD)
- indications
  - bridge to transplantation
  - postoperative mechanical support when unable to separate from cardiopulmonary bypass despite inotropic and intra-aortic balloon pump (IABP) support
  - IABP is a catheter based device inserted into the aorta via the femoral artery that decreases myocardial O2 demand and increases blood flow to coronary arteries
  - postoperative cardiogenic shock

Influence of Ejection Fraction on Cardiovascular Outcomes in a Broad Spectrum of Heart Failure Patients

Methods: 7599 patients from the CHARM study (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; RCT comparing placebo vs. candesartan in patients with NYHA class II to IV). Compared LVEF to cardiovascular outcomes and causes of death.

Results: All-cause mortality increased by 39% per 10% reduction in LVEF below 45% (Hazard ratio 1.39, 95%CI 1.32-1.46). For LVEF>45%, ejection fraction does not further contribute to assessment of cardiovascular risk in HF patients.

Conclusions: At LVEF<45%, lower ejection fractions were associated with poorer cardiovascular outcomes.

<table>
<thead>
<tr>
<th>LVEF</th>
<th>CHF Hospitalization</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤22%</td>
<td>14.9%</td>
<td>15.4%</td>
</tr>
<tr>
<td>23-32%</td>
<td>10.9%</td>
<td>10.8%</td>
</tr>
<tr>
<td>33-42%</td>
<td>7.2%</td>
<td>7.4%</td>
</tr>
<tr>
<td>43-52%</td>
<td>5.7%</td>
<td>5.2%</td>
</tr>
<tr>
<td>&gt;52%</td>
<td>6.9%</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

Higher New York Heart Association Classes and Increased Mortality and Hospitalization in Patients with Heart Failure and Preserved Left Ventricular Function

Methods: Retrospective follow-up study (median 30.5 mo) of 988 patients with heart failure with ejection fraction >45%. Estimated risks of various outcomes using Cox proportional hazard models.

Results: Adjusted hazard ratio for all-cause mortality for NYHA class II, III, IV patients was 1.54, 2.16, and 0.46, respectively. Adjusted hazard ratio for all-cause hospitalization for NYHA class II, III, IV patients was 1.33, 1.71, and 2.4, respectively.

Conclusions: Higher NYHA classes were associated with poorer outcomes in patients with heart failure and preserved systolic function.

<table>
<thead>
<tr>
<th>NYHA</th>
<th>Proportion of All-Cause Hospitalization</th>
<th>Proportion of All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>60.7%</td>
<td>14.3%</td>
</tr>
<tr>
<td>II</td>
<td>65.2%</td>
<td>21.3%</td>
</tr>
<tr>
<td>III</td>
<td>77.7%</td>
<td>35.9%</td>
</tr>
<tr>
<td>IV</td>
<td>75.0%</td>
<td>58.3%</td>
</tr>
</tbody>
</table>

Effects of Donor Pre-treatment with Dopamine on Survival After Heart Transplantation: A Cohort Study of Heart Transplant Recipients Nested in a Randomized Controlled Multicenter Trial

Purpose: To establish the association between NYHA class and outcomes with heart failure and preserved systolic function.

Methods: Retrospective follow-up study (median 38.5 mo) of 988 patients with heart failure.

Results: Adjusted hazard ratio for all-cause mortality >45%. Risk peaks early during the first few months after transplantation and then declines to a low persistence rate.

Conclusions: Higher NYHA classes were associated with poorer outcomes in patients with heart failure and preserved systolic function.
Myocardial Disease

Definition of Cardiomyopathy
- intrinsic or primary myocardial disease not secondary to congenital, hypertensive, coronary, valvular, or pericardial disease
- functional classification: dilated, hypertrophic, or restrictive
- LV dysfunction 2º to MI often termed “ischemic cardiomyopathy”, is not a true cardiomyopathy (i.e. primary myocardial disorder) since the primary pathology is obstructive CAD

Table 12. Summary Table for CHF and Myocardial Disease

<table>
<thead>
<tr>
<th>SYSTOLIC HEART FAILURE</th>
<th>Secondary Causes</th>
<th>DIASTOLIC HEART FAILURE</th>
<th>Restricted Cardiomyopathy</th>
<th>Secondary Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated Cardiomyopathy</td>
<td>CAD, MI, DM, valvular (e.g. AR, MR)</td>
<td>Hypertrrophic Cardiomyopathy</td>
<td>Amyloidosis,</td>
<td>HTN, DM, valvular (e.g. AS), post-MI, transiently by ischemia, etc.</td>
</tr>
<tr>
<td>Idiopathic, infectious (e.g. myocarditis), alcohol, familial, collagen vascular disease, etc.</td>
<td>Genetic disorder affecting cardiac sarcomeres (most common cause of sudden cardiac death in young athletes)</td>
<td>sarcoïdosis, scleroderma, hemochromatosis, Fabry’s, Pompe’s Disease, Leofler’s, etc.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Myocarditis

Definition
- inflammatory process involving the myocardium ranging from acute to chronic; an important cause of dilated cardiomyopathy

Etiology
- idiopathic
- infectious
  - viral: S. aureus, C. perfringens, C. diphtheriae, Mycoplasma, Rickettsia
  - fungi
  - spirochetal (Lyme disease – Borrelia burgdorferi)
  - Chagas disease (Trypanosoma cruzi), toxoplasmosis
- toxic: catecholamines, chemotherapy, cocaine
- hypersensitivity/eosinophilic: drugs (antibiotics, diuretics, lithium, clozapine), insect/snake bites
- systemic diseases: collagen vascular diseases (SLE, RA, others), sarcoidosis, autoimmune
- other: giant cell myocarditis, acute rheumatic fever

Signs and Symptoms
- constitutional symptoms
- acute CHF
- chest pain – due to pericarditis or cardiac ischemia
- arrhythmias
- systemic or pulmonary emboli
- sudden death

Investigations
- ECG: non-specific ST-T changes ± conduction defects
- bloodwork
  - increased CK, troponin, LDH, and AST with acute myocardial necrosis ± increased WBC, ESR, ANA, rheumatoid factor, complement levels
  - blood culture, viral titres and cold agglutinins for Mycoplasma
- CXR: enlarged cardiac silhouette
- echo: dilated, hypokinetic chambers, segmental wall motion abnormalities
- myocardial biopsy

Management
- supportive care
- restrict physical activity
- treat CHF
- treat arrhythmias
- anticoagulation
- treat underlying cause if possible

Prognosis
- usually self-limited and often unrecognized, many recover
- sudden death in young adults
- may progress to dilated cardiomyopathy
Dilated Cardiomyopathy (DCM)

Definition
- unexplained dilation and impaired systolic function of one or both ventricles

Etiology
- idiopathic (presumed viral or idiopathic) ~50% of DCM
- alcohol
- familial/genetic
- uncontrolled tachycardia (e.g. persistent rapid AFib)
- collagen vascular disease: SLE, polyarteritis nodosa, dermatomyositis, progressive systemic sclerosis
- infectious: viral (coxsackie B, HIV), Chagas disease, Lyme disease, Rickettsial diseases, acute rheumatic fever, toxoplasmosis
- neuromuscular disease: Duchenne muscular dystrophy, myotonic dystrophy, Friedreich's ataxia
- metabolic: uremia, nutritional deficiency (thiamine, selenium, carnitine)
- endocrine: hyper/hypothyroidism, DM, pheochromocytoma
- peripartum
- toxic: cocaine, heroin, organic solvents
- drugs: chemotherapies (doxorubicin, cyclophosphamide), antiretrovirals, chloroquine, clozapine, TCA
- radiation

Signs and Symptoms
- may present as:
  - CHF
  - systemic or pulmonary emboli
  - arrhythmias
  - sudden death (major cause of mortality due to fatal arrhythmia)

Investigations
- bloodwork: CBC, electrolytes, Cr, bicarbonate, BNP, CK, troponin, LFTs, TSH, TIBC
- ECG: variable ST-T wave abnormalities, poor R wave progression, conduction defects (e.g. BBB), arrhythmias (non-sustained VT)
- CXR: global cardiomegaly (globular heart), signs of CHF, pleural effusion
- echo: chamber enlargement, global hypokinesis, depressed LVEF, MR and TR, mural thrombi
- endomyocardial biopsy: not routine, used to rule out a treatable cause
- coronary angiography: in selected patients to exclude ischemic heart disease

Management
- treat underlying disease: e.g. abstinence from alcohol
- treat CHF: see Heart Failure, C30
- thromboembolism prophylaxis: anticoagulation with warfarin
- indicated for: AFib, history of thromboembolism or documented thrombus
- LVEF <30% (controversial)
- treat symptomatic or serious arrhythmias
- immunize against influenza and S. pneumoniae
- consider surgical options (e.g. LVAD, transplant, volume reduction surgery) in appropriate candidates with severe, drug refractory disease
- consider ICD among patients with a LVEF <30%

Prognosis
- depends on etiology
- better with reversible underlying cause, worst with infiltrative diseases, HIV, drug-induced
- cause of death usually CHF (due to pump failure) or sudden death 2nd to ventricular arrhythmias
- systemic emboli are significant source of morbidity
- 20% mortality in 1st yr, 10% per year after

Hypertrophic Cardiomyopathy (HCM)

- see 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy for details

Definition
- defined as unexplained ventricular hypertrophy
- various patterns of HCM are classified, but most causes involve pattern of septal hypertrophy

Etiology and Pathophysiology
- histopathologic features include myocyte disarray, myocyte hypertrophy, and interstitial fibrosis
- cause is felt to be a genetic defect involving one of the cardiac sarcomeric proteins (>400 mutations associated with autosomal dominant inheritance, incomplete penetrance)
- prevalence of 1/500-1/1000 in general population
- generally presents in early adulthood
Hemodynamic Classification
- hypertrophic obstructive cardiomyopathy (HOCM): dynamic LV outflow tract (LVOT) obstruction, either at rest or with provocation, defined as LVOT gradient of at least 30 mmHg
- non-obstructive HCM: no LVOT obstruction
- many patients have diastolic dysfunction (impaired ventricular filling secondary to LV hypertrophy which decreases compliance)

Signs and Symptoms
- clinical manifestations: asymptomatic (common, therefore screening is important), SOB on exertion, angina, presyncope/syncope (due to LV outflow obstruction or arrhythmia), CHF, arrhythmias, SCD
- pulses: rapid upstroke, "spike and dome" pattern in carotid pulse (in HCM with outflow tract obstruction)
- precordial palpation: PMI localized, sustained, double impulse, ‘triple ripple’ (triple apical impulse in HOCM), LV lift
- precordial auscultation: normal or paradoxically split S2, S4, harsh systolic diamond-shaped murmur at LLSB or apex, enhanced by squat to standing or Valsalva (murmur secondary to LVOT obstruction as compared to AS); often with pansystolic murmur due to mitral regurgitation

Investigations
- ECG/Holter monitor: LVH, high voltages across precordium, prominent Q waves (lead I, aVL, V5, V6), tall R wave in V1, P wave abnormalities
- transthoracic echocardiography and echo-Doppler study: asymmetric septal hypertrophy (less commonly apical), systolic anterior motion (SAM) of mitral valve and MR; LVOT gradient can be estimated by Doppler measurement
- genetic cardiac resonance magnetic resonance imaging indicated when echocardiography is inconclusive for diagnosis
- cardiac catheterization (only when patient being considered for invasive therapy)

Management
- avoid factors which increase obstruction (e.g. volume depletion)
- avoidance of all competitive sports
- treatment of obstructive HCM
  - medical agents: β-blockers, verapamil, phenylephrine, disopyramide
  - avoid nitrates, diuretics and ACEI as they increase LVOT gradient and worsen symptoms
- patients with drug-refractory symptoms
  - surgical myectomy
  - ICD placement
  - septal ethanol ablation
  - dual chamber pacing (rarely done)
- treatment of ventricular arrhythmias: amiodarone or ICD
- first-degree relatives of patients with HCM should be screened annually during adolescence (physical, ECG, 2D echo), then serially every 5 yr during adulthood
- first-degree genetic testing and family screening
- screening for sudden cardiac death: VF, VT, family history, unexplained syncope, maximal LV wall thickness ≥30 mm

Prognosis
- potential complications: AFib, VT, CHF, sudden cardiac death (1% risk/yr; most common cause of SCD in young athletes)
  - major risk factors for sudden death (consider ICD placement)
  - history of survived cardiac arrest/sustained VT
  - family history of multiple premature sudden deaths
  - other factors associated with increased risk of sudden cardiac death
  - syncope (presumed to be arrhythmic in origin)
  - non-sustained VT on ambulatory monitoring
  - marked ventricular hypertrophy (maximum wall thickness ≥30 mm)
  - abnormal BP in response to exercise (in patients <40 yr old with HCM)

Restrictive Cardiomyopathy (RCM)

Definition
- impaired ventricular filling with preserved systolic function in a non-dilated, non-hypertrophied ventricle secondary to factors that decrease myocardial compliance (fibrosis and/or infiltration)

Etiology
- infiltrative: amyloidosis, sarcoidosis
- non-infiltrative: scleroderma, idiopathic myocardial fibrosis
- storage diseases: hemochromatosis, Fabry’s disease, Gaucher’s disease, glycogen storage diseases
- endomyocardial
  - endomyocardial fibrosis, Loeffler’s endocarditis or eosinophilic endomyocardial disease
  - radiation heart disease
- carcinoid syndrome (may have associated tricuspid valve or pulmonary valve dysfunction)

RCM vs. Constrictive Pericarditis (CP)
- Present similarly but CP is treatable with surgery.
Clinical Manifestations
• CHF (usually with preserved LV systolic function), arrhythmias
• elevated JVP with prominent x and y descents, Kussmaul’s sign
• S3, S4, MR, TR
• thromboembolic events

Investigations
• ECG: low voltage, non-specific, diffuse ST-T wave changes ± non-ischemic Q waves
• CXR: mild cardiac enlargement
• echo: LAE, RAE; specific Doppler findings with no significant respiratory variation
• cardiac catheterization: increased end-diastolic ventricular pressures
• endomyocardial biopsy: to determine etiology (especially for infiltrative RCM)

Management
• exclude constrictive pericarditis
• treat underlying disease: control HR, anticoagulate if AFib
• supportive care and treatment for CHF, arrhythmias
• heart transplant: might be considered for CHF refractory to medical therapy

Prognosis
• depends on etiology

Valvular Heart Disease


Infective Endocarditis (IE)

• see Infectious Diseases, ID17
• American Heart Association (AHA) 2007 guidelines recommend IE prophylaxis
  • only for patients with:
    • prosthetic valve material
    • past history of IE
    • certain types of congenital heart disease
    • cardiac transplant recipients who develop valvulopathy
  • only for the following procedures:
    • dental
    • respiratory tract
    • procedures on infected skin/skin structures/MSK structures
    • not GI/GU procedures specifically

Rheumatic Fever

• see Pediatrics, P61

Prognosis
• acute complications: myocardiitis (DCM/CHF), conduction abnormalities (sinus tachycardia, AFib), valvulitis (acute MR), acute pericarditis (not constrictive pericarditis)
• chronic complications: rheumatic valvular heart disease – fibrous thickening, adhesion, calcification of valve leaflets resulting in stenosis/regurgitation, increased risk of IE ± thromboembolism
• onset of symptoms usually after 10-20-yr latency from acute carditis of rheumatic fever
• mitral valve most commonly affected

Choice of Valve Prosthesis

Table 13. Mechanical Valve vs. Bioprosthetic Valve

<table>
<thead>
<tr>
<th>Mechanical Valve</th>
<th>Bioprosthetic Valve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good durability</td>
<td>Limited-term durability (mitral &lt; aortic)</td>
</tr>
<tr>
<td>Less preferred in small aortic root sizes</td>
<td>Good flow in small aortic root sizes</td>
</tr>
<tr>
<td>Increased risk of thromboembolism (1-3%/yr): requires long-term anticoagulation with coumadin</td>
<td>Decreased risk of thromboembolism: long-term anticoagulation not needed for aortic valves</td>
</tr>
<tr>
<td>Target INR</td>
<td>Some recommendation for limited anticoagulation for mitral valves</td>
</tr>
<tr>
<td>Aortic valves: 2.0-3.0 (mean 2.5)</td>
<td>Decreased risk of hemorrhage</td>
</tr>
<tr>
<td>Mitral valves: 2.5-3.5 (mean 3.0)</td>
<td>Increased risk of hemorrhage: 1-2%/yr</td>
</tr>
</tbody>
</table>

A Bedside Clinical Prediction Rule for Detecting Moderate or Severe Aortic Stenosis


Study Design: Blinded cross sectional study with 124 patients of an ambulatory cardiology clinic. Patients were examined for: 1) murmur over the right clavicle 2) murmur loudest at second right intercostal space 3) reduced intensity of S2 4) reduced volume of the carotid pulse 5) delayed carotid upstroke.

Methods: Patients were examined by blinded investigators and the clinical examination findings were compared to findings on subsequent echocardiography. Moderate to severe aortic stenosis was defined as a valve area < 1.2 cm² or a peak intensity gradient of > 2.5 mHg.

Results: Absence of a murmur over the right clavicle ruled out aortic stenosis while presence of ≥ 3 of the 4 associated symptoms ruled in aortic stenosis (LR = 40).

Conclusions: Bedside techniques can accurately rule in and rule out moderate to severe aortic stenosis.
## Summary of Valvular Disease

### Table 14. Valvular Heart Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Etiology</th>
<th>Definition</th>
<th>Pathophysiology</th>
<th>Symptoms</th>
<th>Physical Exam</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Surgical Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aortic Stenosis (AS)</strong></td>
<td>Congenital (bicuspid, unicuspid valve), calcification (wear and tear), rheumatic disease</td>
<td>Normal aortic valve area = 3-4 cm²</td>
<td>Reduced valve area, pressure gradient, LVH, reduced LV function</td>
<td>Asymptomatic: serial echos, avoid exertion</td>
<td>Physical Exam: narrow pulse pressure, brachial-radial delay, pulsus parvus et tardus, sustained PMI</td>
<td>ECG: LVH and strain, LBBB, LAE, AFib</td>
<td>Symptomatic: decrease preload (diuretics), decrease afterload (ACEI)</td>
<td>Valve replacement: aortic valve replacement and trileaflet valve</td>
</tr>
<tr>
<td><strong>Mitral Stenosis (MS)</strong></td>
<td>Rheumatic disease most common cause, congenital (rare)</td>
<td>Severe MS is mitral valve area (MVA) &lt; 1.2 cm²</td>
<td>MS → fixed CO and LAE → increased LA pressure → pulmonary vascular resistance and CHF, worse with Afib (no atrial kick), tachycardia (decreased atrial emptying time) and pregnancy (increased preload)</td>
<td>Physical Exam: Aortic root replacement (Bentall procedure): Valve repair: very limited role</td>
<td>Physical Exam: Auscultation: crescendo-decrescendo SEM radiating to R clavicle and carotid, musical quality at apex (Gallavardin phenomenon), S4, soft S2 with paradoxical splitting, S3 (late)</td>
<td>ECG: LVH, LAE, CHF</td>
<td>Surgery if: NYHA class III-IV CHF; LV dilatation and/or LVEF &lt;50% with/without symptoms</td>
<td>Valve replacement: most patients</td>
</tr>
<tr>
<td><strong>Aortic Regurgitation (AR)</strong></td>
<td>Supravalvular: aortic root disease (Marfan’s, atherosclerosis and dissecting aneurysm, connective tissue disease)</td>
<td>Valve: congenital (bicuspid aortic valve, large VSD), IE</td>
<td>Volume overload → LV dilatation → increased SV, high SBP and low dBP → increased wall tension → pressure overload → LVH (low dBP → decreased coronary perfusion)</td>
<td>Physical Exam: Waterhammer pulse, bisferiens pulse, femoral-brachial SBP &gt; 20 (Hill’s test wide pulse pressure), hyperdynamic apex, displaced PMI, heaving apex</td>
<td>Physical Exam: Auscultation: early diastolic diastolic murmur at LLSB (cusp pathology) or RLSB (aortic root pathology), best heard sitting, leaning forward, on full expiration, soft S1, absent S2, S3 (late)</td>
<td>ECG: LVH, LAE, Aortic root dilatation</td>
<td>Surgery if: NYHA class III-IV CHF; LV dilatation and/or LVEF &lt;50% with/without symptoms</td>
<td>Valve repair: very limited role</td>
</tr>
<tr>
<td><strong>Mitral Regurgitation (MR)</strong></td>
<td>Volume overload → LV diastolic → increased SV, high SBP and low dBP → increased wall tension → pressure overload → LVH (low dBP → decreased coronary perfusion)</td>
<td>Acute Onset: IE, aortic dissection, trauma, failed prosthetic valve</td>
<td><strong>Pathophysiology</strong></td>
<td><strong>Symptoms</strong></td>
<td><strong>Investigations</strong></td>
<td><strong>Treatment</strong></td>
<td><strong>Surgical Options</strong></td>
<td><strong>Interventional Options</strong></td>
</tr>
<tr>
<td><strong>Summary of Valvular Disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 14. Valvular Heart Disease

- **Aortic Stenosis (AS)**
- **Mitral Stenosis (MS)**
- **Aortic Regurgitation (AR)**
- **Mitral Regurgitation (MR)**

### Aortic Stenosis (AS)
- **Etiology**
  - Congenital (bicuspid, unicuspid valve), calcification (wear and tear), rheumatic disease
- **Definition**
  - Normal aortic valve area = 3-4 cm²
- **Pathophysiology**
  - MS → fixed CO and LAE → increased LA pressure → pulmonary vascular resistance and CHF, worse with Afib (no atrial kick), tachycardia (decreased atrial emptying time) and pregnancy (increased preload)
- **Symptoms**
  - Exertional angina, syncope, dyspnea, PND, orthopnea, peripheral edema
- **Physical Exam**
  - Narrow pulse pressure, brachial-radial delay, pulsus parvus et tardus, sustained PMI
- **Investigations**
  - ECG: LVH and strain, LBBB, LAE, AFib
  - CXR: LVH, LAE, aortic root dilatation
  - Echo: reduced valve area, pressure gradient, LVH, reduced LV function
- **Treatment**
  - Asymptomatic: serial echos, avoid exertion
  - Symptomatic: avoid nitrates/arterial dilators and ACEI in severe AS
- **Surgical Options**
  - Valve replacement: aortic valve replacement and trileaflet valve
  - Prior to pregnancy (if AS significant) and CHF; worse with AFib (no atrial kick), tachycardia (decreased atrial emptying time)
- **Interventional Options**
  - Percutaneous valve replacement (transfemoral or transapical approach) is an option in selected patients who are not considered good candidates for surgery

### Mitral Stenosis (MS)
- **Etiology**
  - Rheumatic disease most common cause, congenital (rare)
- **Definition**
  - Severe MS is mitral valve area (MVA) < 1.2 cm²
- **Pathophysiology**
  - MS → fixed CO and LAE → increased LA pressure → pulmonary vascular resistance and CHF, worse with Afib (no atrial kick), tachycardia (decreased atrial emptying time) and pregnancy (increased preload)
- **Symptoms**
  - SOB on exertion, orthopnea, fatigue, palpitations, peripheral edema, malar flush, pinched and blue facies (severe MS)
- **Physical Exam**
  - AFib, no "a" wave on JVP, left parasternal lift, displaced hyperdynamic apex, left parasternal lift, apical thrill
- **Investigations**
  - ECG: NSR/Afib, LAE (P mitrale), RVH, RAD
  - CXR: LVH, LAE, CHF, mitral valve calcification
- **Treatment**
  - Avoid exertion, fever (increased LA pressure), treat Afib and CHF, increase diastolic filling time (β-blockers, digitalis)
  - Surgery if: NYHA class III-IV CHF and failure of medical therapy

### Aortic Regurgitation (AR)
- **Etiology**
  - Supravalvular: aortic root disease (Marfan’s, atherosclerosis and dissecting aneurysm, connective tissue disease)
- **Definition**
  - Valve: congenital (bicuspid aortic valve, large VSD), IE
- **Pathophysiology**
  - Volume overload → LV dilatation → increased SV, high SBP and low dBP → increased wall tension → pressure overload → LVH (low dBP → decreased coronary perfusion)
- **Symptoms**
  - Usually only becomes symptomatic late in disease when LV failure develops
- **Physical Exam**
  - Waterhammer pulse, bisferiens pulse, femoral-brachial SBP > 20 (Hill’s test wide pulse pressure), hyperdynamic apex, displaced PMI, heaving apex
- **Investigations**
  - ECG: LVH, LAE, Aortic root dilatation
  - CXR: LVH, LAE, aortic root dilatation
- **Treatment**
  - Asymptomatic: serial echos, afterload reduction (e.g. ACEI, nifedipine, hydralazine)
  - Symptomatic: avoid exertion, treat CHF
  - Surgery if: NYHA class III-IV CHF; LV dilatation and/or LVEF <50% with/without symptoms
- **Surgical Options**
  - Valve replacement: most patients
  - Valve repair: very limited role
  - Aortic root replacement (Bentall procedure): when ascending aortic aneurysm present, valvular conduit used

### Mitral Regurgitation (MR)
- **Etiology**
  - Mitral valve prolapse, congenital cleft leaflets, LV dilatation/aneurysm (CHF, DCM, myxomatosis), IE abscess, Marfan’s syndrome, HOCM, acute MI, myxoma, mitral valve annulus calcification, chordae/papillary muscle trauma/trauma/ischemia/rupture (acute), rheumatic disease
- **Pathophysiology**
  - Reduced CO → increased LV and LA pressure → LV and LA dilatation → CHF and pulmonary HTN
- **Symptoms**
  - Dyspnea, PND, orthopnea, palpitations, peripheral edema
- **Physical Exam**
  - Displaced hyperdynamic apex, left parasternal lift, apical thrill
- **Investigations**
  - ECG: LAE, LVH, pulmonary venous HTN
  - CXR: LVH, LAE, pulmonary venous HTN
- **Treatment**
  - Asymptomatic: serial echos
  - Symptomatic: decrease preload (diuretics), decrease afterload (ACEI) for severe MR and poor surgical candidates; stabilize acute MR with vasodilators before surgery
  - Surgery if: acute MR with CHF, papillary muscle rupture, NYHA class III-IV CHF, AF; increasing LV size or worsening LV function, earlier surgery if valve repairable (>90% likelihood) and patient is low-risk for surgery
  - Surgical Options
  - Valve repair: >75% of pts with MR and myxomatous mitral valve prolapse – annuloplasty rings, leaflet repair, chordae transfers/shorten/replacement
  - Valve replacement: failure of repair, heavily calcified annulus
  - Advantage of repair: low rate of endocarditis, no anticoagulation, less chance of re-operation
Table 14. Valvular Heart Disease (continued)

### Tricuspid Stenosis (TS)

**Etiology**
Rheumatic disease, congenital, carcinoid syndrome, fibroelastosis; usually accompanied by MS

**Pathophysiology**
Increased RA pressure → right heart failure → decreased CO and fixed on exertion

**Symptoms**
Peripheral edema, fatigue, palpitations

**Physical Exam**
Prominent "s" waves in JVP, +ve abdominojugular reflex, Kussmaul’s sign, diastolic rumble 4th left intercostal space

**Investigations**
ECG: normal, RAE, RVH
CXR: prominent pulmonary arteries if pulmonary HTN; enlarged RV

**Treatment**
Preload reduction (diuretics), slow HR
Surgery if: only if other surgery required (e.g. mitral valve replacement)

**Surgical Options**
- Valve Replacement:
  - if severely diseased valve
  - bioprosthesis preferred

### Pulmonary Stenosis (PS)

**Etiology**
Usually congenital, rheumatic disease (rare), carcinoid syndrome

**Pathophysiology**
Increased RV pressure → RV hypertrophy → right heart failure

**Symptoms**
Chest pain, syncope, fatigue, peripheral edema

**Physical Exam**
Systolic murmur at 2nd left intercostal space accentuated by inspiration, pulmonary ejection click, right-sided S4

**Investigations**
ECG: RVH
CXR: prominent pulmonary arteries enlarged RV
Echo: diagnostic

**Treatment**
Balloon valvuloplasty if severe symptoms

**Surgical Options**
Percutaneous or open balloon valvuloplasty

### Tricuspid Regurgitation (TR)

**Etiology**
RV dilatation, IE (partially due to IV drug use), rheumatic disease, congenital (Ebstein anomaly), carcinoid

**Pathophysiology**
RV dilatation → TR → further RV dilatation → right heart failure

**Symptoms**
Peripheral edema, fatigue, palpitations

**Physical Exam**
"cv" waves in JVP, +ve abdominojugular reflux, Kussmaul’s sign, holosystolic murmur at LLSB accentuated by inspiration, left parasternal lift

**Investigations**
ECG: RAE, RVH, AFib
CXR: RAE, RV enlargement
Echo: diagnostic

**Treatment**
Preload reduction (diuretics)
Surgery if: only if other surgery required (e.g. mitral valve replacement)

**Surgical Options**
Annuloplasty (i.e. repair, rarely replacement)

### Mitral Valve Prolapse (MVP)

**Etiology**
Myxomatous degeneration of chordae, thick, bulky leaflets that crowd orifice, associated with Marfan’s syndrome, pectus excavatum, straight back syndrome, other MSK abnormalities; <3% of population

**Pathophysiology**
Mitrail valve displaced into LA during systole; no causal mechanisms found for symptoms

**Symptoms**
Prolonged, stabbing chest pain, dyspnea, anxiety/panic, palpitations, fatigue, presyncope

**Physical Exam**
Auscultation: mid-systolic click (due to billowing of mitral leaflet into LA); tensing of redundant valve tissue); mid to late systolic murmur at apex, accentuated by Valsalva or squat-to-stand maneuvers

**Investigations**
ECG: non-specific ST-T wave changes, paroxysmal SVT, ventricular ectopy
Echo: systolic displacement of thickened mitral valve leaflets into LA

**Treatment**
Asymptomatic: no treatment; reassurance
Symptomatic: β-blockers and avoidance of stimulants (caffeine) for significant palpitations, anticoagulation if AFib

**Surgical Options**
Mitrail valve surgery (repair favoured over replacement) if symptomatic and significant MR
Figure 37. Hemodynamics of aortic stenosis
Stenosis across the aortic valve results in the generation of a significant pressure gradient between the left ventricle and the aorta and a crescendo-decrescendo murmur during systolic contraction. The stenosis decreases the intensity of aortic valve closure hence diminishing S2.

Figure 38. Hemodynamics of aortic regurgitation
Regurgitation across the aortic valve during diastole causes the aortic pressure to rapidly decrease and a decrescendo murmur can be heard at the onset of diastole (after S2 is audible). The presence of regurgitant blood from the aorta increases left-ventricular end-diastolic volume.

Figure 39. Hemodynamics of acute mitral regurgitation
During systolic contraction, blood regurgitates from the left ventricle into the left atrium across the incompetent mitral valve resulting in an audible holosystolic murmur between S1 and S2. The presence of regurgitant blood from the aorta increases left atrial pressures resulting in a tall V-wave (in the JVP).

Figure 40. Hemodynamics of mitral stenosis
First note that the left atrial pressure exceeds the left ventricular pressure during diastole due to mitral stenosis and the consequent generation of a pressure gradient across the left atrium and left ventricle. In diastole the stenotic mitral valve opens which corresponds to the opening snap (OS) and the passage of blood across the mitral stenosis results in an audible decrescendo murmur. Left atrial contraction prior to S1 increases the pressure gradient resulting in accentuation of the murmur before S1 is audible.
Pericardial Disease

Acute Pericarditis

Etiology of Pericarditis/Pericardial Effusion
- idiopathic is most common: presumed to be viral
- infectious
  - viral: Coxsackie virus A, B (most common), echovirus
  - bacterial: *S. pneumoniae*, *S. aureus*
  - TB
  - fungal: histoplasmosis, blastomycosis
- post-MI: acute (direct extension of myocardial inflammation, 1-7 d post-MI), Dressler's syndrome (autoimmune reaction, 2-8 wk post-MI)
- post-cardiac surgery (e.g. CABG), other trauma
- metabolic: uremia (common), hypothyroidism
- neoplasm: Hodgkin's, breast, lung, renal cell carcinoma, melanoma
- collagen vascular disease: SLE, polyarteritis, RA, scleroderma
- vascular: dissecting aneurysm
- other: drugs (e.g. hydralazine), radiation, infiltrative disease (sarcoid)

Signs and Symptoms
- diagnostic triad: chest pain, friction rub, and ECG changes
- pleuritic chest pain: alleviated by sitting up and leaning forward
- pericardial friction rub: may be uni-, bi- or triphasic
- ± fever, malaise

Investigations
- ECG: initially diffuse elevated ST segments ± depressed PR segment, the elevation in the ST segment is concave upwards → 2-5 d later ST isoelectric with T wave flattening and inversion
- CXR: normal heart size, pulmonary infiltrates
- echo: performed to assess for pericardial effusion

Treatment
- treat the underlying disease
- anti-inflammatory agents (high dose NSAIDs/ASA, steroids if severe or recurrent), analgesics

Complications
- recurrent episodes of pericarditis, atrial arrhythmia, pericardial effusion, tamponade, constrictive pericarditis

Pericardial Effusion

Etiology
- transudative (serous)
- CHF, hypoalbuminemia/hypoproteinemia, hypothyroidism
- exudative (serosanguinous or bloody)
  - causes similar to the causes of acute pericarditis
  - may develop acute effusion secondary to hemopericardium (trauma, post-MI myocardial rupture, aortic dissection)
  - physiologic consequences depend on type and volume of effusion, rate of effusion development, and underlying cardiac disease

Signs and Symptoms
- may be asymptomatic or similar to acute pericarditis
- dyspnea, cough
- extra-cardiac (esophageal/recurrent laryngeal nerve/tracheo-bronchial/phrenic nerve irritation)
- JVP increased with dominant “x” descent
- arterial pulse normal to decreased volume, decreased pulse pressure
- auscultation: distant heart sounds ± rub
- Ewart's sign

Investigations
- ECG: low voltage, flat T waves, electrical alternans
- CXR: cardiomegaly, rounded cardiac contour
- echo (procedure of choice): fluid in pericardial sac
- pericardiocentesis: definitive method of determining transudate vs. exudate, identify infectious agents, neoplastic involvement

Treatment
- mild: frequent observation with serial echos, treat underlying cause, anti-inflammatory agents
- severe: treat as in tamponade (see Cardiac Tamponade, C43)
### Cardiac Tamponade

**Etiology**
- major complication of rapidly accumulating pericardial effusion
- cardiac tamponade is a clinical diagnosis
- any cause of pericarditis but especially trauma, malignancy, uremia, proximal aortic dissection with rupture

**Pathophysiology**
- high intra-pericardial pressure → decreased venous return → decreased diastolic ventricular filling → decreased CO → hypotension and venous congestion

**Signs and Symptoms**
- tachypnea, dyspnea, shock, muffled heart sounds
- pulsus paradoxus (inspiratory fall in systolic BP >10 mmHg during quiet breathing)
- JVP “x” descent only, blunted “y” descent
- hepatic congestion/peripheral edema

**Investigations**
- ECG: electrical alternans (pathognomonic variation in R wave amplitude), low voltage
- echo: pericardial effusion, compression of cardiac chambers (RA and RV) in diastole
- cardiac catheterization

**Treatment**
- pericardiocentesis – echo-guided
- pericardiectomy
- avoid diuretics and vasodilators (these decrease venous return to already under-filled RV → decrease LV preload → decrease CO)
- IV fluid may increase CO
- treat underlying cause

### Constrictive Pericarditis

**Etiology**
- chronic pericarditis resulting in fibrosed, thickened, adherent, and/or calcified pericardium
- any cause of acute pericarditis may result in chronic pericarditis
- major causes are idiopathic, post-infectious (viral, TB), radiation, post-cardiac surgery, uremia, MI, collagen vascular disease

**Signs and Symptoms**
- dyspnea, fatigue, palpitations
- abdominal pain
- may mimic CHF (especially right-sided HF)
  - ascites, hepatosplenomegaly, edema
- increased JVP, Kussmaul’s sign (paradoxical increase in JVP with inspiration), Friedreich’s sign (prominent “y” descent)
- BP usually normal (and usually no pulsus paradoxus)
- precordial examination: ± pericardial knock (early diastolic sound)
- see Table 15 for differentiation from cardiac tamponade

**Investigations**
- ECG: non-specific – low voltage, flat T wave, ± AFib
- CXR: pericardial calcification, effusions
- echo/CT/MRI: pericardial thickening
- cardiac catheterization: equalization of end-diastolic chamber pressures (diagnostic)

**Treatment**
- medical: diuretics, salt restriction
- surgical: pericardiectomy (only if refractory to medical therapy)
- prognosis best with idiopathic or infectious cause and worst in post-radiation. Death may result from heart failure

### Table 15. Differentiation of Constrictive Pericarditis vs. Cardiac Tamponade

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Constrictive Pericarditis</th>
<th>Cardiac Tamponade</th>
</tr>
</thead>
<tbody>
<tr>
<td>JVP</td>
<td>“y” &gt; “x”</td>
<td>“x” &gt; “y”</td>
</tr>
<tr>
<td>Kussmaul’s sign</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Pulsus paradoxus</td>
<td>Uncommon</td>
<td>Always</td>
</tr>
<tr>
<td>Pericardial knock</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Variable</td>
<td>Severe</td>
</tr>
</tbody>
</table>
VASCULAR DISEASE


Peripheral Arterial Disease

Peripheral Vascular Anatomy

- see Figure 41

Acute Arterial Occlusion/Insufficiency

Definition

- acute occlusion/rupture of a peripheral artery
- urgent management required: treat within 6 h or irreversible ischemia and myonecrosis may result
- tends to be lower extremity > upper extremity; femoropopliteal > aortoiliac

Etiology and Risk Factors

Table 16. Clinical Categories of Acute Limb Ischemia

<table>
<thead>
<tr>
<th>Grade</th>
<th>Category</th>
<th>Sensory loss</th>
<th>Motor deficit</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Viable</td>
<td>None</td>
<td>None</td>
<td>No immediate threat</td>
</tr>
<tr>
<td>II A</td>
<td>Marginally threatened</td>
<td>None or minimal</td>
<td>None</td>
<td>Salvageable if promptly treated</td>
</tr>
<tr>
<td>II B</td>
<td>Immediately threatened</td>
<td>More than toes</td>
<td>Mild/moderate</td>
<td>Salvageable if promptly revascularized</td>
</tr>
<tr>
<td>III</td>
<td>Irreversible</td>
<td>Profound, anesthetic</td>
<td>Profound, paralysis (rigor)</td>
<td>Major tissue loss Amputation, Permanent nerve damage inevitable</td>
</tr>
</tbody>
</table>

Hypercoagulable States

- congenital
  - group I (reduced anticoagulants): anti-thrombin, protein C, protein S
  - group II: factor V leiden, prothrombin, factor VIII, hyper-homocysteinemia
- acquired: immobility, cancer, pregnancy/OCP, anti-phospholipid antibody syndrome, inflammatory disorders (e.g. IBD), myeloproliferative disorders (e.g. ET), nephrotic syndrome (acquired deficit in protein C and S), disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia with thrombosis (HITT)
  - for presentation of embolus vs. thrombus see Table 17

Investigations

- history and physical exam: depending on degree of ischemia may have to forego investigations and go straight to OR
- ABI: extension of physical exam, easily performed at bedside
- ECG, troponin: rule out recent MI or arrhythmia
- CBC: rule out leukocytosis, thrombocytosis or recent drop in platelets in patients receiving heparin
- PT/INR: patient anticoagulated/sub-therapeutic INR
- echo: identify wall motion abnormalities, intracardiac thrombus, valvular disease, aortic dissection (type A)
- CT angiogram: underlying athelosclerosis, aneurysm, aortic dissection
- conventional catheter based angiography: can be obtained in OR, prelude to thrombolytics

Treatment

- immediate heparinization with 5000 IU bolus and continuous infusion to maintain PTT >60 s
- if absent power and sensation: emergent revascularization
- if present power and sensation: work-up (including angiogram)
- definitive treatment
  - embolus: embolectomy
  - thrombus: thrombectomy ± bypass graft ± endovascular therapy
  - irreversible ischemia: primary amputation
- identify and treat underlying cause
- continue heparin post-op, start warfarin post-op day 1 x 3 mo depending on underlying etiology

Figure 41. Peripheral vascular anatomy

Hypercoagulable State

Congenital
- Group I (reduced anticoagulants)
  - Antithrombin
  - Protein C
  - Protein S
- Group II (increased coagulants)
  - Factor V Leiden
  - Prothrombin
  - Factor VIII
  - Hyper-homocysteinemia

Acquired
- Immobility
- Cancer
- Pregnancy/OCP
- Antiphospholipid antibody syndrome
- Inflammatory disorders (e.g. IBD)
- Myeloproliferative disorders (e.g. ET)
- Nephrotic syndrome (acquired deficit in Protein C and S)
- Disseminated Intravascular Coagulation (DIC)
- Heparin-Induced Thrombocytopenia
### Table 17. Arterial Embolism vs. Thrombosis

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Embolus</th>
<th>Thrombus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Progressive, acute-on-chronic</td>
</tr>
<tr>
<td>Loss of function/sensation</td>
<td>Prominent</td>
<td>Less profound (due to underlying collaterals)</td>
</tr>
<tr>
<td>Hx of claudication</td>
<td>No</td>
<td>Maybe</td>
</tr>
<tr>
<td>Atrophic changes</td>
<td>No</td>
<td>Maybe</td>
</tr>
<tr>
<td>Contralateral limb pulses</td>
<td>Classically normal</td>
<td>Decreased or absent</td>
</tr>
</tbody>
</table>

### Complications
- compartment syndrome with prolonged ischemia; requires fasciotomy
- renal failure and multi-organ failure due to toxic metabolites from ischemic muscle

### Prognosis
- 12-15% mortality rate
- 5-40% morbidity rate (amputation)

## Chronic Arterial Occlusion/Insufficiency

### Etiology
- predominantly due to atherosclerosis; primarily lower extremities

### Risk Factors
- major: smoking, DM
- minor: HTN, hyperlipidemia, family history, obesity, sedentary lifestyle

### Clinical Features
- claudication
  1. pain with exertion: usually in calves or any exercising muscle group
  2. relieved by short rest: 2 to 5 min, and no postural changes necessary
  3. reproducible: same distance to elicit pain, same location of pain, same amount of rest to relieve pain
- critical limb ischemia
  1. includes rest pain, night pain, tissue loss (ulceration or gangrene)
  2. ankle pressure <40 mmHg, toe pressure <30 mmHg, ABI <0.40
- pulses may be absent at some locations, bruits may be present
- signs of poor perfusion: hair loss, hypertrophic nails, atrophic muscle, skin ulcerations and infections, slow capillary refill, prolonged pallor with elevation and rubor on dependency, venous troughing (collapse of superficial veins of foot)
- other manifestations of atherosclerosis: CVD, CAD, impotence, splanchnic ischemia

### Investigations
- non-invasive
  - routine bloodwork, fasting metabolic profile
  - ABI: take highest brachial and highest ankle [dorsalis pedis (DP) or posterior tibial (PT)] pressures for each side generally
    - ABI <0.90 abnormal, rest pain appears at <0.3 (see Table 18)
  - CTA and MRA: excellent for large arteries (aorta, iliac, femoral, popliteal), may have difficulty with tibial arteries (especially in the presence of disease). Both require IV injection of nephrotoxic contrast (iodinated contrast for CT, gadolinium for MR)
- invasive
  - arteriography: superior resolution to CTA/MRA, better for tibial arteries, can be done intraoperatively

### Table 18. Ankle-Brachial Indices

<table>
<thead>
<tr>
<th>ABI Recording</th>
<th>Degree of Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.2</td>
<td>Suspect wall calcification (most common in diabetics)</td>
</tr>
<tr>
<td>&gt;0.95</td>
<td>Normal/no ischemia</td>
</tr>
<tr>
<td>0.50 – 0.8</td>
<td>Claudication range</td>
</tr>
<tr>
<td>&lt;0.4</td>
<td>Possible critical ischemia</td>
</tr>
</tbody>
</table>

### Symptoms of Acute Limb Ischemia
- 6 Ps – all may not be present
  - Pain: absent in 20% of cases
  - Pallor: within a few hours becomes mottled cyanosis
  - Paraesthesia: light touch lost first then sensory modalities
  - Paralysis/Power loss: most important, heralds impending gangrene
  - Petechiae/Poikilothermia (cold)
  - Pulselessness: not reliable

### Differential of Claudication

#### Vascular
- Atherosclerotic disease
- Vasculitis (e.g. Buerger’s disease, Takayasu’s arteritis)
- Diabetic neuropathy
- Venous disease (e.g. DVT, varicose veins)
- Popliteal entrapment syndrome (e.g. Baker’s cyst, tumour)

#### Neurologic
- Neuropathic disease (e.g. spinal stenosis)
- Reflex sympathetic dystrophy

#### MSK
- Osteoarthritis
- Rheumatoid arthritis/connective tissue disease
- Remote trauma
Treatment (see Figure 42)

- conservative
  - risk factor modification (smoking cessation, treatment of HTN, hyperlipidemia, DM)
  - exercise program: improves collateral circulation, oxygen extraction at the muscle level
  - foot care (especially in DM): keep wounds clean/dry, avoid trauma and pressure on wounds
- pharmacotherapy
  - antiplatelet agents (ECASA, clopidogrel or more rarely ticlopidine)
  - cilostazol (cAMP-phosphodiesterase inhibitor with antiplatelet and vasodilatory effects) – improves walking distance for some patients with claudication (not available in Canada)
- surgical/endovascular
  - indications: severe lifestyle impairment, vocational impairment, critical ischemia
  - surgical options:
    - endovascular (stenting/angioplasty) (see Medical Imaging, MI28)
    - endarterectomy: removal of plaque and repair with patch (usually distal aorta or common/profunda femoral)
    - bypass graft sites: aortofemoral, axillofemoral, femoropopliteal, distal arterial (see Figure 42)
      - graft choices: vein graft (reversed or in situ), synthetic – polytetrafluoroethylene graft (e.g. Gore-Tex® or Dacron®)
    - chemical sympathectomy: sympathetic plexus destroyed with EtOH injection into nerve plexus, may stimulate vasodilation (rarely effective)
    - amputation: if not suitable for revascularization, persistent serious infections/gangrene

Prognosis

- claudication: conservative therapy: 60-80% improve, 20-30% stay the same, 5-10% deteriorate, 5% will require intervention within 5 yr, <4% will require amputation
- for patients with critical ischemia (rest pain, night pain, ulceration or gangrene): high risk of limb loss

Figure 42. Treatment options for critical limb ischemia

(A) Algorithm for the treatment of critical limb ischemia
(B) Surgical treatment options for the treatment of aortoiliac disease

Modified from Beard JD. Chronic lower limb ischemia. BMJ. 2000;320:854-857

Hypertension

- see Family Medicine, FM37

Pulmonary Hypertension

- see Respirology, R16
Aortic Disease


Aortic Anatomy

- see Figure 43

Aortic Dissection

Definition
- tear in aortic intima allowing blood to dissect into the media; acute <2 wk (initial mortality 1% per hour for type A dissections), chronic >2 wk (mortality levels up to 75-80%)

Etiology
- most common: HTN → degenerative/cystic changes → damage to aortic media
- other: connective tissue disease (e.g. Marfan’s, Ehlers-Danlos), cystic medial necrosis, atherosclerosis, congenital conditions (e.g. coarctation of aorta, bicuspid aortic valves, patent ductus arteriosus), infection (e.g. syphilis), trauma, arteritis (e.g. Takayasu’s)

Epidemiology
- incidence of 5.2 in 1,000,000
- male:female = 3:2:1
- small increased incidence in African-Canadians (related to higher incidence of HTN)
- lowest incidence in Asians
- peak incidence 50-65 yr old; 20-40 yr old with connective tissue diseases

Clinical Features
- sudden onset tearing chest pain that radiates to back with:
  - HTN (75-85% of patients)
  - asymmetric BPs and pulses between arms (>30 mmHg difference indicates poor prognosis)
  - ischemic syndromes due to occlusion of aortic branches: coronary (MI), carotids (ischemic stroke, Horner's syndrome), splanchic (mesenteric ischemia), renal (AKI), peripheral (ischemic leg), intercostal vessels (spinal cord ischemia)
  - “unseating” of aortic valve cusps (new diastolic murmur in 20-30%)
  - rupture into pleura (dyspnea, hemothorax) or peritoneum (hypotension, shock) or pericardium (cardiac tamponade)
  - syncope

Investigations
- CXR
  - pleural cap (pleural effusion in lung apices)
  - widened mediastinum
  - left pleural effusion with extravasation of blood
- TEE: can visualize aortic valve and thoracic aorta but not abdominal aorta
- ECG: LVH ± ischemic changes, pericarditis, heart block
- CT (gold standard), aortography, MRA: 100% sensitive and specific
- bloodwork: lactate (r/o ischemic gut), amylase (r/o pancreatitis), troponin (r/o MI)

Treatment
- pharmacologic
  - β-blocker to lower BP and decrease cardiac contractility
  - use nondihydropyridine calcium channel blocker if there is a clear contraindication to β-blockers
  - target sBP of 110 mmHg and HR of less than 60 bpm
  - ACEI and/or other vasodilators if insufficient BP or HR control
- surgical
  - urgent surgical consult if thoracic aortic dissection diagnosed or highly suspected
  - resection of segment with intimal tear
  - reconstitution of flow through true lumen
  - replacement of the affected aorta with prosthetic graft
  - correction of any predisposing factors
Post-operative complications: renal failure, intestinal ischemia, stroke, paraplegia, persistent leg ischemia, death
2/3 of patients die of operative or post-operative complications
Type A: requires emergent surgery with cardiopulmonary bypass;
  - hypothermic circulation for transverse arch dissections
  - resuspension of aortic valve
  - aortic valve replacement
  - coronary re-implantation for aortic root involvement
  - initial mortality rate without surgery is 3% per h for first 24 h, 30% 1 wk, 80% 2 wk
Type B: managed medically in absence of malperfusion syndrome
  - <10-20% require urgent operation for complications
  - treatment can be surgical or endovascular
  - with treatment, 60% 5 yr survival, 40% 10 yr survival

Aortic Aneurysm

Definition of Aneurysm
- localized dilatation of an artery having a diameter at least 1.5 times that of the expected normal diameter
  - true aneurysm: involving all vessel wall layers (intima, media, adventitia)
  - false aneurysm (also known as pseudo-aneurysm): disruption of the aortic wall or the anastomotic site between vessel and graft with containment of blood by a fibrous capsule made of surrounding tissue
- aneurysms can rupture, thrombose, embolize, erode, and fistulize

Classification
- thoracic aortic aneurysm (TAA): ascending, transverse arch, descending
- thoracoabdominal
- abdominal aortic aneurysm (AAA): 90-98% are infrarenal

Etiology
- degenerative (atherosclerotic)
- traumatic
- mycotic (Salmonella, Staphylococcus, usually suprarenal aneurysms)
- connective tissue disorder (Marfan syndrome, Ehlers-Danlos syndrome)
- vasculitis
- infectious (syphilis, fungal)
- ascending thoracic aneurysms are associated with bicuspid aortic valve
- risk factors: smoking, HTN, age >70, family history

Epidemiology
- incidence 4.7 to 31.9 per 100 000 for AAA and 5.9 per 100 000 for TAA
- high risk groups
  - 65 yr and older
  - male:female = 3.8:1
  - PVD, CAD, CVD
  - family history of AAA

ACC/AHA 2005 Guidelines define an AAA when the minimum AP diameter of abdominal aorta ≥3.0 cm.
Clinical Features
- common presentation: due to acute expansion or disruption of wall
  - syncope
  - pain (chest, abdominal, flank, back)
  - hypotension
  - palpable pulsatile mass above the umbilicus, pulsatile abdominal mass in two directions (expansible)
  - airway or esophageal obstruction, hoarseness (left recurrent laryngeal nerve paralysis), hemoptysis, or hematemesis (indicates thoracic or thoracoabdominal aortic aneurysm)
  - distal pulses may be intact
- 75% asymptomatic (discovered incidentally)
- uncommon presentation
- ureretic obstruction and hydronephrosis (often with inflammatory aortic aneurysm)
- GI bleed (duodenal mucosal hemorrhage, aortoduodenal fistula)
- aortocaval fistula
- distal embolization (blue toe syndrome)
- associated diseases
  - HTN, PVD, CAD, COPD, renal insufficiency
  - most commonly in the abdominal aorta (50% abdominal aorta, 40% thoracic aorta, 10% ascending aorta)

Investigations
- bloodwork: CBC, electrolytes, urea, creatinine, PTT, INR, type and cross
- abdominal U/S (100% sensitive, up to ± 0.6 cm accuracy in size determination)
- CT (accurate visualization, size determination)
- aortogram (only for EVAR)
- Doppler/duplex (r/o vascular tree aneurysms elsewhere, e.g. popliteal)

Treatment
- conservative
  - cardiovascular risk factor reduction: smoking cessation; control of HTN, DM, and hyperlipidemia
  - regular exercise
  - watchful waiting, U/S every 6 mo to 3 yr depending on size and location
- surgical
  - when risk of rupture greater than or equal to risk of surgery (>5.5 cm)
  - risk of rupture depends on
    - size
    - rate of enlargement (if >0.4 cm/yr)
    - symptoms, comorbidities (HTN, COPD, dissection), smoking
  - elective AAA repair mortality 2-5%; elective TAA repair mortality <10% (highest with proximal aortic and thoracoabdominal repairs)
  - consider revascularization for patients with CAD before elective repair of aneurysm
  - indications
    - general: ruptured, symptomatic, mycotic, associated with acute Type A dissection or complicated Type B dissection or when risk of rupture is greater than risk of surgery (size >5.5 cm or >2x normal lumen size)
    - ascending thoracic aortic aneurysms
      - symptomatic, enlarging, diameter >5.5 cm or >2x normal lumen size; >4.5 cm and aortic regurgitation (annuloaortic ectasia); ≥4.5-5.5 cm in Marfan syndrome
    - contraindications: life expectancy <1 yr, terminal disease (e.g. cancer), significant comorbidities (e.g. recent MI, unstable angina), decreased mental acuity, advanced age
  - surgical options
    - open surgery (laparotomy or retroperitoneal) with graft replacement
      - possible complications
        - early: renal failure, spinal cord injury (paraparesis or paraplegia), impotence, arterial thrombosis, anastomotic rupture or bleeding, peripheral emboli
        - late: graft infection/thrombosis, aortoenteric fistula, anastomotic (pseudo) aneurysm
    - endovascular aneurysm repair (EVAR)
      - newer procedure; high success rates in patients with suitable anatomy and experienced centres
      - advantages: decreased morbidity and mortality, procedure time, need for transfusion, ICU admissions, length of hospitalization, and recovery time
      - disadvantages: endoleak rates as high as 20-30%, device failure increasing as longer follow-up periods are achieved, re-intervention rates 10-30%, cost-effectiveness is an issue (devices are very expensive), radiation exposure
      - complications
        - early: immediate conversion to open repair, groin hematoma, arterial thrombosis, iliac artery rupture, and thromboemboli
        - late: endoleak (see sidebar), severe graft kinking, migration, thrombosis, rupture of aneurysm
Peripheral Venous Disease

Deep Venous Thromboembolism

• see Hematology, H31

Superficial Venous Thrombosis (SVT)

Definition
• erythema, induration, and tenderness along the superficial vein; usually spontaneous but can follow venous cannulation

Etiology
• infectious: suppurative phlebitis (complication of IV cannulation; associated with fever/chills)
• trauma
• inflammatory: varicose veins, migratory superficial thrombophlebitis, Buerger’s disease, SLE
• hematologic: polycythemia, thrombocytosis
• neoplastic: occult malignancy (especially pancreatic)
• idiopathic

Clinical Features
• most common in greater saphenous vein and its tributaries
• pain and cord-like swelling along course of involved vein
• areas of induration, erythema, and tenderness correspond to dilated and often thrombosed superficial veins
• complications
  ▪ simultaneous DVT (up to 20% of cases), PE (rare unless DVT)
  ▪ recurrent superficial thrombophlebitis

Investigations
• non-invasive tests (e.g. Doppler) to exclude associated DVT

Treatment
• conservative
  ▪ moist heat, compression bandages, mild analgesic, anti-inflammatory and anti-platelet (e.g. ASA), LMWH, ambulation
• surgical excision of involved vein
  ▪ indication: failure of conservative measures (symptoms that persist over 2 wk)
  ▪ suppurative thrombophlebitis: broad-spectrum IV antibiotics and excision

Varicose Veins

Definition
• distention of tortuous superficial veins resulting from incompetent valves in the deep, superficial, or perforator systems
• distribution: greater saphenous vein and tributaries (most common), esophagus, anorectum, scrotum

Etiology
• primary
  ▪ main factor: inherited structural weakness of valves
  ▪ contributing factors: increasing age, female gender, OCP use, occupations requiring long hours of standing, pregnancy, obesity
• secondary
  ▪ malignant pelvic tumours with venous compression
  ▪ congenital anomalies, arteriovenous fistulae

Epidemiology
• primary varicose veins are the most common form of venous disorder of lower extremity
• 10-20% of population
Clinical Features
- diffuse aching, fullness/tightness, nocturnal cramping
- aggravated by prolonged standing (end of day), premenstrual
- visible long, dilated and tortuous superficial veins along thigh and leg
- ulceration, hyperpigmentation, and induration (secondary varicosities)
- Brodie-Trendelenberg test (valvular competence test)
- with patient supine, raise leg and compress saphenous vein at thigh, have patient stand – if veins fill quickly from top down then incompetent valves; use multiple tourniquets to localize incompetent veins

Complications
- recurrent superficial thrombophlebitis
- hemorrhage: external or subcutaneous
- ulceration, eczema, lipodermatosclerosis, and hyperpigmentation

Treatment
- largely a cosmetic problem
- conservative: elevation of leg and/or elastic compression stockings
- surgical: high ligation and stripping of the long saphenous vein and its tributaries, ultrasound-guided foam sclerotherapy, endovenous laser therapy (EVLT)
- indications for surgery: symptomatic varix (pain, bleeding, recurrent thrombophlebitis), tissue changes (hyperpigmentation, ulceration), failure of conservative treatment, cosmetics

Prognosis
- benign course with predictable complications
- almost 100% symptomatic relief with treatment if varicosities are primary
- good cosmetic results with treatment
- significant post-operative recurrence, especially with sclerosing agent injection

Chronic Venous Insufficiency (CVI)

Definition
- venous insufficiency and skin damage

Etiology
- calf muscle pump dysfunction and valvular incompetence (valvular reflux) due to phlebitis, varicosities, or DVT
- venous obstruction
- AV fistulas, venous malformations

Clinical Features
- pain (most common), ankle and calf edema – relieved by foot elevation
- pruritus, brownish hyperpigmentation (hemosiderin deposits)
- stasis dermatitis, subcutaneous fibrosis if chronic (lipodermatosclerosis)
- ulceration: shallow, above medial malleolus, weeping (wet), painless, irregular outline
- signs of DVT/varicose veins/thrombophlebitis

Investigations
- ambulatory venous pressure measurement (gold standard)
- Doppler U/S (most commonly used)
- photoplethysmography

Treatment
- conservative
  - elastic compression stockings, leg elevation, avoid prolonged sitting/standing
  - ulcers: zinc-oxide wraps, split-thickness skin grafts, antibiotics, debridement
- surgical
  - if conservative measures fail, if recurrent/large ulcers
  - surgical ligation of perforators in region of ulcer, (GSV/LSV ligation and stripping)
**Lymphedema**

**Definition**
- obstruction of lymphatic drainage resulting in edema with high protein content

**Etiology**
- primary: Milroy’s syndrome (congenital hereditary lymphedema)
- secondary:
  - infection: filariasis (#1 cause worldwide), post-operative
  - malignant infiltration: axillary, groin or intrapelvic
  - radiation/surgery (axillary, groin lymph node removal): #1 cause in North America

**Clinical Features**
- classically non-pitting edema
- impaired limb mobility, discomfort/pain, psychological distress

**Treatment**
- avoid limb injury (can precipitate or worsen lymphedema)
- skin hygiene
  - daily skin care with moisturizers
  - topical treatment of fungal infection; systemic treatment of bacterial infection
- external support
  - intensive: compression bandages
  - maintenance: lymphedema sleeve
- exercise
  - gentle daily exercise of affected limb, gradually increasing ROM
  - must wear a compression sleeve/bandages when doing exercises
- massage and manual lymph drainage therapy

**Prognosis**
- if left untreated becomes resistant to treatment due to subcutaneous fibrosis
- cellulitis causes rapid increase in swelling: can lead to sepsis and death
**Common Medications**

Table 19. Commonly Used Cardiac Therapeutics

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)</strong></td>
<td>enalapril (Vasotec®), perindopril (Coversyl®), ramipril (Altace®), lisinopril (Zestril®)</td>
<td>Inhibit ACE-mediated conversion of angiotensin I to angiotensin II (AT II), causing peripheral vasodilation and decreased aldosterone synthesis</td>
<td>HTN, CAD, CHF, post-MI, DM</td>
<td>Dry cough, 10% hypotension, fatigue, hyperkalemia, renal insufficiency, angioedema</td>
<td>Bilateral renal artery stenosis, pregnancy, caution in decreased GFR</td>
</tr>
<tr>
<td><strong>ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)</strong></td>
<td>candesartan, irbesartan, valsartan</td>
<td>Block AT II receptors, causing similar effects to ACEI</td>
<td>Same as ACEI, although evidence is generally less for ARBs. Often used when ACEI are not tolerated</td>
<td>Similar to ACEI, but do not cause dry cough</td>
<td>Same as ACEI</td>
</tr>
<tr>
<td><strong>DIRECT RENIN INHIBITORS (DRIs)</strong></td>
<td>aliskiren</td>
<td>Directly blocks renin thus inhibiting the conversion of angiotensinogen to angiotensin I. This also causes a decrease in AT II</td>
<td>HTN (exact role of this drug remains unclear)</td>
<td>Diarrhea, hyperkalemia (higher risk if used with an ACEI), rash, cough, angioedema, reflux, hypotension, rhabdomyolysis, seizure</td>
<td>Pregnancy, severe renal impairment</td>
</tr>
<tr>
<td><strong>β-BLOCKERS</strong></td>
<td>atenolol, metoprolol, bisoprolol</td>
<td>Block β1-adrenergic receptors, decreasing HR, BP, contractility, and myocardial oxygen demand, slow conduction through the AV node</td>
<td>HTN, CAD, acute MI, post-MI, CHF (start low and go slow), AFib, SVT</td>
<td>Hypotension, fatigue, light-headedness, depression, bradycardia, hyperkalemia, bronchospasm, impotence, depression of counterregulatory response to hypoglycemia, exacerbation of Raynaud’s phenomenon and claudication</td>
<td>Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, WPW. Caution in asthma, claudication, Raynaud’s phenomenon, and decompensated CHF</td>
</tr>
<tr>
<td><strong>CALCIUM CHANNEL BLOCKERS (CCBs)</strong></td>
<td>diltiazem, verapamil</td>
<td>Block smooth muscle and myocardial calcium channels causing effects similar to β-blockers Also vasodilate</td>
<td>HTN, CAD, SVT, diastolic dysfunction</td>
<td>Hypotension, bradycardia, edema Negative inotrope</td>
<td>Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, WPW, CHF</td>
</tr>
<tr>
<td><strong>DIURETICS</strong></td>
<td>hydrochlorothiazide, chlorothalidone, metolazone</td>
<td>Reduce Na⁺ reabsorption in the distal convoluted tubule (DCT)</td>
<td>HTN (drugs of choice for uncomplicated HTN)</td>
<td>Hypotension, hypokalemia, polyuria</td>
<td>Sulfur allergy, pregnancy</td>
</tr>
<tr>
<td></td>
<td>furosemide (Lasix®)</td>
<td>Blocks Na⁺/K⁺-ATPase in the loop of Henle</td>
<td>CHF, pulmonary or peripheral edema</td>
<td>Hypovolemia, hypokalemic metabolic alkalosis</td>
<td>Hypovolemia, hypokalemia</td>
</tr>
<tr>
<td></td>
<td>spironolactone, eplerenone</td>
<td>Antagonize aldosterone receptors</td>
<td>HTN, CHF, hypokalemia</td>
<td>Edema, hyperkalemia, gynecomastia</td>
<td>Renal insufficiency, hyperkalemia, pregnancy</td>
</tr>
<tr>
<td><strong>INOTROPES</strong></td>
<td>digoxin (Lanoxin®)</td>
<td>Inhibit Na⁺/K⁺-ATPase, leading to increased intracellular Na⁺ and Ca²⁺ concentration and increased myocardial contractility. Also slows conduction through the AV node</td>
<td>CHF, AFib</td>
<td>AV block, tachyarrhythmias, bradyarrhythmias, blurred or yellow vision (van Gogh syndrome), anorexia, nausea and vomiting</td>
<td>2nd or 3rd degree AV block, hypokalemia, WPW</td>
</tr>
</tbody>
</table>
### Table 19. Commonly Used Cardiac Therapeutics (continued)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTICOAGULANTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coumarins</td>
<td>warfarin (Coumadin®)</td>
<td>Antagonizes vitamin K, leading to decreased synthesis of clotting factors II, VII, IX, and X</td>
<td>AFib, LV dysfunction, prosthetic valves</td>
<td>Bleeding (by far the most important side effect), paradoxical thrombosis, skin necrosis</td>
<td>Recent surgery or bleeding, bleeding diathesis, pregnancy</td>
</tr>
<tr>
<td>Heparins</td>
<td>Unfractionated heparin, LMWHs: dalteparin, enoxaparin, tinzaparin</td>
<td>Antithrombin III agonist, leading to decreased clotting factor activity</td>
<td>Acute MI; when immediate anticoagulant effect needed</td>
<td>Bleeding, osteoporosis, heparin-induced thrombocytopenia (less in LMWHs)</td>
<td>Recent surgery or bleeding, bleeding diathesis, thrombocytopenia, renal insufficiency (for LMWHs)</td>
</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td>dabigatran, melagatran</td>
<td>Competitive, direct thrombin inhibitor; thrombin enables fibrinogen conversion to fibrin during the coagulation cascade, thereby preventing thrombus development</td>
<td>Atrial fibrillation</td>
<td>Bleeding, GI upset</td>
<td>Severe renal impairment, recent surgery, active bleeding</td>
</tr>
<tr>
<td>Direct Factor Xa inhibitors</td>
<td>rivaroxaban</td>
<td>Direct, selective and reversible inhibition of factor Xa in both the intrinsic and extrinsic coagulation pathways</td>
<td>Atrial fibrillation</td>
<td>Bleeding, GI upset, elevated liver enzymes</td>
<td>Hepatic disease, active bleeding, bleeding diathesis, pregnancy, lactation</td>
</tr>
<tr>
<td><strong>ANTIPLATELETS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salicylates</td>
<td>ASA (Aspirin®)</td>
<td>Irreversibly acetylates platelet COX-1, preventing thromboxane A2-mediated platelet aggregation</td>
<td>CAD, acute MI, post-MI, post-PCI, CABG</td>
<td>Bleeding, GI ulceration, impaired renal perfusion</td>
<td>Active bleeding or peptic ulcer disease (PUD)</td>
</tr>
<tr>
<td>Thienopyridines</td>
<td>clopidogrel (Plavix®), ticlopidine (Ticlid®)</td>
<td>Block platelet ADP receptors</td>
<td>Acute MI, post-MI, post-PCI, CABG</td>
<td>Bleeding, thrombotic thrombocytopenic purpura, neutropenia (ticlopidine)</td>
<td>Active bleeding or PUD</td>
</tr>
<tr>
<td>GPIIb/IIIa inhibitors</td>
<td>eptifibatide, tirofiban, abciximab</td>
<td>Block binding of fibrinogen to Gp IIb/IIIa</td>
<td>Acute MI, particularly if PCI is planned</td>
<td>Bleeding</td>
<td>Recent surgery or bleeding, bleeding diathesis</td>
</tr>
<tr>
<td><strong>THROMBOLYTICS</strong></td>
<td>alteplase, reteplase, tenecteplase, streptokinase</td>
<td>Convert circulating plasminogen to plasmin, which lyses cross-linked fibrin</td>
<td>Acute STEMI</td>
<td>Bleeding</td>
<td>See Table 6, C25</td>
</tr>
<tr>
<td><strong>NITRATES</strong></td>
<td>nitroglycerin</td>
<td>Relax vascular smooth muscle, producing venous and arteriolar dilation</td>
<td>CAD, MI, CHF (isosorbide dinitrate plus hydralazine)</td>
<td>Headache, dizziness, weakness, postural hypotension</td>
<td>Concurrent use of cGMP phosphodiesterase inhibitors, angle closure glaucoma, increased intracranial pressure</td>
</tr>
<tr>
<td><strong>LIPID LOWERING AGENTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>atorvastatin (Lipitor®), pravastatin (Pravachol®), rosuvastatin (Crestor®), simvastatin (Zocor®), lovastatin (Meracor®)</td>
<td>Inhibit HMG CoA reductase, which catalyzes the rate-limiting step in cholesterol synthesis</td>
<td>Dyslipidemia (1st prevention of CAD), CAD, post-MI</td>
<td>Myalgia, rhabdomyolysis, abdominal pain</td>
<td>Liver or muscle disease</td>
</tr>
</tbody>
</table>
Antiarrhythmics

Figure 46. Representative cardiac action potential

Table 20. Antiarrhythmic* Drugs (Vaughan-Williams Classification)

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>quinidine, procainamide, disopyramide</td>
<td>SVT, VT</td>
<td>Torsades de Pointes (all Ia), diarrhea, Anticholinergic effects</td>
<td>Moderate Na⁺ channel blockade, Slows phase 0 upstroke, Prolongs repolarization, slowing conduction</td>
</tr>
<tr>
<td>Ib</td>
<td>lidocaine, mexiletine</td>
<td>VT</td>
<td>Confusion, stupor, seizures, GI upset, tremor</td>
<td>Mild Na⁺ channel blockade, Shortens phase 3 repolarization</td>
</tr>
<tr>
<td>Ic</td>
<td>propafenone, flecainide, encainide</td>
<td>SVT, VT, AFib</td>
<td>Exacerbation of VT (all Ic), Negative inotropy (all Ic), Bradycardia and heart block (all Ic)</td>
<td>Marked Na⁺ channel blockade, Markedly slows phase 0 upstroke</td>
</tr>
<tr>
<td>II</td>
<td>propranolol, metoprolol, etc.</td>
<td>SVT, AFib</td>
<td>Bronchospasm, negative inotropy, bradycardia, AV block, impotence, fatigue</td>
<td>β-blocker, Decreases phase 4 depolarization</td>
</tr>
<tr>
<td>III</td>
<td>amiodarone**, sotalol</td>
<td>SVT, VT, AFib</td>
<td>Photosensitivity, pulmonary toxicity, hepatotoxicity, thyroid disease, increased INR, Torsades de Pointes, bradycardia, heart block, β-blocker side effects</td>
<td>Blocks K⁺ channel, Prolongs phase 3 repolarization, which prolongs refractory period</td>
</tr>
<tr>
<td>IV</td>
<td>verapamil, diltiazem</td>
<td>SVT, AFib</td>
<td>Bradycardia, AV block, Hypotension</td>
<td>Calcium channel blocker, Slows phase 4 spontaneous depolarization, slowing AV node conduction</td>
</tr>
</tbody>
</table>

*All antiarrhythmics have potential to be proarrhythmic  **Amiodarone has class I, II, III, and IV properties

Table 21. Actions of α and β Adrenergic Receptors

<table>
<thead>
<tr>
<th>Target System</th>
<th>α1 RECEPTORS</th>
<th>α2 RECEPTORS</th>
<th>β1 RECEPTORS</th>
<th>β2 RECEPTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Constriction of vascular smooth muscle, Constriction of skin, skeletal muscle, and splanchnic vessels, Increased myocardial contractility, Decreased heart rate</td>
<td>Same as α1</td>
<td>Increased myocardial contractility, Accelerate SA node, Accelerate ectopic pacemakers</td>
<td>Decreased vascular smooth muscle tone</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Bronchodilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermal</td>
<td>Pilocomotor smooth muscle contraction, Apocrine constriction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular</td>
<td>Radial muscle contraction</td>
<td></td>
<td>Ciliary muscle relaxation</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Inhibition of myenteric plexus, Anal sphincter contraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Pregnant uterine contraction, Penile and seminal vesicle ejaculation, Urinary bladder contraction</td>
<td>Smooth muscle wall relaxation, Stimulation of renal renin release</td>
<td>Bladder wall relaxation, Uterine relaxation</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>Stimulate liver gluconeogenesis and glycogenolysis at the liver, Same as α1</td>
<td>Fat cell lipolysis</td>
<td>Glycogenolysis, Fat cell lipolysis</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from the Family Practice Notebook (www.fpnotebook.com/NEU194.htm)
Table 22. Commonly Used Drugs that Act on α and β Adrenergic Receptors

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>α1</th>
<th>α1 and α2</th>
<th>α2</th>
<th>β1</th>
<th>β1 and β2</th>
<th>β2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agonist</strong></td>
<td>Phenylephrine</td>
<td>Methoxamine</td>
<td>Epinephrine</td>
<td>Norepinephrine</td>
<td>Clonidine</td>
<td>Methyldopa</td>
</tr>
<tr>
<td><strong>Antagonist</strong></td>
<td>Prazosin</td>
<td>Phenoxylbenzamine</td>
<td>Phentolamine</td>
<td>Yohimbine</td>
<td>Mirtazapine</td>
<td>Metoprolol</td>
</tr>
</tbody>
</table>

Adapted from the Family Practice Notebook (http://www.fpnotebook.com/NEU194.htm)

**Landmark Cardiac Trials**

**ISCHEMIC HEART DISEASE**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOT-LLA</td>
<td>Lancet 2003; 361:1149-58</td>
<td>In hypertensive patients with risk factors for CHD and average or below-average cholesterol, atorvastatin reduced nonfatal MI, fatal CHD, fatal/nonfatal stroke, coronary events but not all-cause mortality</td>
</tr>
<tr>
<td>CAPRIE</td>
<td>Lancet 1996; 348:1329-39</td>
<td>In atherosclerotic vascular disease clopidogrel reduced the primary combined endpoint of stroke, MI or vascular death and improved PAD compared to ASA</td>
</tr>
<tr>
<td>CARE</td>
<td>NEJM 1996; 335:1001-9</td>
<td>Pravastatin reduced MI and stroke in patients with previous MI and average cholesterol</td>
</tr>
<tr>
<td>CURE</td>
<td>NEJM 2001; 345:494-502</td>
<td>Clopidogrel plus ASA reduced death from CV causes, non fatal MI, or stroke but increased bleeding complications</td>
</tr>
<tr>
<td>EUROPA</td>
<td>Lancet 2003; 362:782-88</td>
<td>With stable CAD and no CHF perindopril reduced cardiovascular death, MI, and total mortality</td>
</tr>
<tr>
<td>HOPE</td>
<td>NEJM 2000; 342:154-50</td>
<td>In high-risk patients without low LVEF or CHF ramipril reduced rates of death, MI, stroke, revascularization, new diagnosis of diabetes and complications due to diabetes. Vitamin E had no effect on outcomes</td>
</tr>
<tr>
<td>HPS</td>
<td>Lancet 2002; 360:7-22</td>
<td>In high-risk patients with various cholesterol values simvastatin reduced all-cause mortality, coronary deaths and major vascular events</td>
</tr>
<tr>
<td>JUPITER</td>
<td>NEJM 2008; 359:2195-2207</td>
<td>With low to normal LDL-C and elevated hsCRP treatment with rosuvastatin significantly reduced major cardiovascular events. NNT with rosuvastatin for 2 yr to prevent one primary endpoint = 95</td>
</tr>
<tr>
<td>SYNTAX</td>
<td>NEJM 2009; 360:961-972</td>
<td>CABG has lower rate of major cardiac or cerebrovascular events. The rate of stroke was increased with CABG, whereas the rate of repeat revascularization was increased with PCI</td>
</tr>
<tr>
<td>TNT</td>
<td>NEJM 2005; 352:1425-35</td>
<td>Lipid-lowering therapy with atorvastatin 80 mg/d in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/d</td>
</tr>
<tr>
<td>WHI</td>
<td>JAMA 2002; 288:321-333</td>
<td>Estrogen plus progestin therapy is associated with increased risks of cardiovascular disease and breast cancer but decreased risks of hip fracture and colorectal cancer in postmenopausal women</td>
</tr>
</tbody>
</table>

**MYOCARDIAL INFARCTION**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHAT</td>
<td>JAMA 1982; 247:1707-14</td>
<td>In acute MI propranolol reduced all-cause mortality, cardiovascular death and sudden death from atherosclerotic heart disease</td>
</tr>
<tr>
<td>COURAGE</td>
<td>NEJM 2007; 356:1503-16</td>
<td>Compared with optimal medical therapy alone PCI + medical therapy did not reduce all-cause mortality and non fatal MI, and it did not reduce the incidence of major cardiovascular events</td>
</tr>
<tr>
<td>ISIS-2</td>
<td>Lancet 1988; 2:349-60</td>
<td>Early therapy with SK and ASA in patients with MI individually and in combination significantly reduced all-cause mortality and in combination demonstrated additive effect</td>
</tr>
<tr>
<td>ISIS-4</td>
<td>Lancet 1995; 345:669-85</td>
<td>In patients with suspected or definite acute MI early treatment with captopril reduced all-cause mortality at 35 d and during long-term follow up</td>
</tr>
<tr>
<td>OASIS-5</td>
<td>NEJM 2006; 354:1464-76</td>
<td>Compared to enoxaparin, fondaparinux reduced mortality rates, major bleeds at 9 and MI at 30 and 180 d</td>
</tr>
<tr>
<td>PROVE IT – TIMI 22</td>
<td>NEJM 2004; 350:1495-1504</td>
<td>In patients hospitalized for ACS high-dose atorvastatin reduced all-cause mortality, MI, unstable angina, revascularization, and stroke compared with pravastatin</td>
</tr>
</tbody>
</table>

Useful app “CHF Trials” available on iTunes®.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEART FAILURE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIRE</td>
<td>Lancet 1993; 342:821-8</td>
<td>Ramipril commenced 3-10 d after MI and continued for a mean 15-month period significantly reduced all-cause mortality in patients with non-severe CHF</td>
</tr>
<tr>
<td>CHARM</td>
<td>Lancet 2003; 362:759-66</td>
<td>Candesartan reduced overall mortality, cardiovascular death and CHF hospitalizations</td>
</tr>
<tr>
<td>CIBIS II</td>
<td>Lancet 1999; 353:9-13</td>
<td>Bisoprolol reduced all-cause mortality, cardiovascular death, all-cause hospitalization, and CHF hospitalization</td>
</tr>
<tr>
<td>COMET</td>
<td>Lancet 2003; 362:7-13</td>
<td>Carvedilol was associated with a reduction in all cause mortality compared with metoprolol</td>
</tr>
<tr>
<td>CONSENSUS</td>
<td>NEJM 1987; 316:1428-35</td>
<td>Enalapril reduced all-cause mortality, death due to progression of heart failure</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>NEJM 2001; 344:1651-8</td>
<td>Carvedilol in addition to standard treatment significantly reduced the risk of death or hospitalization in patients with severe CHF</td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td>NEJM 2008; 359:2456-2467</td>
<td>In patients with CHF and normal LVEF treatment with ARB (irbesartan) did not improve mortality or cardiovascular morbidity compared to placebo</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>Lancet 1999; 353:2001-7</td>
<td>Metoprolol CR/XL daily in addition to optimum standard therapy improved survival in clinically stable patients equating to prevention of 1 death per 27 patients treated per year</td>
</tr>
<tr>
<td>RALES</td>
<td>NEJM 1999; 341:709-17</td>
<td>In severe CHF (class III/IV) and LVEF &lt; 35% spironolactone reduced all-cause mortality, sudden death, and death due to progression of heart failure</td>
</tr>
<tr>
<td>SAVE</td>
<td>NEJM 1992; 327:669-77</td>
<td>Patients with LV dysfunction post-MI long-term captopril over 3.5 yr reduced the risk of death due to cardiovascular causes, recurrent MI, development of severe CHF, and CHF hospitalization</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>NEJM 2005; 352:225-237</td>
<td>In mild-to-moderate CHF shock-only ICD significantly reduces risk of death. Amiodarone had no benefit compared with placebo in treating patients with mild-to-moderate CHF</td>
</tr>
<tr>
<td>SOLVD</td>
<td>NEJM 1991; 325:93-302</td>
<td>In stable chronic CHF with decreased LVEF (&lt;0.35) long-term enalapril reduced death due to all causes and death or hospitalization due to CHF</td>
</tr>
<tr>
<td>TRACE</td>
<td>NEJM 1995; 333:1670-6</td>
<td>In patients with LV dysfunction post-MI long-term trandolapril reduced the risk of death or progression to severe CHF and reduced risk of sudden death</td>
</tr>
<tr>
<td>V-HeFT II</td>
<td>NEJM 1991; 325:303-10</td>
<td>In chronic CHF enalapril reduced mortality more than hydralazine-isosorbide for at least 2 yr. Treatment with either enalapril or hydralazine-isosorbide increased LVEF</td>
</tr>
<tr>
<td>DIABETES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARDS</td>
<td>Lancet 2004; 264:685-96</td>
<td>Atorvastatin reduces the risk of cardiovascular events in patients with type 2 DM</td>
</tr>
<tr>
<td>ONTARGET</td>
<td>NEJM 2008; 358:1547-59</td>
<td>In patients with vascular disease or DM without CHF telmisartan is equally as effective as ramipril, with telmisartan causing a reduced risk of cough and angioedema, and an increased risk of hypotensive symptoms. Combination therapy offers no advantage</td>
</tr>
<tr>
<td>ARHYTHMIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFFIRM</td>
<td>NEJM 2002; 347:1825-33</td>
<td>No significant difference in mortality rates between rate or rhythm control of AFib</td>
</tr>
<tr>
<td>AF-CHF</td>
<td>NEJM 2008; 358:2667-77</td>
<td>In patients with atrial fibrillation and congestive heart failure there is no significant difference in mortality rates from cardiovascular causes between rate and rhythm control</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>NEJM 2011; 365:883-891</td>
<td>In patients with atrial fibrillation rivoxabarin in non-inferior to warfarin for stroke prevention, and major and non-major bleeding.</td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HYVET</td>
<td>NEJM 2008; 359:1897-98</td>
<td>In hypertensive patients &gt;80 yr treatment with indapamide, with or without perindopril, showed a trend towards reduced relative risk of fatal or non fatal stroke</td>
</tr>
<tr>
<td>UKHDS (UKPDS)</td>
<td>BMJ 1998; 317:703-13</td>
<td>Hypertensive patients with DM and tight BP control at &lt;150/85 mmHg by use of ACEI or</td>
</tr>
<tr>
<td>VALUE</td>
<td>Lancet 2004; 363:2022-2031</td>
<td>Valsartan group had higher incidence of MI than amlodipine group, whereas amlodipine had a higher incidence of new onset diabetes</td>
</tr>
</tbody>
</table>
References

Ischemic Heart Disease

Nuclear Cardiology

Cardiomyopathies

Guidelines

Ambulatory ECG

Stress Testing

Echocardiography

Nuclear Cardiology

MR

CT
Arhythmic


Percutaneous Angiography/PCI


Cardiovascular Surgery


Clinical Pharmacology

General Principles ................. 2
Drug Nomenclature
Phases of Clinical Testing
Drug Administration

Pharmacokinetics (ADME) .......... 3
Absorption
Mechanisms of Drug Absorption
Factors Affecting the Rate and Extent of Drug Absorption
Bioavailability
First-Pass Effect
Efflux Pump

Distribution
Factors Affecting the Rate and Extent of Drug Distribution
Volume of Distribution
Plasma Protein Binding
Depots
Barriers

Metabolism (Biotransformation)
Drug Metabolizing Pathways
Factors Affecting Drug Biotransformation

Elimination
Routes of Drug Elimination

Pharmacokinetic Calculation
Time-Course of Drug Action
Half-Life
Steady State
Clearance
Elimination Kinetics

Pharmacodynamics .................... 7
Dose-Response Relationship
Efficacy
Potency
Effects of Drugs on Receptors
Agonists
Antagonists

Effectiveness and Safety

Therapeutic Indices

Therapeutic Drug Monitoring (TDM) .... 9

Adverse Drug Reactions (ADRs) ........ 10
Type A Drug Reactions
Type B Drug Reactions
Type C Drug Reactions
Type D Drug Reactions
Other ADR Categories

Approach to Suspected ADRs

Variability in Drug Response .......... 11

Drug Interactions ..................... 12

Autonomic Pharmacology .......... 12
Parasympathetic Nervous System (PNS)
Sympathetic Nervous System (SNS)

Common Drug Endings ............... 14

References ..................... 14

Acronyms

ACh  acetylcholine
ADR  adverse drug reaction
BBB  blood brain barrier
Cl clearance
CYP cytochrome P450 protein
F bioavailability
GFR glomerular filtration rate
NE norepinephrine
PD pharmacodynamics
PK pharmacokinetics
P<sub>low</sub> partition coefficient of a drug
Pgp p-glycoprotein
TI therapeutic index
Vd volume of distribution
General Principles

Drug Nomenclature

- **chemical name**: describes chemical structure; same in all countries
  - e.g. N-(4-hydroxyphenyl)acetamide is acetaminophen
- **drug identification number (DIN) or national drug code (NDC)**: DIN assigned by Health Canada; NDC assigned by FDA (US)
- **non-proprietary name**: approved name (post-phase III trial), official name (listed in pharmacopoeia), or generic name (off-patent)
  - e.g. acetaminophen
- **proprietary (trade) name**: the brand name or registered trademark
  - e.g. Tylenol®
- **street name**: slang term used for a drug of abuse

Phases of Clinical Testing

- **phase I**: first administration to healthy human volunteers, following animal studies; to determine PK and PD
- **phase II**: first administration to patients, small sample sizes; to determine initial safety and effectiveness, dose range, PK, PD
- **phase III**: large sample sizes, often double-blind RCT; comparative (new drug vs. placebo or standard of care) to establish safety and efficacy
- **phase IV**: post-marketing surveillance, wide distribution; to determine rare adverse reactions, effects of long-term use, ideal dosing, effects in real world practice

Drug Administration

- choice of route of administration depends on
  - drug properties
  - local and systemic effects (limiting action or adverse events)
  - desired onset and/or duration of action
  - patient characteristics

<table>
<thead>
<tr>
<th>Route</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (PO)</td>
<td>Convenient, easy to administer</td>
<td>Drug metabolism by GI secretions</td>
</tr>
<tr>
<td></td>
<td>Large surface area for absorption</td>
<td>Incomplete absorption</td>
</tr>
<tr>
<td></td>
<td>Inexpensive relative to parenteral administration</td>
<td>Hepatic first-pass effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential GI irritation</td>
</tr>
<tr>
<td>Buccal/Sublingual (SL)</td>
<td>Rapid onset of action</td>
<td>Must be lipid-soluble, non-irritating</td>
</tr>
<tr>
<td>Rectal (PR)</td>
<td>Almost no hepatic first-pass effect</td>
<td>Inconvenient, irritation at site of application</td>
</tr>
<tr>
<td></td>
<td>Convenient if NPO, vomiting or unconscious</td>
<td>Eratic absorption</td>
</tr>
<tr>
<td>Intravenous (IV)</td>
<td>Direct to systemic circulation</td>
<td>Requires IV access, aseptic technique</td>
</tr>
<tr>
<td></td>
<td>No hepatic first-pass effect</td>
<td>Hard to remove once administered</td>
</tr>
<tr>
<td></td>
<td>Slow infusion or rapid onset of action</td>
<td>Risk of infection, bleeding, vascular injury,</td>
</tr>
<tr>
<td></td>
<td>Easy to titrate dose</td>
<td>extravasation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expensive</td>
</tr>
<tr>
<td>Intra-arterial</td>
<td>Direct to specific organs (heart, brain)</td>
<td>Risk of infection, bleeding, vascular complications</td>
</tr>
<tr>
<td></td>
<td>No hepatic first-pass effect</td>
<td></td>
</tr>
<tr>
<td>Intramuscular (IM)</td>
<td>Depot storage if oil-based = slow release of</td>
<td>Pain at site of injection</td>
</tr>
<tr>
<td></td>
<td>drug</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aqueous solution = rapid onset of action</td>
<td></td>
</tr>
</tbody>
</table>

At the time of drug launch, only data from phases I-III are available; thus true effectiveness (in contrast to efficacy) and safety may be unknown because real-world patients and usage patterns sometimes differ significantly from those in premarket phases.

Common Latin Abbreviations

- **q**: each, every
- **OD/bid/tid/qid**: once/twice/three/four times a day
- **hs**: at bedtime
- **ac/pc/cc**: before/after/with meals
- **pm**: as necessary
- **gtt**: drops
- **ung**: ointment
- **ud**: as directed
- **od/ou/ou**: right/left/each eye
- **ad/au**: right/left/each ear
Table 1. Routes of Drug Administration (continued)

<table>
<thead>
<tr>
<th>Route</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous (SC)</td>
<td>Non-irritating drugs, small volumes</td>
<td>Pain at site of injection</td>
</tr>
<tr>
<td></td>
<td>Constant, even absorption</td>
<td>Smaller volumes than IM</td>
</tr>
<tr>
<td></td>
<td>Alternative to IV</td>
<td>May have tissue damage from multiple injections</td>
</tr>
<tr>
<td>Intrathecal</td>
<td>Direct into cerebrospinal fluid (CSF)</td>
<td>Risk of infection</td>
</tr>
<tr>
<td></td>
<td>Bypass BBB and blood-CSF barrier</td>
<td>Possibility of brain herniation and coning</td>
</tr>
<tr>
<td>Inhalation</td>
<td>Immediate (local) action in lungs</td>
<td>Must be a gas, vapour or aerosol</td>
</tr>
<tr>
<td></td>
<td>Rapid delivery to blood (systemic action)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No hepatic first-pass effect</td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td>Easy to administer</td>
<td>Effects are mainly limited to site of application</td>
</tr>
<tr>
<td></td>
<td>Localized (limited systemic absorption)</td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td>Drug absorption through intact skin</td>
<td>Irritation at site of application</td>
</tr>
<tr>
<td></td>
<td>No hepatic first-pass effect</td>
<td>Delayed onset of action</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydrophilic drugs are not easily absorbed</td>
</tr>
<tr>
<td>Others (intraperitoneal, intra-articular)</td>
<td>Local effect</td>
<td>Risk of infection</td>
</tr>
</tbody>
</table>

### Pharmacokinetics (PK)

- **study of “what the body does to a drug”**
- **definition:** relationship between drug administration, time-course/rate of distribution, concentrational changes in the body compartments, and the drug’s removal from the body

#### Absorption

- **definition:** movement of the drug from the site of administration into plasma

#### Mechanisms of Drug Absorption

- most drugs are absorbed into the systemic circulation via passive diffusion
- other mechanisms: active transport, facilitated diffusion, pinocytosis/phagocytosis

#### Factors Affecting the Rate and Extent of Drug Absorption

- **partition coefficient** of a drug ($P_{ow}$), i.e. its relative solubility in oil (lipid) vs. water
- **local blood flow** at the site of administration (e.g. sublingual vessels facilitate rapid absorption from SL)
- **molecular size** (e.g. small molecular weight drugs absorb faster)
- **pH** and **drug ionization**
  - drugs are usually weak acids (e.g. acetylsalicylic acid) or weak bases (e.g. ketoconazole) and thus have both ionized and non-ionized forms
  - body compartment pH and drug $pK_a$ determine the ratio of ionized:non-ionized ratio (using the Henderson-Hasselbach equation)
  - non-ionized forms cross cell membranes much faster than ionized (charged) forms
- **total surface area for absorption**
  - small intestinal villi (large surface area) is the primary site of absorption for most oral drugs

#### Bioavailability (F)

- **definition:** fraction of dose after administration that reaches systemic circulation in an unchanged state
- affected by: drug absorption, gut metabolism, and hepatic first-pass effect
- IV dose has 100% bioavailability ($F = 1$)
- drugs with a low bioavailability by PO may require a much larger oral dose when compared to the IV dose (e.g. $\beta$-blockers: metoprolol 5 mg IV vs. metoprolol 50 mg PO)

#### First-Pass Effect

- **definition:** drug metabolism by the liver and sometimes the gut before it reaches systemic circulation, resulting in reduced drug bioavailability
- occurs with PO administration of a drug: GI tract (absorption) $\rightarrow$ portal vein to liver (first-pass metabolism) $\rightarrow$ systemic circulation
- occurs to much lesser extent with PR administration because drug absorbed in colon bypasses the portal system: colon (absorption) $\rightarrow$ internal pudendal veins $\rightarrow$ IVC $\rightarrow$ systemic circulation

---

**Partition Coefficient ($P_{ow}$)**

- Ratio of a drug’s solubility in oil/lipid (e.g. cell membrane) as compared to water (e.g. extracellular fluid)
- A large $P_{ow}$ (e.g. anesthetics) means that a drug is highly soluble in lipid and will cross membranes easily

**Drug Ionization Reaction and the Henderson-Hasselbach Equation**

- for a weak acid: $HA \rightarrow A^{-} + H^{+}$; $pK_a = pH + \log [HA/A^{-}]$
- e.g. drug $pK_a = 4.4$ at a gastric pH of 1.4, non-ionized:ionized $= HA:A^{-} = 1:0.001$
- Thus, weak acids are mainly non-ionized and more readily absorbed in stomach.

- for a weak base: $B^{-} + H^{+}$; $pK_b = pH + \log [B^{-}/B]$
- Weak bases more readily absorbed in small intestine (pH ~6.0-9.0)

**Examples of Drugs with High First Pass Effect (Hepatic Extraction)**

- Levodopa
- Morphine
- Propranolol
- Lidocaine
- Organic nitrates

**Examples of Drugs with Low First Pass Effect**

- Diazepam
- Digoxin
- Phenytoin
- Warfarin
**Efflux Pump**
- P-glycoprotein (Pgp) is a protein in the GI tract, renal epithelium, and elsewhere that acts as a multidrug efflux pump involved in the transport of drugs out of cells
- acts to reduce intestinal absorption and enhance renal elimination of certain drugs, e.g. digoxin, dabigatran, etoposide, paclitaxel, tacrolimus, cyclosporine
- some drugs (e.g. macrolide antibiotics) inhibit Pgp function, leading to increased levels of Pgp substrates. Pgp inducers (e.g. St. John’s Wort) do the opposite
- some tumours overexpress Pgp leading to multi-drug resistance to chemotherapy agents

**Distribution**
- definition: movement of drugs between different body compartments and to the site of action
- major body fluid compartments: plasma, interstitial fluid, intracellular fluid, transcellular fluid (e.g. CSF, peritoneal, pleural)
- tissue compartments: fat, brain

**Factors Affecting the Rate and Extent of Drug Distribution**
- physicochemical properties of the drug (e.g. partition coefficient)
- pH of fluid
- plasma protein binding
- binding within compartments (depots, e.g. % body fat)
- cardiac output
- regional blood flow

**Volume of Distribution (Vd)**
- maximum actual \(V_d\) (anatomic fluid volume accessible to drug) = total body water (TBW~40 L for average adult) (see Figure 1)
- \(V_d\): the apparent volume of fluid into which a drug dissolves
  - a calculated value = amount of drug in body + plasma drug concentration
  - a theoretical value that does not correspond to an anatomical space (can exceed TBW)
- the value takes into account drug distribution into tissues and protein binding
- small \(V_d\) corresponds to a drug which concentrates in plasma and/or binds plasma proteins to a high degree
- large \(V_d\) corresponds to a drug which distributes into tissues; most is not in blood (measured) space, and it therefore “appears” to distribute in a large volume
- volume of distribution of plasma-protein bound drugs can be altered by liver and kidney disease
- example: amiodarone distributes into TBW (actual \(V_d = 40 \text{ L}\)), but it also concentrates in fat tissues giving instead an apparent \(V_d\) of 400 L; i.e. to achieve a given plasma concentration of amiodarone, we dose as though the drug distributes into 400 L of body fluid

**Plasma Protein Binding**
- drug molecules in the blood exist in an equilibrium of two forms:
  1. bound to plasma proteins
    - acidic drugs bind to albumin
    - basic drugs bind to α1-acid glycoprotein
  2. free or unbound
    - can leave the circulation to distribute into tissues and exert an effect; subject to metabolism and elimination
- bound fraction is determined by
  - drug concentration, binding affinity, and plasma protein concentration (# of binding sites)
- reduced # of binding sites (e.g. hypoalbuminemia) or saturation of binding sites (e.g. competition/displacement) may result in a an increase in free drug concentration, potentially leading to toxicity (see sidebar). However, more commonly most free drug will be metabolized and toxicity will not be seen

**Depots**
- a body compartment where drug molecules tend to be stored and released slowly over a long period of time
- fat is a depot for very lipid soluble drugs (e.g. diazepam)
- some oil-based medications are injected IM for slow release (e.g. depot medroxyprogesterone acetate q3mo; depot risperidone q2wks)

**Barriers (relative)**
- body structures that limit or prevent diffusion of drug molecules
  - e.g. the placenta or blood brain barrier (BBB – a barrier composed of tight junctions between capillary endothelial cells and astrocytes)

---

**Figure 1. Distribution of total body water (TBW)**

- Intravascular Plasma 4%
- Intracellular Fluid 40-44%
- Extracellular Fluid 16-20%
- Total Body Water 60% of body weight

**Special consideration must be given in dosing patients in hypoalbuminemic states (liver failure or nephrotic syndrome) to prevent drug toxicity.**
**Highly protein-bound drugs (e.g. warfarin, digoxin, diazepam, furosemide, amoxicillin, amitriptyline) will exert a greater effect in these patients than in healthy individuals because of higher levels of free drug.

**Main Factors Governing Penetration of Blood Brain Barrier (BBB)**
- Small molecular size (<500 Daltons)
- High lipid solubility
- Active transport mechanisms (e.g. Pgp multidrug efflux pump)

**Many Drugs Cross BBB:**
- General anesthetics
- Alcohol
- Nicotine
- Caffeine
- L-dopa
- Opioids
- Psychotropic medications
In many of these barriers result, in part, from the activity of multidrug efflux pumps (e.g. Pgp) which serve as a natural defense mechanism against drugs and xenobiotics. need to consider dosing route if drugs are meant to cross these barriers.

### Metabolism (Biotransformation)

- **Definition:** Chemical transformation of a drug in vivo
- **Sites of Biotransformation:** Liver (main), GI tract, lung, plasma, kidney
- **Goal:** To make compounds more hydrophilic to enhance renal elimination
- **As a result of the process of biotransformation:**
  - A pro-drug may be **activated** (e.g. tamoxifen to endoxifen; codeine to morphine)
  - A drug may be **changed** to another active metabolite (e.g. diazepam to oxazepam)
  - A drug may be **changed** to a toxic metabolite (e.g. meperidine to normeperidine)
  - A drug may be **inactivated** (most drugs)

#### Drug Metabolizing Pathways

- **Phase I (P450) reactions**
  - Small molecular changes introduce or unmask polar chemical groups on a parent compound to increase its water solubility (e.g. oxidation-reduction, hydrolysis, hydroxylation); the change in $P_{ow}$ is typically minimal compared to phase II, and often phase I places a polar ‘handle’ on a lipophilic drug to allow for phase II
  - Mediated by cytochrome P450 enzymes found in the endoplasmic reticulum
  - Product of the reaction can be excreted or undergo further phase II reactions
- **Phase II (conjugation) reactions**
  - Conjugation with large polar endogenous substrates (e.g. glucuronidation, glutathione conjugation, sulfation)
  - Dramatically increases water solubility and renal elimination
  - Can occur independently of phase I reactions

#### Factors Affecting Drug Biotransformation

- **Genetic polymorphism** of metabolizing enzymes
  - Individuals may metabolize drugs faster or slower depending on their genotype resulting in poor, intermediate, extensive or ultrarapid metabolizers
  - May lead to toxicity or ineffectiveness of a drug at a normal dose, e.g. tamoxifen and codeine are prodrugs activated by CYP2D6 (nonfunctional alleles reduce effectiveness, whereas overactive/duplicated alleles impart “ultrarapid metabolizer” phenotype), while warfarin is metabolized by CYP2C9 (nonfunctional alleles lead to lower dose requirements)
- **Enzyme inhibition** may sometimes be due to other drugs
  - P450 enzyme inhibition leads to an increased concentration and bioavailability of the substrate drug
  - E.g. erythromycin, ketoconazole, indinavir and grapefruit juice (CYP3A4 inhibitors) can predispose a patient to drug toxicity from other drugs also metabolized by CYP3A4 (e.g. simvastatin)
- **Enzyme induction**
  - Certain medications enhance gene transcription leading to an increase in the activity of a metabolizing enzyme
  - A drug may induce its own metabolism (e.g. carbamazepine) or that of other drugs (e.g. phenobarbital can induce the metabolism of OCP and bilirubin) by inducing the P450 enzyme system
- **Liver dysfunction** (e.g. hepatitis, alcoholic liver, biliary cirrhosis, or hepatocellular carcinoma) may decrease drug metabolism but this may not be clinically significant due to the liver’s reserve capacity
- **Renal disease** often results in decreased drug clearance if it is renally cleared
- **Extravasation of age** (neonates or elderly) have reduced biotransformation capacity, and doses should be adjusted accordingly
- **Nutrition**
  - Insufficient protein and fatty acid intake decrease P450 biotransformation
  - Vitamin and mineral deficiencies may also impact metabolizing enzymes
- **Alcohol:** While acute alcohol ingestion inhibits CYP2E1, chronic consumption can induce CYP2E1 and increase the risk of hepatocellular damage from acetaminophen by increasing the generation of acetaminophen’s toxic metabolite
- **Smoking** can induce CYP1A2, thus increasing the metabolism of some drugs (e.g. smokers may require higher doses of theophylline, which is metabolized by CYP1A2)

### Notes

- The very young and the very old are very sensitive to the actions of drugs.

### Common Examples of P450 Inhibitors and Inducers

**P450 inhibitors “MINCE”**
- 

<table>
<thead>
<tr>
<th>Metavonildazole (CYP 2C9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (CYP 2B6)</td>
</tr>
<tr>
<td>Estriol (CYP 3A4)</td>
</tr>
<tr>
<td>risperidone (CYP 3A4)</td>
</tr>
<tr>
<td>Isoniazid (CYP 2C9), etretinate (CYP 3A4)</td>
</tr>
<tr>
<td>Simvastatin (CYP 2C9), efavirenz (CYP 3A4)</td>
</tr>
<tr>
<td>Ciprofloxacin (CYP 3A4, 1A2)</td>
</tr>
<tr>
<td>Erythromycin (macrolides) (CYP 3A4)</td>
</tr>
</tbody>
</table>

**P450 inducers**
- 

<table>
<thead>
<tr>
<th>Phenyltoin (CYP 3A4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone (CYP 3A4)</td>
</tr>
<tr>
<td>Phenobarbital (CYP 3A4)</td>
</tr>
<tr>
<td>Rifampin (CYP 2B6, 3A4)</td>
</tr>
<tr>
<td>Smoking (CYP 1A2)</td>
</tr>
<tr>
<td>St John’s Wort (CYP3A4, CYP2C19, pgp)</td>
</tr>
</tbody>
</table>

Note: The above list is not exhaustive.
Elimination

- definition: removal of drug from the body

Routes of Drug Elimination

- kidney (main organ of elimination)
  - two mechanisms for renal elimination
    1. glomerular filtration
       - a passive process, so that only the free drug fraction can be filtered
       - drug filtration rate depends on GFR, degree of protein binding of drug, and size of drug
    2. tubular secretion
       - an active process that is saturable, allowing both protein-bound and free drug fractions to be excreted
       - distinct transport mechanisms for weak acids (e.g. penicillin, salicylic acid, probenecid, chlorothiazide) and weak bases (e.g. quinine, quaternary ammonium compounds such as choline)
       - drugs may competitively block mutual secretion if both use the same secretion system
       - tubular reabsorption: drugs can be passively reabsorbed back to the systemic circulation, countering elimination mechanisms
    - renal function (decreases with age and is affected by many disease states) is assessed clinically by using serum creatinine (Cr) levels
    - stool
      - some drugs and metabolites are actively excreted in the bile (e.g. corticosteroids) or directly into the intestinal tract from systemic circulation
      - enterohepatic reabsorption counteracts stool elimination, and thus can substantially prolong the drug's duration in the body
      - some glucuronic acid conjugates that are excreted in the bile will be hydrolyzed in the intestines by bacteria back to its original form that can be systemically reabsorbed
    - lungs
      - elimination of anesthetic gases and vapours by exhalation
    - saliva
      - saliva concentrations of some drugs parallel their plasma levels (e.g. rifampin)

Pharmacokinetic Calculation

- definition: the quantitative description of the rates of the various steps of drug disposition (i.e. how drugs move through the body)
- the pharmacokinetic principles of ADME (absorption, distribution, metabolism, and elimination) can be graphically represented on the concentration vs. time graph (see Figure 2)

Time-Course of Drug Action

- many kinetic parameters are measured using IV dosing, such that absorption is immediate and distribution for most drugs is rapid; thus elimination is the main process being measured
- the concentration axis is converted to a log<sub>10</sub> concentration to allow for easier mathematical calculations (see Figure 3)

Half-Life (t<sub>1/2</sub>)

- definition: time taken for the serum drug level to fall 50% during elimination
- for drugs with first order kinetics: takes five half-lives to reach steady state with repeated dosing or for drug elimination once dosing is stopped
- see sidebar for calculation

<table>
<thead>
<tr>
<th># of Half Lives</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>3.3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>50%</td>
<td>75%</td>
<td>87.5%</td>
<td>90%</td>
<td>93.8%</td>
<td>96.9%</td>
</tr>
</tbody>
</table>

Steady State

- drug concentration stays constant when the same amount of drug entering the system is eliminated from the system
- appropriate timing is important for therapeutic monitoring since drug levels are reliable only when the drug has reached steady state (see Figure 4)
• special situations
  ▪ use a loading dose for drugs with a long half-life and when there is clinical need to rapidly achieve therapeutic levels (e.g. amiodarone, digoxin, phenytoin)
  ▪ use continuous infusion for drugs with a very short half-life and when there is need for a long-term effect and multiple or frequently repeated doses are too inconvenient (e.g. nitroprusside, insulin, unfractionated heparin)

Clearance (Cl)
• a quantitative measurement of the body fluid volume from which a substance is removed per unit time
• Cl = rate of elimination of drug ÷ plasma drug concentration
• must consider clearance from a specific part of the body and total body clearance

Elimination Kinetics (see Figure 5)
• first-order kinetics (most common type)
  ▪ constant fraction of drug eliminated per unit time
  ▪ some drugs can follow first-order kinetics until elimination is saturated (usually at large doses) at which point the clearance decreases
  ▪ becomes linear relationship when plotted on a log(concentration) vs. time graph (see Figure 3)
• zero-order kinetics (less common, associated with toxicities, e.g. alcohol)
  ▪ a constant rate of drug eliminated regardless of concentration; concept of half-life does not apply

Table 2. Loading vs. Maintenance Dosing

<table>
<thead>
<tr>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use when you need an IMMEDIATE effect</td>
<td>After a loading dose OR beginning with maintenance doses</td>
</tr>
<tr>
<td>Often parenteral medication</td>
<td>Steady-state levels achieved after ~5 half lives</td>
</tr>
<tr>
<td>Rationale: give large dose of medication to &quot;fill up&quot; the volume of distribution</td>
<td>Can be given as either a continuous infusion (relatively rare, short half-life drug) OR much more commonly as intermittent doses</td>
</tr>
</tbody>
</table>

Pharmacodynamics (PD)
• study of “what a drug does to the body”

Dose-Response Relationship
• graded dose-response relationships: the response of the drug reflects the number of receptors that are effectively occupied

Efficacy
• measured as $E_{\text{max}}$ = the maximal response that a drug can elicit in an RCT or under optimal circumstances (see Figure 6)

Potency
• measured as $E_{50}$ = the effective concentration of a drug needed to produce 50% of $E_{\text{max}}$ (see Figure 6)
• the drug that reaches its $E_{50}$ at the lower dose is the more potent
• overcome low potency by increasing the dose of the drug (e.g. 30 mg vs. 15 mg) to achieve desired response, provided that the higher dose not cause adverse effects
**Effects of Drugs on Receptors**

**Agonists**
- drugs that mimic endogenous ligands and exert an effect
- have two main properties
  - **affinity**: the ability of the agonist to bind to the receptor (e.g., the β2-agonist salbutamol has greater affinity for β2-receptors than β1-receptors)
  - **efficacy**: the ability to recapitulate endogenous response via the receptor interaction (e.g., binding of salbutamol to β2-receptors results in smooth muscle relaxation)
- **full agonists**: can elicit a maximal effect at a receptor
- **partial agonists**: can only elicit a partial effect, no matter how high the concentration
  - e.g., reduced efficacy compared to full agonists

**Antagonists**
- drugs that have affinity (can bind to a receptor) but exert no effect
- these are drugs that block the action of an agonist or of an endogenous ligand
- **chemical antagonism**: direct chemical interaction between agonist and antagonist that prevents agonist binding to receptor
  - e.g., chelating agents for removal of heavy metals
- **functional antagonism**: two agonists that act independently at different receptors but have opposite physiological effects
  - e.g., acetylcholine at the muscarinic receptor decreases HR, constricts pupils, and stimulates intestinal motility; whereas epinephrine at the adrenergic receptor increases HR, dilates pupils, and decreases intestinal motility
- **reversible competitive antagonism** (most common in clinical practice, see Figure 8)
  - antagonist reversibly binds to the same receptor as the agonist, thus displacing it (e.g., naloxone is an antagonist to morphine or heroin)
- **irreversible antagonism** (see Figure 9)
  - antagonist irreversibly binds to the same receptor as the agonist, blocking it from binding (e.g., Phenoxybenzamine forms a permanent covalent bond with adrenergic receptors preventing adrenaline and noradrenaline from binding)
- **non-competitive antagonism** (see Figure 7)
  - antagonist binds to an alternate site separate but near the agonist site, producing allosteric effects that change the ability of the agonist to bind (e.g., organophosphates irreversibly bind acetylcholinesterase)

![Figure 7. Mechanism of agonists and antagonists](image)

**Figure 8. The log(dose)-response curve for competitive reversible antagonism**

A → C increasing dose of competitive antagonist
At each dose of antagonist, increasing the concentration of agonist can overcome the inhibition.

**Figure 9. The log(dose)-response curve for irreversible antagonism**

A → D increasing dose of irreversible antagonist
With co-administration of antagonist, increasing dose of agonist does not completely overcome antagonism, as seen in B. Eventually with high enough antagonist concentrations, no amount of agonist can elicit a response, as seen in D.
Effectiveness and Safety

Effectiveness
- ED₅₀ (Effective Dose – 50%): the dose of a drug needed to cause a therapeutic effect in 50% of a test population of subjects

Safety
- LD₅₀ (Lethal Dose – 50%): the dose of a drug needed to cause death in 50% of a test population of subjects (usually rodents)
- TD₅₀ (Toxic Dose – 50%): the dose needed to cause a harmful effect in 50% of a test population of subjects

Therapeutic Indices

Therapeutic Index (TI): TD₅₀/ED₅₀ (see Figure 10)
- reflects the “margin of safety” for a drug – the likelihood of a therapeutic dose causing serious toxicity or death
- the larger the TI, the safer a drug (e.g. warfarin has a narrow TI and requires accurate therapeutic monitoring)
- factors that can change the ED₅₀, LD₅₀ or TD₅₀
  - presence of interacting drugs
  - changes in drug absorption, distribution, metabolism, elimination

Certain Safety Factor (CSF): TD₁/ED₉₉
- CSF>1 translates to a dose effective in at least 99% of the population and toxic in less than 1% of the population.
- unlike TI, CSF does not take into account the shape of the cumulative dose-response curves of the therapeutic and toxic effects

Figure 10. ED₅₀, TD₅₀, and the therapeutic index (TI)

Therapeutic Drug Monitoring (TDM)

- definition: using serum drug concentration data to optimize drug therapy (e.g. dose adjustment, monitor compliance)
  - serum drug samples are usually taken when the drug has reached steady state (e.g. trough level – the lowest level before the next dose)
- TDM can serve to monitor for side effects (e.g. vancomycin trough levels) and for desired effect (e.g. INR when on warfarin therapy)
- TDM is often used for drugs that have:
  - narrow therapeutic index (TI)
  - unpredictable dose-response relationship
  - significant consequences associated with therapeutic failure or toxicity
  - wide inter-patient pharmacokinetic variability

Examples of drugs whose levels need to be monitored: warfarin (via INR levels), digoxin, lithium, anti-epileptics (e.g. phenytoin, carbamazepine), and many others.
Adverse Drug Reactions (ADRs)

Table 3. Comparison of Characteristics of Type A and Type B Reactions

<table>
<thead>
<tr>
<th>Type A</th>
<th>Type B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictable extension of drug’s pharmacologic effect</td>
<td>Unpredictable</td>
</tr>
<tr>
<td>Usually dose dependent</td>
<td>Rarely dose dependent</td>
</tr>
<tr>
<td>Low mortality (some exceptions)</td>
<td>High mortality (some exceptions)</td>
</tr>
<tr>
<td>Responds to dose reduction</td>
<td>Responds to drug withdrawal</td>
</tr>
</tbody>
</table>

Type A Drug Reactions

- definition: undesirable normal/augmented responses to the drug (>80% of all ADRs)
- extension of a drug's pharmacological effects (e.g. β-blockers causing bradycardia; acetaminophen causing hepatitis)
- overdose/toxicity: exaggerated but characteristic pharmacological effect from supra-therapeutic dose
- teratogen: drug may produce developmental defects in fetus (not always in a dose-related manner)

Type B Drug Reactions

- definition: reactions unrelated to the known pharmacological actions of the drug
- idiosyncratic: uncharacteristic response to drug, unrelated to pharmacology (e.g. sulfa-containing medications causing toxic epidermal necrolysis)
- allergic/immune-mediated: does not occur on first exposure (up to 7 d), immediate with subsequent exposure, may occur with low doses, often resolves within 3-4 d of discontinuation
- pseudoallergenic: mimics immune-mediated reaction

Type C Drug Reactions

- associated with long-term drug therapy
- effects are well-known and can be anticipated
- i.e. benzodiazepine dependence, analgesic nephropathy

Type D Drug Reactions

- delayed effects
- carcinogenic or teratogenic

Other ADR Categories

- type E (end-of-treatment effects)
- type F (failure of therapy)

Approach to Suspected ADRs

- history and physical examination: signs and symptoms of the reaction (e.g. rash, fever, hepatitis, anaphylaxis), timing, risk factors, detailed medication history including all drugs and timing, dechallenge (response when drug is removed) and rechallenge (response when drug is given again)
- differentiate between drug therapy vs. disease pathophysiology
- treatment: stop the drug, supportive care, symptomatic relief
- resources: check recent literature, Health Canada and FDA; contact the pharmaceutical company; call Poison Control (1-888-268-9017) if overdose or poisoning suspected; check with Motherisk (www.motherisk.org) in cases involving pregnant or breastfeeding women
- Canadian Adverse Drug Reaction Monitoring Program available online for reporting
- report all suspected ADRs that are: 1) unexpected, 2) serious, or 3) reactions to recently marketed drugs (on the market <5 yr) regardless of nature or severity

In Canada, an estimated 1.6% of patients admitted to hospitals experience a serious adverse drug reaction. Furthermore, up to 24% of hospitalizations are drug related, of which 35.5% are adverse drug reactions.
### Variability in Drug Response

- recommended patient dosing is based on clinical research and represents mean values for a select population, but each person may be unique in their dosing requirements
  - the majority (but not all) of the patients will experience the desired therapeutic effect of a drug with minimal ADRs on the recommended dose
  - may need to adjust dosing or alter medication altogether
- possible causes of individual variability in drug response include problems with:
  - intake
    - patient adherence, e.g. hard to follow dosing schedule, unpalatable drug, costly drug
  - pharmacokinetics (review pages CP3-CP7)
    - absorption
      - decreased by vomiting, diarrhea or steatorrhea
      - first pass effect too high due to enzyme induction or too low due to liver disease
      - absorption change due to drug interactions (e.g. calcium carbonate complexes with iron, thyroxine, fluoroquinolones)
    - distribution
      - very high or low percentage body fat, intact or disrupted BBB
      - patient is elderly or a neonate or has liver dysfunction
  - biotransformation and elimination
    - certain genetic polymorphisms or enzymes deficiencies to metabolize drugs (e.g. acetylcholinesterase deficiency, CYP polymorphism)
    - kidney or liver dysfunction or obstruction of bile elimination pathway
  - pharmacodynamics
    - genetic variability in drug response (e.g. malignant hyperthermia due to specific anesthetic agents)
    - disease process that affects drug pharmacodynamics
    - drug tolerance or cross-tolerance

---

### Table 4. Sample of Clinically Relevant Adverse Drug Reactions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drug(s)</th>
<th>Adverse Drug Reaction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>β-blockers</td>
<td>Bradycardia</td>
<td>Dose dependent</td>
</tr>
<tr>
<td>A</td>
<td>ACEI</td>
<td>Cough</td>
<td>Switch ACEI to ARB</td>
</tr>
<tr>
<td>A</td>
<td>NSAIDs</td>
<td>GI bleeding</td>
<td>Interruption of mucosal barrier via COX-1 inhibition</td>
</tr>
<tr>
<td>A</td>
<td>Opiates</td>
<td>GI upset, constipation, urinary retention</td>
<td>Wean patients to lowest possible opioid dose</td>
</tr>
<tr>
<td>A</td>
<td>Acetaminophen</td>
<td>Hepatotoxicity</td>
<td>Depletes pools of glutathione allowing buildup of toxic metabolites</td>
</tr>
<tr>
<td>A</td>
<td>Vancomycin</td>
<td>Red Man Syndrome</td>
<td>Pruritic erythematous rash on upper body related to rapid infusion; histamine release Not considered an allergy</td>
</tr>
<tr>
<td>A</td>
<td>Aminoglycosides</td>
<td>Ototoxicity and nephrotoxicity</td>
<td>Dose dependent</td>
</tr>
<tr>
<td>B</td>
<td>Sulfa Drugs</td>
<td>Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis</td>
<td>Life threatening; do not rechallenge under any circumstance</td>
</tr>
<tr>
<td>B</td>
<td>Penicillins</td>
<td>Rash</td>
<td>Many children with EBV infection will develop a rash when given amoxicillin; this is NOT a true penicillin allergy</td>
</tr>
<tr>
<td>B</td>
<td>Valproic acid, Chinese herbs</td>
<td>Hepatotoxicity</td>
<td>Many other drugs are hepatotoxic (e.g. statins, OCPs, isoniazid)</td>
</tr>
</tbody>
</table>

---

### Sulfonamides Containing Medications

- Sulfamethoxazole
- Sulfasalazine
- Dapsone
**Drug Interactions**

- concomitant prescriptions: one drug alters the effect of another by changing its PK fate and/or PD action
- pharmacokinetic interactions involve:
  - absorption: alterations in gastrointestinal pH, gastric emptying, intestinal motility, gut mucosal function
  - biotransformation: alterations in drug metabolizing enzymes
  - excretion: alterations in renal elimination
- pharmacodynamic interactions are drug-induced alterations in the effects of other drugs due to exertion of similar changes to the body’s physiology (additive) or opposing changes (subtractive)
- drug interactions can also involve herbal medications (e.g. St. John’s Wort) and food (e.g. grapefruit)

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Potential Effect</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin plus ciprofloxacin, clarithromycin, erythromycin, metronidazole or trimethoprim-sulfamethoxazole</td>
<td>Increased effect of warfarin</td>
<td>Use alternative antibiotic. Antibiotics inhibit intestinal production of vitamin K. Inhibition of hepatic metabolism of warfarin.</td>
</tr>
<tr>
<td>Oral contraceptive pills plus rifampin, antibiotics</td>
<td>Decreased effectiveness of oral contraception</td>
<td>Avoid if possible. Increased metabolism of exogenous estrogen.</td>
</tr>
<tr>
<td>Sildenafil plus nitrates</td>
<td>Hypotension</td>
<td>Absolute contraindication. Vasodilation.</td>
</tr>
<tr>
<td>SSRI plus St. John’s wort, naratriptan, rizatriptan, zolmitriptan</td>
<td>Serotonin syndrome</td>
<td>Avoid if possible. Monitor for signs and symptoms of serotonin syndrome.</td>
</tr>
<tr>
<td>SSRI plus selegiline or non-selective MAO-I</td>
<td>Serotonin syndrome</td>
<td>Avoid. Additive serotonergic effects.</td>
</tr>
<tr>
<td>Some HMG-CoA reductase inhibitors plus niacin, gemfibrozil, erythromycin or itraconazole</td>
<td>Possible rhabdomyolysis</td>
<td>Avoid if possible.</td>
</tr>
</tbody>
</table>

**Autonomic Pharmacology**

- most organs are innervated by both sympathetic and parasympathetic nerves; these have opposing effects (see Neurology, Figure 8, N6)
- almost all ANS efferent tracts are divided into preganglionic and postganglionic nerves, which synapse in the autonomic ganglion (see Figure 12)
- sympathetic preganglionic fibers originate in the spinal cord at spinal levels T1-L3, and terminate in one of two ganglia
  1. paravertebral ganglia (i.e. the sympathetic trunk) that lie in a chain close to the vertebral column
  2. pre-vertebral ganglia (i.e. celiac and mesenteric ganglia) that lie within the abdomen
- parasympathetic preganglionic fibers originate in the lower brainstem from cranial nerves III, VII, IX, X, and in the sacral spinal cord at levels S2-S4; they terminate in the ganglionic cells located near or within the target organ
- blood vessels, sweat glands, spleen capsule, adrenals, do NOT have parasympathetic innervation

**Figure 11. Subdivisions of the peripheral nervous system**

**Figure 12. Autonomic nervous system (ANS) efferent tracts**
**Parasympathetic Nervous System (PNS)**

- **acetylcholine (ACh)** is the main neurotransmitter of the parasympathetic nervous system
- **ACh** receptors include
  - **nicotinic (pre-ganglionic) receptors** located in the autonomic ganglia
  - **nicotinic (post-ganglionic) receptors** in the adrenal medulla
  - **muscarnic (only post-ganglionic) receptors**
    - M₁ located in the CNS
    - M₂ receptors located on smooth muscle, cardiac muscle, and glandular epithelium
- **ACh action** is terminated by metabolism in the synaptic cleft by **acetylcholinesterase** and in the plasma by **pseudocholinesterase**
  - e.g. **acetylcholinesterase inhibitors** (donepezil, galantamine, rivastigmine) are used to increase ACh levels in conditions such as myasthenia gravis and Alzheimer’s disease

**Sympathetic Nervous System (SNS)**

- **norepinephrine (NE)** is the major neurotransmitter of the SNS
- **receptors** include
  - β₁: predominately in cardiac tissue
  - β₂: predominately in smooth muscle and glands
  - α₁: predominately on post-synaptic receptors in smooth muscles and glands
  - α₂: predominately on pre-synaptic terminals, where they feed back to inhibit further NE release; also exist as post-synaptic terminals in the brain, uterus, and vascular smooth muscle
- **NE action** is terminated by reuptake by the presynaptic membrane, diffusion from the synaptic cleft and degradation by **monoamine oxidase** (MAO) and **catechol-O-methyl transferase** (COMT)

**Table 6. Direct Effects of Autonomic Innervation on the Cardiorespiratory System**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Sympathetic Nervous System</th>
<th>Parasympathetic Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Receptor</td>
<td>Action</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Sinoatrial</td>
<td>β1</td>
<td>Increased HR</td>
</tr>
<tr>
<td>2. Atrioventricular node</td>
<td>β1</td>
<td>Increased conduction</td>
</tr>
<tr>
<td>3. Atria</td>
<td>β1</td>
<td>Increased contractility</td>
</tr>
<tr>
<td>4. Ventricles</td>
<td>β1</td>
<td>Increased contractility</td>
</tr>
<tr>
<td>Blood Vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Skin, splanchnic</td>
<td>α1, α2</td>
<td>Constriction</td>
</tr>
<tr>
<td>2. Skeletal muscle</td>
<td>α</td>
<td>Constriction</td>
</tr>
<tr>
<td>3. Coronary</td>
<td>β2 – large muscles</td>
<td>Dilatation</td>
</tr>
<tr>
<td></td>
<td>α1, α2</td>
<td>Constriction</td>
</tr>
<tr>
<td></td>
<td>β2</td>
<td>Dilatation</td>
</tr>
<tr>
<td>Lungs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Bronchial smooth muscle</td>
<td>β2</td>
<td>Relaxation</td>
</tr>
<tr>
<td>2. Bronchial glands</td>
<td>α1, β2</td>
<td>Increased secretion</td>
</tr>
</tbody>
</table>
# Common Drug Endings

## Table 7. Common Drug Endings

<table>
<thead>
<tr>
<th>Ending</th>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>-afil</td>
<td>5-PDE inhibitor</td>
<td>sildenafil</td>
</tr>
<tr>
<td>-ane</td>
<td>Inhaled general anesthetic</td>
<td>halothane</td>
</tr>
<tr>
<td>-azepam</td>
<td>Benzodiazepine</td>
<td>lorazepam</td>
</tr>
<tr>
<td>-azole</td>
<td>Antifungal</td>
<td>ketoconazole</td>
</tr>
<tr>
<td>-caïne</td>
<td>Local anesthetic</td>
<td>lidocaine</td>
</tr>
<tr>
<td>-olol</td>
<td>β-blocker</td>
<td>propranolol</td>
</tr>
<tr>
<td>-prazole</td>
<td>Proton pump inhibitor</td>
<td>omeprazole</td>
</tr>
<tr>
<td>-pril</td>
<td>ACE inhibitor</td>
<td>captopril</td>
</tr>
<tr>
<td>-sartan</td>
<td>ARB</td>
<td>candesartan</td>
</tr>
<tr>
<td>-statin</td>
<td>HMG-CoA inhibitor</td>
<td>atorvastatin</td>
</tr>
<tr>
<td>-terol</td>
<td>β2 agonist</td>
<td>albuterol</td>
</tr>
<tr>
<td>-tidine</td>
<td>HZ antagonist</td>
<td>cimetidine</td>
</tr>
<tr>
<td>-tropin</td>
<td>Pituitary hormone</td>
<td>somatotropin</td>
</tr>
<tr>
<td>-vir</td>
<td>Antiviral</td>
<td>acyclovir</td>
</tr>
<tr>
<td>-zosin</td>
<td>α1 antagonist</td>
<td>prazosin</td>
</tr>
</tbody>
</table>

Note: Some medications are exceptions to the rule, e.g. methimazole (antithyroid)

## References

**Principles of Clinical Pharmacology**


**Adverse Drug Reactions**


**Drug Interactions**


Dermatology

Amanda Carleton, Thanh-Cat Ho, Anjali Papneja and Yuliya Velykoredko, chapter editors
Maria Jogova and Howard Meng, associate editors
Melini Gupta, EBM editor
Dr. David Adam, Dr. Yvette Miller-Monthrope and Dr. Jensen Yeung, staff editors

Acronyms ........................................ 2
Introduction to Skin .......................... 2
Skin Anatomy
Skin Function
Definitions ................................. 3
Primary Morphological Lesions
Secondary Morphological Lesions
Other Morphological Lesions
Patterns and Distribution

Differential Diagnoses of Common Presentations ............................................. 5
Common Skin Lesions ...................... 5
Cysts
Fibrous Lesions
Hyperkeratotic Lesions
Keloids
Pigmented Lesions
Vascular Lesions

Acneiform Eruptions ....................... 11
Acne Vulgaris/Common Acne
Perioral Dermatitis
Rosacea

Dermatitis (Eczema) ......................... 13
Asteatotic Dermatitis
Atopic Dermatitis
Contact Dermatitis
Dyshidrotic Dermatitis
Nummular Dermatitis
Seborrheic Dermatitis
Stasis Dermatitis
Lichen Simplex Chronicus

Papulosquamous Diseases ............... 17
Lichen Planus
Pityriasis Rosea
Psoriasis

Vesiculobullous Diseases ................. 20
Bullous Pemphigoid
Pemphigus Vulgaris
Dermatitis Herpetiformis
Porphyria Cutanea Tarda

Drug Eruptions .............................. 22
Drug Hypersensitivity Syndrome
Erythema Multiforme (EM)
Stevens-Johnson Syndrome (SJS)
Toxic Epidermal Necrolysis (TEN)
Exanthematous Eruptions (Maculopapular Eruptions/Morbilliform)
Fixed Drug Eruptions
Photosensitivity Eruptions
Serum Sickness-Like Reaction

Heritable Disorders ...................... 23
Ichthyosis Vulgaris
Neurofibromatosis
Vitiligo

Infections ................................. 25
Bacterial Infections
Dermatophytoses
Parasitic Infections
Viral Infections
Yeast Infections
Sexually Transmitted Infections

Pre-Malignant Skin Conditions ........ 32
Actinic Keratosis (Solar Keratosis)
Leukoplakia

Malignant Skin Tumours ................. 33
Non-Melanoma Skin Cancers
Basal Cell Carcinoma (BCC)
Squamous Cell Carcinoma (SCC)
Other Forms of Squamous Cell Carcinoma (SCC)
Malignant Melanoma (MM)
Other Cutaneous Cancers
Cutaneous T-cell Lymphoma

Alopecia (Hair Loss) ...................... 37
Hair Growth
Non-Scarring (Non-Cicatricial) Alopecia
Scarring (Cicatricial) Alopecia

Nails and Disorders of the Nail Apparatus .. 39

Skin Manifestations of Systemic Disease .. 39

Pediatric Exanthems ........................ 40

Miscellaneous Lesions ................... 41
Angioedema and Urticaria
Erythema Nodosum
Pruritus
Wounds and Ulcers

Common Medications ..................... 43
Sunscreens and Preventative Therapy
Topical Steroids
Dermatologic Therapies

References .............................. 47
Introduction to Skin

Skin Anatomy

- **Epidermis**
  - avascular: receives its nutrition from the dermal capillaries
  - derived from keratinocytes with the youngest presenting at the stratum basale (Figure 1A)
  - stratum basale (germinativum): mitotic figures that give rise to keratinocytes
  - stratum spinosum (prickle cells): junctions in this layer (tonofilaments) give the epidermis its strength
  - stratum granulosum: flat cells containing basophilic granules which characterize skin
  - stratum lucidum: comprised of transparent layers of packed dead cells
  - stratum corneum: flat scales of the water-resistant protein keratin

- **Dermis**: comprised of connective tissue divided into two regions (Figure 1B):
  - papillary: contains numerous capillaries that supply nutrients to the dermis and epidermis
  - reticular: provides a strong structure for skin; consists of collagen bundles woven together along with elastic fibres, fibroblasts, and macrophages

- **Subcutaneous tissue** (subdermal)
  - consists primarily of adipose cells, larger caliber vessels, nerves and fascia

Cells in Epidermis

- keratinocytes: located in all layers of the epidermis, except the stratum corneum; connected to each other by desmosomes
- melanocytes: located in the stratum basale; keratinocyte to melanocyte ratio in the basal layer is 10:1; melanocyte number is equal among races
- Langerhans cells: important for immune surveillance
- Merkel cells: involved in touch sensation

Skin Appendages

- epidermal in origin; can extend into the dermis, includes hair, nails, and cutaneous glands

Cutaneous Glands

- **Sebaceous glands**: part of pilosebaceous unit, produces sebum which is secreted into the hair follicle via the sebaceous duct, where it covers the skin surface (protective function)
  - sebum has some antifungal properties
  - these glands cover entire skin surface except palms and soles

- **Apocrine sweat gland**: apocrine duct empties into hair follicle above sebaceous gland
  - found in axillae and perineum
  - likely a vestigial structure, functions in other species to produce scent (e.g. pheromones)

- **Eccrine sweat gland**: not part of pilosebaceous unit
  - found over entire skin surface except lips, nail beds and glans penis
  - important in temperature regulation via secretion of sweat to cool skin surface

Figure 1. Histologic layers of the skin. Epidermal layer is detailed in A

Acronyms

- AAFP: American Association of Family Physicians
- AD: atopic dermatitis
- AK: actinic keratosis
- ASA: acetylsalicylic acid
- ASO: anti-streptolysin O
- BCC: basal cell carcinoma
- BSA: body surface area
- BUN: blood urea nitrogen
- C&S: culture and sensitivity
- CBC: complete blood count
- CNS: central nervous system
- Cr: creatinine
- DLE: discoid lupus erythematosus
- DM: diabetes mellitus
- DVT: deep vein thrombosis
- EM: erythema multiforme
- ESR: erythrocyte sedimentation rate
- Fe: iron
- FTA-ABS: fluorescent treponemal antibody-absorption
- GAS: group A β-hemolytic Streptococcus
- GVHD: graft-versus-host disease
- HHV: human herpes virus
- HPA: hypothyroid-pituitary-adrenal
- HPV: human papilloma virus
- HRT: hormone replacement therapy
- HSV: herpes simplex virus
- HEV: herpes zoster virus
- IFN: interferon
- IVG: intravenous immunoglobulin
- LFT: liver function test
- MDI: monoamine oxidase inhibitor
- MM: malignant melanoma
- MMR: measles/mumps/rubella
- MTP: metatarsal phalangeal
- NB-UVB: narrow band ultraviolet wavelength B
- NCM: neocellular nevus
- ND: Yag: neodymium-doped yttrium aluminium garnet
- MMN: nevus melanocytic nevi
- NMSC: nevus melanoma skin cancers
- NSAID: nonsteroidal anti-inflammatory drug
- OTC: over-the-counter
- PABA: para-aminobenzoic acid
- PASI: Psoriasis Area and Severity Index
- PDD: purified protein derivative
- PUVA: psoralens and long wave ultraviolet radiation
- RA: rheumatoid arthritis
- SCC: squamous cell carcinoma
- SHBG: sex hormone-binding globulin
- SJS: Stevens-Johnson Syndrome
- SL: systemic lupus erythematosus
- SPF: sun protection factor
- SRR: selective serotonin reuptake inhibitor
- SSSS: staphylococcal scalded skin syndrome
- STI: sexually transmitted infection
- TB: tuberculosis
- TEN: toxic epidermal necrolysis
- TMP/SMX: trimethoprin-sulfamethoxazole
- TSH: thyroid stimulating hormone
- UC: ulcerative colitis
- URTI: upper respiratory tract infection
- UV: ultraviolet
- UVA: ultraviolet wavelength A
- UVB: ultraviolet wavelength B
- UVC: ultraviolet wavelength C
- VDRL: venereal disease research laboratory
- VZV: varicella zoster virus
Skin Function

- protection
  - due to continuous recycling and avascularity of epidermis
  - barrier to: UV radiation, mechanical/chemical insults, pathogens and dehydration
- thermal regulation
  - insulation to maintain body temperature in cool environments, via peripheral vasoconstriction, hair and subcutaneous adipose tissue
  - dissipation of heat in warm environments, via increased activity of sweat glands and increased blood flow within dermal vascular networks
- sensation
  - touch, pain, and temperature sensation
- metabolic function
  - vitamin D synthesis
  - energy storage (mainly in the form of triglycerides)

Definitions

Primary Morphological Lesions

Definition
- an initial lesion that has not been altered by trauma or manipulation and has not regressed
- macule: flat lesion <1 cm
- patch: flat lesion ≥1 cm
- papule: elevated, palpable lesion <1 cm
- plaque: elevated, palpable lesion ≥1 cm
- nodule: deep, palpable lesion <1 cm, often dermal or subcutaneous in origin
- tumour: deep, palpable lesion ≥1 cm
- vesicle: fluid-filled lesion <1 cm
- bulla: fluid-filled lesion ≥1 cm
- cyst: an epithelial-lined collection containing semi-solid or fluid material
- pustule: an elevated lesion containing purulent fluid (white, grey, yellow, green)
- erosion: a disruption of the skin involving the epidermis alone; heals without scarring
- ulcer: a disruption of the skin that extends into the dermis or deeper; heals with scarring
- indurated: descriptive term for a lesion that is hard or firm
- scar: replacement fibrosis of dermis and subcutaneous tissue (hypertrophic or atrophic)
- wheal: a special form of papule or plaque that is blanchable and transient, formed by edema in the dermis (e.g. urticaria)

Table 1. Types of Lesions

<table>
<thead>
<tr>
<th>Profile</th>
<th>&lt;1 cm Diameter</th>
<th>≥1 cm Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flat lesion</td>
<td>Macule (e.g. freckle)</td>
<td>Patch (e.g. vitiligo)</td>
</tr>
<tr>
<td>Raised superficial lesion</td>
<td>Papule (e.g. wart)</td>
<td>Plaque (e.g. psoriasis)</td>
</tr>
<tr>
<td>Deep palpable (dermal or subcutaneous)</td>
<td>Nodule (e.g. dermatofibroma)</td>
<td>Tumour (e.g. lipoma)</td>
</tr>
<tr>
<td>Elevated fluid-filled lesions</td>
<td>Vesicle (e.g. HSV)</td>
<td>Bulla (e.g. bullous pemphigoid)</td>
</tr>
</tbody>
</table>

Secondary Morphological Lesions

Definition
- develop during the evolutionary process of skin disease, or created by manipulation, or due to complication of primary lesion (e.g. rubbing, scratching, infection)
- crust: dried fluid (serum, blood, or purulent exudate) originating from a lesion (e.g. impetigo)
- scale: excess keratin (e.g. seborrheic dermatitis)
- lichenification: thickening of the skin and accentuation of normal skin markings (e.g. chronic atopic dermatitis)
- fissure: a linear slit-like cleavage of the skin
- excoriation: a scratch mark
- xerosis: pathologic dryness of skin (xerodermia), conjunctiva (xerophthalmia), or mucous membranes
- atrophy: histological decrease in size and number of cells or tissues, resulting in thinning or depression of the skin

Skin Phototypes (Fitzpatrick)

<table>
<thead>
<tr>
<th>Phototype</th>
<th>Colour of Skin</th>
<th>Skin’s Response to Sun Exposure (without SPF protection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>White</td>
<td>Always burns, never tans</td>
</tr>
<tr>
<td>II</td>
<td>White</td>
<td>Always burns, little tan</td>
</tr>
<tr>
<td>III</td>
<td>White</td>
<td>Slight burn, slow tan</td>
</tr>
<tr>
<td>IV</td>
<td>Pale brown</td>
<td>Slight burn, faster tan</td>
</tr>
<tr>
<td>V</td>
<td>Brown</td>
<td>Rarely burns, dark tan</td>
</tr>
<tr>
<td>VI</td>
<td>Dark brown or black</td>
<td>Never burns, dark tan</td>
</tr>
</tbody>
</table>
Other Morphological Lesions

- **comedones**: collection of sebum and keratin
  - open comedo (blackhead)
  - closed comedo (whitehead; differentiated from pustule)
- **purpura**: extravasation of blood into dermis resulting in hemorrhagic lesions; non-blanchable, 3 mm-1 cm in size
  - petechiae: small pinpoint purpura, <3 mm in size
  - ecchymoses: larger flat purpura, >1 cm in size, aka a “bruise”
- **telangiectasia**: dilated superficial blood vessels; blanchable

Patterns and Distribution

- **acral**: relating to the hands and feet (e.g. hand, foot and mouth disease)
- **annular**: ring-shaped (e.g. granuloma annulare)
- **follicular**: involving hair follicles (e.g. folliculitis)
- **guttate**: lesions following a “drop-like” pattern (e.g. guttate psoriasis)
- **Koebner phenomenon**: aka isomorphic response, appearance of lesions at an injury site (e.g. lichen planus, psoriasis, vitiligo). An isomorphic reaction that develops in areas of trauma (linear exposure, excoriation), after the traumatic event. This can be differentiated from other lesions by arrangement, as Koebner phenomena may not follow dermatomes or the lines of Blaschko
- **morbilliform**: a maculopapular rash resembling measles
- **reticular**: lesions following a net-like pattern (e.g. livedo reticularis)
- **satellite**: lesions scattered outside of primary lesion (e.g. candida diaper dermatitis)
- **serpiginous**: lesions following a snake-like pattern (e.g. cutaneous larva migrans)
- **target/targetoid**: concentric ring lesions, like a dartboard (e.g. EM)
- **other descriptive terms**: discrete, clustered, linear, confluent, dermatitic, indurated
Dermatology

Differential Diagnoses of Common Presentations/Common Skin Lesions

Table 3. Cysts

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Infectious</th>
<th>Inflammatory</th>
<th>Drug/Toxin</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cysts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Differential Diagnosis of Common Presenting Problems**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Infectious</th>
<th>Inflammatory</th>
<th>Drug/Toxin</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discrete Red Papule</td>
<td>Folliculitis</td>
<td>Acne vulgaris</td>
<td>Bites/stings</td>
<td>Vascular: hemangiomma, pyogenic granuloma Other: dermatofibroma, milia rubra</td>
</tr>
<tr>
<td>Red Scales</td>
<td>Pityriasis rosea</td>
<td>Dermatitis (atopic, contact, nummular, seborrheic)</td>
<td>Gold</td>
<td>Neoplastic: mycosis fungoides</td>
</tr>
<tr>
<td>Vesicle</td>
<td>Cat-Scratch disease Impetigo Viral: HSV, HZV, VZV, Molluscum, Coxsackie Scabies</td>
<td>Acute contact dermatitis Dyshidrotic eczema</td>
<td>Other: dermatitis herpetiformis, porphyria cutanea tarda</td>
<td></td>
</tr>
<tr>
<td>Bulla</td>
<td>Bullous impetigo</td>
<td>Acute dermatitis</td>
<td>Fixed drug eruption</td>
<td>Autoimmune: bullous pemphigoid, pemphigus vulgaris Other: dermatitis herpetiformis, porphyria cutanea tarda</td>
</tr>
<tr>
<td>Pustule</td>
<td>Candida</td>
<td>Acne vulgaris</td>
<td>Acute generalized exanthematous pustulosis (usually secondary to drug reaction)</td>
<td>Other: hidradenitis suppurativa</td>
</tr>
<tr>
<td>Oral Ulcer</td>
<td>Aspergillosis CMV</td>
<td>Allergic stomatitis</td>
<td>Chemotherapy Radiation therapy</td>
<td>Autoimmune: pemphigus vulgaris Congenital: XXY Hematologic: sickle cell disease Neoplasia: BCC, SCC</td>
</tr>
<tr>
<td>Skin Ulcer</td>
<td>Plague</td>
<td>RA, SLE, vasculitis</td>
<td>Autoimmune: necrobiosis lipoidica diabetica (e.g. DM) Congenital: XXY Hematologic: sickle cell disease Neoplasia: SCC Vascular: arterial, neurotropic, pressure, venous, aphythous, leukoplakia, traumatic</td>
<td></td>
</tr>
</tbody>
</table>

Common Skin Lesions

Table 3. Cysts

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Epidermal Cyst</th>
<th>Pilar Cyst (Trichilemmal)</th>
<th>Dermoid Cyst</th>
<th>Ganglion Cyst</th>
<th>Milium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cysts</td>
<td>Round, yellow/flesh coloured, slow growing, mobile, firm, fluctuant, nodule or tumour</td>
<td>Multiple, hard, variable sized nodules under the scalp, lacks central punctum</td>
<td>Most commonly found at lateral third of eyebrow or midline under nose</td>
<td>Usually solitary, rubbery, translucent; a clear gelatinous viscous fluid may be extruded</td>
<td>1-2 mm superficial, white to yellow subepidermal papules occuring on eyelids, cheeks, and forehead</td>
</tr>
</tbody>
</table>

**Clinical Presentation**

Epithelial cells displaced into dermis, epidermal lining becomes filled with keratin and lipid-rich debris

May be post-traumatic, rarely synechial

**Pathophysiology**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Epidermal Cyst</th>
<th>Pilar Cyst (Trichilemmal)</th>
<th>Dermoid Cyst</th>
<th>Ganglion Cyst</th>
<th>Milium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cysts</td>
<td>Round, yellow/flesh coloured, slow growing, mobile, firm, fluctuant, nodule or tumour</td>
<td>Multiple, hard, variable sized nodules under the scalp, lacks central punctum</td>
<td>Most commonly found at lateral third of eyebrow or midline under nose</td>
<td>Usually solitary, rubbery, translucent; a clear gelatinous viscous fluid may be extruded</td>
<td>1-2 mm superficial, white to yellow subepidermal papules occuring on eyelids, cheeks, and forehead</td>
</tr>
</tbody>
</table>

**Clinical Course**

Central punctum may rupture (foul, cheesy odour), creamy colour and produce inflammatory reaction

Increase in size and number over time, especially in pregnancy

**Management**

Excise completely before it becomes infected

Excision

Excision

Drainage ± steroid injection if painful

Compression daily for 6 wk

Excision if bothersome

Incision and expression of contents Laser ablation and electrodessication Multiple facial milia respond to topical retinoid therapy
Fibrous Lesions

DERMATOFIBROMA

Clinical Presentation
- button-like, firm dermal papule or nodule, skin-coloured to red-brown colouring
- majority are asymptomatic but may be pruritic and/or tender
- site: legs > arms > trunk
- dimple sign: lateral compression causes dimpling of the lesion

Pathophysiology
- benign tumour due to fibroblast proliferation in the dermis

Etiology
- unknown; may be associated with history of minor trauma (e.g. shaving or insect bites)
- eruptive dermatofibromata can be associated with SLE

Epidemiology
- adults, F>M

Differential Diagnosis
- dermatofibrosarcoma protruberans, malignant melanoma, Kaposi’s sarcoma, blue nevus

Investigations
- biopsy if diagnosis is uncertain

Management
- no treatment required
- excision or cryosurgery if bothersome

SKIN TAGS

Clinical Presentation
- small (1-10 mm), soft, skin-coloured or darker pedunculated papule, often polypoid
- sites: eyelids, neck, axillae, inframammary, and groin

Pathophysiology
- benign outgrowth of skin

Epidemiology
- middle-aged and elderly, F>M, obese, can increase in size and number during pregnancy

Differential Diagnosis
- pedunculated seborrheic keratosis, compound or dermal melanocytic nevus, neurofibroma, fibroepithelioma of Pinkus (rare variant of BCC)

Management
- excision, electrodesiccation, cryosurgery

Hyperkeratotic Lesions

SEBORRHEIC KERATOSIS

Clinical Presentation
- well-demarcated waxy papule/plaque with classic “stuck on” appearance
- large variety in colour, size and shape
- over time lesions appear more warty, greasy and pigmented
- sites: face, trunk, upper extremities (may occur at any site except palms or soles)

Pathophysiology
- very common benign epithelial tumour

Epidemiology
- unusual <30 yr old
- autosomal dominant inheritance

Differential Diagnosis
- malignant melanoma (lentigo maligna, nodular melanoma), melanocytic nevi, pigmented BCC, solar lentigo, spreading pigmented actinic keratosis
Investigations
• biopsy only if diagnosis uncertain

Management
• none required, for cosmetics only
• cryotherapy, curettage

ACTINIC KERATOSIS (SOLAR KERATOSIS)

Clinical Presentation
• ill-defined, scaly erythematous papules or plaques on a background of sun-damaged skin (solar heliosis)
• sandpaper-like, gritty sensation felt on palpation, often easier to appreciate on palpation rather than inspection
• sites: areas of sun exposure (face, ears, scalp if bald, neck, sun-exposed limbs)

Pathophysiology
• UV radiation damage to keratinocytes from repeated sun exposure (especially UVB)
• risk of transformation of actinic keratosis (AK) to SCC (~1/1000), but higher likelihood if AK is persistent

Epidemiology
• common with increasing age, outdoor occupation, M>F
• skin phototypes I-III (see sidebar, D3), rare in darker skin as melanin is protective

Differential Diagnosis
• SCC in situ, superficial BCC, seborrheic keratosis, cutaneous lupus erythematosus

Investigations
• biopsy lesions that are refractory to treatment

Management
• destructive: cryotherapy, electrodessication and curettage
• pharmacotherapy: 5-fluorouracil cream for 2-3 wk, imiquimod cream for 8-10 wk, photodynamic therapy

KERATOACANTHOMA

Clinical Presentation
• rapidly growing, firm, dome-shaped, erythematous or skin-coloured nodule with central keratin-filled crater, resembling an erupting volcano
• often spontaneously regresses within a year, leaving a scar
• sites: sun-exposed skin

Pathophysiology
• epithelial neoplasm with atypical keratinocytes in epidermis
• low grade variant of SCC

Etiology
• HPV, UV radiation, chemical carcinogens (tar, mineral oil)

Epidemiology
• >50 yr, rare <20 yr

Differential Diagnosis
• treat as SCC until proven otherwise
• hypertrophic solar keratosis, verruca vulgaris

Management
• surgical excision, treated similarly to SCC

CORNs

Clinical Presentation
• firm papule with a central, translucent, cone-shaped, hard keratin core
• painful with direct pressure
• sites: most commonly on dorsolateral fifth toe and dorsal aspects of other toes

Pathophysiology
• localized hyperkeratosis induced by pressure on hands and feet
Epidemiology
• F>M, can be caused by chronic microtrauma

Differential Diagnosis
• tinea pedis, plantar warts

Management
• relieve pressure with padding or alternate footwear, orthotics
• paring, curettage

Keloids

Clinical Presentation
• firm, shiny, skin-coloured or red-bluish papules/nodules that most often arise from cutaneous injury (e.g. piercing, surgical scar, acne), but may appear spontaneously
• extends beyond the margins of the original injury, and may continue to expand in size for years with claw-like extensions
• can be pruritic and painful
• sites: earlobes, shoulders, sternum, scapular area

Pathophysiology
• excessive deposition of randomly organized collagen fibers following trauma to skin
• differentiated from a hypertrophic scar which is confined to the borders of the original injury

Epidemiology
• most common in black patients, followed by those of Asian descent (predilection for darker skin)
• M=F, all age groups

Management
• intralesional corticosteroid injections
• cryotherapy
• silicone compression

Pigmented Lesions

Table 4. Comparison of Pigmented Lesions

<table>
<thead>
<tr>
<th>Ephelides (Freckles)</th>
<th>Solar Lentigo (Liver Spot)</th>
<th>Dermal Melanocytosis (historically known as Mongolian Spot)</th>
<th>Becker’s Nevus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Presentation</strong></td>
<td>Small (&lt;5 mm) well-demarcated light brown macules Sites: sun-exposed skin</td>
<td>Well-demarcated brown/black irregular macules Sites: sun-exposed skin</td>
<td>Congenital grey-blue solitary or grouped macules commonly on lumbosacral area</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Increased melanin within basal layer keratinocytes secondary to sun exposure</td>
<td>Benign melanocytic proliferation in dermal-epidermal junction due to chronic sun exposure</td>
<td>Ectopic melanocytes in dermis</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Skin phototypes I and II</td>
<td>Most common in Caucasians &gt;40 yr Skin phototype I-III</td>
<td>99% occurs in Asian and Aboriginal infants M&gt;F Often becomes noticeable at puberty</td>
</tr>
<tr>
<td><strong>Differential Diagnosis</strong></td>
<td>Junctional nevi Juvenile lentigines</td>
<td>Lentigo maligna, seborrhoeic keratosis, pigmented solar keratosis</td>
<td>Ecchymosis</td>
</tr>
<tr>
<td><strong>Clinical Course and Management</strong></td>
<td>No treatment required Multiply and darken with sun exposure, fade in winter Sunscreen may prevent the appearance of new freckles</td>
<td>Laser therapy, shave excisions, cryotherapy</td>
<td>Usually fades in early childhood but may persist into adulthood Hair growth follows onset of pigmentation Cosmetic management (usually too large to remove)</td>
</tr>
</tbody>
</table>

Keloids vs. Hypertrophic Scars
• Keloids: extend beyond margins of original injury with claw-like extensions
• Hypertrophic scars: confined to original margins of injury

DDx of Hyperpigmented Macules
• Purpura (e.g. solar, ASA, anticoagulants, steroids, hemosiderin stain)
• Post-inflammatory
• Melasma
• Melanoma
• Fixed drug eruption
NEVOMELANOCYTIC NEVI (NMN) (see Table 5)

- common mole
- be suspicious of new or changing pigmented lesions (signs of melanoma)
- average number of moles per person: 18-40
- 3 stages of evolution:
  - junctional NMN: macular; arise at dermal-epidermal junction
  - compound NMN: papular; nevus cells invade the papillary dermis
  - dermal NMN: skin coloured papules (no longer hyperpigmented); nevus cells completely migrate into dermis

Table 5. Nevomelanocytic Nevi Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Age of Onset</th>
<th>Clinical Presentation</th>
<th>Histology</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>Birth and early infancy</td>
<td>Sharply demarcated pigmented brown plaque with regular/irregular contours ± coarse hairs</td>
<td>Nevomelanocytes in epidermis (clusters) and dermis (strands)</td>
<td>Surgical excision if suspicious, due to increased risk of melanoma</td>
</tr>
<tr>
<td>Acquired</td>
<td>Early childhood to age 40 Involute by age 60</td>
<td>Benign neoplasm of pigment-forming nevus cell Well circumscribed, round, uniformly pigmented macules/papules &lt; 1.5 cm Classified according to site of nevus cells</td>
<td>Same as above</td>
<td>Excisional biopsy can be considered if on scalp, soles, mucous membranes, anogenital area, or if varied colours, irregular borders, pruritic, bleeding, exposed to trauma</td>
</tr>
<tr>
<td>Junctional</td>
<td>Childhood Majority progress to compound nevus</td>
<td>Flat, irregularly bordered, uniformly tan-dark brown, sharply demarcated smooth macule</td>
<td>Melanocytes at dermal-epidermal junction above basement membrane</td>
<td>Same as above</td>
</tr>
<tr>
<td>Compound</td>
<td>Any age</td>
<td>Darkened, regularly bordered, smooth, round, tan-dark brown papule Face, trunk, extremities, scalp NOT found on palms or soles</td>
<td>Melanocytes at dermal-epidermal junction; migration into dermis</td>
<td>Same as above</td>
</tr>
<tr>
<td>Dermal</td>
<td>Adults</td>
<td>Soft, dome-shaped, skin-coloured to tan/brown papules or nodules, often with telangiectasia Sites: face, neck</td>
<td>Melanocytes exclusively in dermis</td>
<td>Same as above</td>
</tr>
<tr>
<td>Dysplastic</td>
<td>Childhood</td>
<td>Variegated macule/papule with irregular indistinct melanocytes in the basal cell layer Risk factors: positive family history</td>
<td>Hyperplasia and proliferation of melanocytes extending beyond dermal compartment of the nevus Often with region of adjacent nests</td>
<td>Follow with colour photographs for changes Excisional biopsy if lesion changing or highly atypical</td>
</tr>
</tbody>
</table>

MELASMA

Clinical Presentation
- dark skin discoloration on sun-exposed areas of face (forehead, upper lip, cheeks, chin)
- usually symmetrical

Pathophysiology
- increase in number and activity of melanocytes
- associated with estrogen and progesterone
- classification determined by depth of hyperpigmentation in the skin (epidermal, dermal, mixed type)
- epidermal pigmentation is most common and can be diagnosed with Wood’s light

Epidemiology
- F>>M
- common in pregnancy (chloasma = ”mask of pregnancy”) and women taking OCP and HRT
- risk factors include sun exposure and dark skin tone
- can occur with mild endocrine disturbances, antiepileptic medications and other photosensitizing drugs
Management

- bleaching cream (hydroquinone), retinoic acid, topical steroids or combination creams
- destructive modalities (chemical peels, laser treatment)
- camouflage make-up
- avoiding sun and using sunscreen are key to preventing melasma
- often fades over several months after stopping hormone treatment or delivering baby

### Vascular Lesions

#### Table 6. Vascular Tumours Compared to Vascular Malformations

<table>
<thead>
<tr>
<th></th>
<th>Vascular Tumours</th>
<th>Vascular Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Endothelial hyperplasia</td>
<td>Congenital malformation with normal endothelial turnover</td>
</tr>
<tr>
<td>Presence at Birth</td>
<td>Usually postnatal</td>
<td>100% at birth (not always obvious)</td>
</tr>
<tr>
<td>M:F</td>
<td>1:3-5</td>
<td>1:1</td>
</tr>
<tr>
<td>Natural History</td>
<td>Phases:</td>
<td>Proportionate growth (can expand)</td>
</tr>
<tr>
<td></td>
<td>• Proliferating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Involuting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Involuted</td>
<td></td>
</tr>
</tbody>
</table>

#### HEMANGIOMAS

**Clinical Presentation**
- red or blue subcutaneous mass that is soft/compressible, blanches with pressure; feels like a “bag of worms” when palpated

**Pathophysiology**
- benign vascular tumour
- includes: cavernous hemangioma, capillary/infantile hemangioma, spider hemangioma

#### Table 7. Vascular Tumours

<table>
<thead>
<tr>
<th></th>
<th>Capillary Hemangioma</th>
<th>Spider Angioma (Campbell telangiectasia)</th>
<th>Cherry Angioma (Campbell De Morgan spot)</th>
<th>Pyogenic Granuloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Presentation</td>
<td>Hot, firm red to blue plaques or tumours</td>
<td>Central red arteriole with slender branches, faintly pulsatile, blanchable Sites: face, forearms, and hands</td>
<td>Bright red to deep maroon, dome-shaped vascular papules, 1-5 mm Site: trunk Less friable compared to pyogenic granulomas</td>
<td>Bright red, dome-shaped sessile or pedunculated friable nodule Sites: fingers, lips, mouth, trunk, toes DDx: glomus tumour, nodular malignant melanoma, SCC, nodular BCC</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Benign vascular proliferation of endothelial lining</td>
<td>Associated with hyperoestrogenic state (e.g. in hepatocellular disease, pregnancy, OCP)</td>
<td>Benign vascular neoplasm</td>
<td>Rapidly developing hemangioma Proliferation of capillaries with erosion of epidermis and neutrophilia</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Appears shortly after birth; rarely may be congenital</td>
<td>&gt;30 yr old</td>
<td>&lt;30 yr old</td>
<td></td>
</tr>
<tr>
<td>Clinical Course</td>
<td>Appears shortly after birth, increases in size over months, then regresses 50% of lesions resolve spontaneously by 5 yr</td>
<td>Increase in number over time</td>
<td>Lesions do not fade in time Lesions bleed infrequently</td>
<td></td>
</tr>
<tr>
<td>Management</td>
<td>10% require treatment due to functional impairment (visual compromise, airway obstruction, high output cardiac failure) or cosmesis Consider treatment if not gone by school age; Propanolol; systemic corticosteroids; laser treatment; surgery</td>
<td>Electro or laser surgery Systemic corticosteroids and IFN-α may be indicated for rapidly growing lesions</td>
<td>Usually no treatment needed Laser or electrocautery for small lesions Excision of large lesions if necessary</td>
<td>Surgical excision with histologic examination Electrocautery; laser; cryotherapy</td>
</tr>
</tbody>
</table>
VASCULAR MALFORMATIONS

1. Nevus Flammeus (Port-wine stain)

Clinical Presentation
• red to blue macule present at birth that follows a dermatomal distribution, rarely crosses midline
• most common site: nape of neck

Pathophysiology
• congenital vascular malformation of dermal capillaries; rarely associated with Sturge-Weber syndrome (V1, V2 distribution)

Management
• laser or make-up

2. Nevus Simplex (salmon patch)

Clinical Presentation
• pink-red irregular patches
• midline macule on glabella known as "Angel Kiss"; on nuchal region known as "Stork Bites"
• present in 1/3 of newborns
• majority regress spontaneously

Pathophysiology
• congenital dilation of dermal capillaries

Management
• no treatment required

Acneiform Eruptions

Acne Vulgaris/Common Acne

Clinical Presentation
• a common inflammatory pilosebaceous disease categorized with respect to severity
  ▪ Type I: comedonal, sparse, no scarring
  ▪ Type II: comedonal, papular, moderate ± little scarring
  ▪ Type III: comedonal, papular, and pustular, with scarring
  ▪ Type IV: nodulocystic acne, risk of severe scarring
• sites of predilection: face, neck, upper chest, and back

Pathogenesis
• hyperkeratinization, at the follicular ostia (opening), blocks the secretion of sebum (microcomedones)
• androgens stimulate sebaceous glands to produce sebum
• anaerobic diphtheroid Propionibacterium acnes bacteria contains lipase, which converts sebum to free fatty acids and produces pro-inflammatory mediators

Epidemiology
• age of onset in puberty (10-17 yr in females, 14-19 yr in males)
• in prepubertal children consider underlying hormonal abnormality (e.g. late onset congenital adrenal hyperplasia)
• more severe in males than in females
• incidence decreases in adulthood
• genetic predisposition: majority of individuals with cystic acne have parent(s) with history of severe acne

Differential Diagnosis
• folliculitis, keratosis pilaris (upper arms, face, thighs), perioral dermatitis, rosacea

Management
• see Table 8

Acne Myths Debunked
• Eating greasy food and chocolate does not cause or worsen acne
• Blackheads (comedones) are black because of oxidized fatty acids, not dirt
• Acne is not caused by poor hygiene; on the contrary, excessive washing of face can be an aggravator

Acne Exacerbating Factors
• Systemic medications: lithium, phenytoin, steroids, halogens, androgens, iodides, bromides, danazol
• Topical agents: steroids, tars, ointments, oily cosmetics
• Mechanical pressure or occlusion, such as leaning face on hands
• Emotional stress

Intralesional Injections
Intralesional corticosteroid injections are effective in the treatment of individual acne nodules.

A combination of topical retinoids and topical erythromycin or clindamycin is more effective than either agent used alone.
Table 8. Management of Acne

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MILD ACNE: Topical Therapies Over-the-Counter</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzoyl peroxide</td>
<td>Bactericidal agent (targets <em>P. acnes</em>) and comedolytic</td>
<td>Helps prevent <em>P. acnes</em> resistance</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>Comedolytic</td>
<td>Used when patients cannot tolerate a topical retinoid due to skin irritation</td>
</tr>
<tr>
<td><strong>MILD ACNE: Prescription Topical Therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin phosphate (e.g. Dalacin T®)</td>
<td>Lincomamide antibiotic; inhibits protein synthesis</td>
<td>High rate of resistance when used as monotherapy</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Macrolide antibiotic; inhibits protein synthesis</td>
<td>High rate of resistance when used as monotherapy</td>
</tr>
<tr>
<td>BenzClin® gel</td>
<td>1% clindamycin and 5% benzoyl peroxide</td>
<td>See above</td>
</tr>
<tr>
<td>Erythromycin + benzoyl peroxide (Benzamycin®)</td>
<td>3% erythromycin and 5% benzoyl peroxide</td>
<td>See above</td>
</tr>
<tr>
<td>Adapalene (e.g. Differin®)</td>
<td>Comedolytic</td>
<td>Less irritating than tretinoin. Not photolabile</td>
</tr>
<tr>
<td>Tretinoin (e.g. Retin-A®)</td>
<td>Comedolytic</td>
<td>Photolabile and irritation</td>
</tr>
<tr>
<td>Adapalene + benzoyl peroxide (e.g. Tactuo®)</td>
<td>0.1% adapalene and 2.5% benzoyl peroxide</td>
<td>See above</td>
</tr>
<tr>
<td><strong>MODERATE ACNE</strong>: After topical treatments have failed, add oral antibiotics, such as tetracycline (250 mg PO bid to 500 mg bid), or erythromycin (500 mg PO bid). Antibiotics require 3-6 mo of use before assessing efficacy. Consider hormonal therapy, including antiandrogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Inhibits protein synthesis</td>
<td>Use caution with regard to drug interactions: do not use with isotretinoin. Sun sensitivity</td>
</tr>
<tr>
<td>Cyproterone acetate-ethinyl estradiol (Diane-35®)</td>
<td>Cyproterone: potent anti-androgenic, progestogenic and antigonadatrophic activity Ethinyl estradiol: increases level of SHBG, reducing circulating plasma levels of androgens</td>
<td>After 35 yr of age, estrogen/progesterone should only be considered in exceptional circumstances, carefully weighing the risk/benefit ratio with physician guidance</td>
</tr>
<tr>
<td>Spirolactone (source ADA)</td>
<td>Blocks androgen receptors</td>
<td>May cause hyperkalemia at higher doses Black box warning for breast cancer</td>
</tr>
<tr>
<td><strong>SEVERE ACNE</strong>: Consider systemic retinoids after above treatments have failed or if significant scarring present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotretinoin (Accutane®, Clarus®)</td>
<td>Retinoid that inhibits sebaceous gland function and regulates keratinization</td>
<td>See Table 29, D46 for full side effect profile Most adverse effects are temporary and will resolve when the drug is discontinued Baseline lipid profile (risk of hypertriglyceridemia), LFTs and β-hCG before treatment May transiently exacerbate acne before patient sees improvement Drug may be discontinued at 16-20 wk when nodule count has dropped by &gt; 70% A second course may be initiated after 2 mo pm Refractory cases may require multiple courses of isotretinoin</td>
</tr>
</tbody>
</table>

**Perioral Dermatitis**

**Clinical Presentation**
- discrete erythematous micropapules that often become confluent, forming inflammatory plaques on perioral, perinasal and periorbital skin
- commonly symmetrical, rim of sparing around vermillion border of lips
- aggravated by topical glucocorticoids

**Epidemiology**
- 15-40 yr old, occasionally in younger children
- predominantly females

**Differential Diagnosis**
- contact dermatitis, rosacea, acne vulgaris

**Antibiotics are used in inflammatory skin conditions since they also have anti-inflammatory properties (e.g. macrolides in acne). Topical antibiotics may also be used to treat secondary bacterial superinfections (e.g. impetigo).**
Management
- avoid all topical steroids
- topical: metronidazole 0.75% gel or 0.75-1% cream to affected area bid
- systemic: tetracycline family antibiotic (utilized for its anti-inflammatory properties)

Rosacea

Clinical Presentation
- dome-shaped papules ± pustules
- flushing, non-transient erythema and telangiectasia
- distribution: typically on central face including forehead, nose, cheeks and chin (see Figure 3); rarely on scalp, neck and upper body
- characterized by remissions and exacerbations
- exacerbating factors: heat, cold, wind, sun, stress, drinking hot liquids, alcohol, caffeine, spices (triggers of vasodilation)
- all forms of rosacea can progress from mild to moderate to severe
- rarely in longstanding rosacea, signs of thickening, induration and lymphedema in the skin can develop
- phyma: a distinct swelling caused by lymphedema and hypertrophy of subcutaneous tissue, particularly affecting the nose (rhinophyma)
- ocular manifestations: blepharoconjunctivitis, keratitis, iritis

Pathophysiology
- unknown

Epidemiology
- although found in all skin types, highest prevalence in fair-skinned people
- 30-50 yr old; F>M

Differential Diagnosis
- acne vulgaris, seborrheic dermatitis, perioral dermatitis, contact dermatitis

Management
- trigger avoidance is key to long term management
- avoid topical corticosteroids
- make-up to mask erythema
- telangiectasia: treated by physical ablation; electrical hyfrecators, vascular lasers, and intense pulsed light therapies
- phymas: treated by physical ablation or removal; paring, electrosurgery, cryotherapy, laser therapy (CO2, argon, Nd:YAG)
- early diagnosis and prompt treatment are recommended to prevent worsening

Table 9. Specific Rosacea Treatments
<table>
<thead>
<tr>
<th>1st Line</th>
<th>2nd Line</th>
<th>3rd Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral tetracyclines (250-500 mg PO bid)</td>
<td>Topical clindamycin</td>
<td>Oral retinoids</td>
</tr>
<tr>
<td>Topical metronidazole</td>
<td>Topical erythromycin 2% solution</td>
<td>Topical sulfur</td>
</tr>
<tr>
<td>Oral erythromycin (250-500 mg PO bid)</td>
<td>Topical benzoyl peroxide</td>
<td></td>
</tr>
<tr>
<td>Topical azelaic acid</td>
<td>Oral metronidazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ampicillin</td>
<td></td>
</tr>
</tbody>
</table>

Dermatitis (Eczema)

Definition
- inflammation of the skin

Clinical Presentation
- symptoms include pruritus and pain
- acute dermatitis: papules, vesicles
- subacute dermatitis: scaling, crusting
- chronic dermatitis: lichenification, xerosis, fissuring

Figure 3. Rosacea distribution

Guidelines for the Diagnosis of Rosacea
J Am Acad Dermatol 2002;46:584-7
Presence of one or more of the following primary features:
- Flushing (transient erythema)
- Nontransient erythema
- Papules and pustules
- Telangiectasia

May include one or more of the following secondary features:
- Burning or stingning
- Dry appearance
- Edema
- Phymatous changes
- Ocular manifestations
- Peripheral location

Subtypes and Variants of Rosacea and Their Characteristics
N.B. the subtypes can all coexist and can be seen on a spectrum of severity

SUBTYPE
- Erythromatotelangiectatic
  - Flushing, persistent central facial erythema ± telangiectasia
- Papulopustular
  - Persistent central facial papules or pustules or both
- Phymatous
  - Thickening skin, irregular surface nodularities and enlargement
  - Nose most commonly, rarely occurs elsewhere (chin, forehead, cheeks or ears)
- Ocular
  - Foreign body sensation in the eye, burning or stinging, dryness, itching, ocular photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, or periocular edema

VARIANT
- Granulomatous
  - Noninflammatory, hard, brown, yellow, or red cutaneous papules or nodules of uniform size
Asteatotic Dermatitis

Clinical Presentation
- diffuse, mild pruritic dermatitis secondary to dry skin
- very common in elderly, especially in the winter (aka “winter itch”) but starts in the fall
- shins predominate, looks like a “dried river bed”

Management
- skin rehydration with moisturizing routine
- ± mild corticosteroid creams

Atopic Dermatitis

Clinical Presentation
- subacute and chronic eczematous reaction associated with prolonged severe pruritus
- distribution
  - infant (onset at 2-6 mo old): face, scalp, extensor surfaces
  - childhood (>18 mo): flexural surfaces, especially antecubital fossae, popliteal fossae, and neck
  - adult: hands, feet, flexures, wrists, face, forehead, eyelids, neck
- inflammation, lichenification, excoriations are secondary to relentless scratching
- atopic palms: hyperlinearity of the palms (associated with ichthyosis vulgaris)
- associated with
  - keratosis pilaris (hyperkeratosis of hair follicles, “chicken skin”)
  - xerosis
  - occupational hand dryness

Epidemiology
- frequently affects infants, children, and young adults
- almost 15% of children in developed countries under the age of 5 are affected
- associated with personal or family history of atopy (asthma, hay fever, anaphylaxis, eosinophilia)
- polygenic inheritance: one parent >60% chance for child; two parents >80% chance for child
- childhood onset and hereditary forms may be associated with null mutations in the protein filagrin
- the earlier the onset, the more severe and persistent the disease
- long-term condition with 1/3 of patients continuing to show signs of AD into adulthood

Pathophysiology
- a T-cell driven process with epidermal barrier dysfunction

Investigations
- clinical diagnosis
- consider: skin biopsy, immunoglobulin serum levels (often elevated serum IgE level), patch testing, and skin prick tests

Management
- goal: reduce signs and symptoms, prevent or reduce recurrences/flares
- better outcome (e.g. less flare-ups, modified course of disease) if diagnosis made early and treatment plan individualized
- avoid triggers of AD
- enhance barrier function of the skin
  - regular application of moisturizers
  - emollients hydrate the skin and reduce pruritus
  - twice daily application is recommended even in absence of symptoms, especially after bathing or swimming
  - bathing promotes hydration when followed by the application of moisturizers to the skin followed by occlusives (e.g. petroleum jelly)
- anti-inflammatory therapies
  A. topical corticosteroids
    - effective, rapid symptomatic relief of acute flares
    - best applied immediately after bathing
    - control inflammation with a potent topical steroid; a milder one following resolution of acute flare
    - systemic immunosuppression may be needed in severe cases
    - flares may respond to systemic anti-staphylococcal therapy
    - side effects: skin atrophy, purpura, striae, steroid acne, perioral dermatitis, and glaucoma when used around the eyes

Triggers for Atopic Dermatitis
- Irritants (detergents, solvents, clothing, water hardness)
- Contact allergens
- Environmental aeroallergens (dust mites)
- Inappropriate bathing habits (long hot showers)
- Sweating
- Microbes (S. aureus)
- Stress
Clinical Presentation

- cutaneous inflammation caused by an external agent(s)

Table 10. Contact Dermatitis

<table>
<thead>
<tr>
<th>Irritant Contact Dermatitis</th>
<th>Allergic Contact Dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Reaction</strong></td>
<td><strong>Cell-mediated delayed (Type IV) hypersensitivity reaction (see Rheumatology, RH2)</strong></td>
</tr>
<tr>
<td><strong>Type of Reaction</strong></td>
<td><strong>Erythema with a papulovesicular eruption, swelling, pruritus</strong></td>
</tr>
<tr>
<td><strong>Frequency of Contact Dermatitis</strong></td>
<td><strong>Minority; patient acquires susceptibility to allergen that persists indefinitely</strong></td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td><strong>Dorsum of hand usually involved; often discrete area of skin involvement</strong></td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td><strong>(See sidebar) Many allergens are irritants, so may coincide with irritant dermatitis</strong></td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td><strong>Patch testing to determine specific allergen</strong></td>
</tr>
</tbody>
</table>


Figure 5. Atopic dermatitis treatment algorithm

D15 Dermatology


See: Systematic review.

Conclusions:
- Use of the atopy patch test (APT) is controversial.
- There is no gold standard for Aeroallergen provocation, so APT is used without comparison to another method.
- APT findings are not consistent among children with atopic dermatitis.
- APT may be valuable:
  - May provide diagnostic information and may aid clinical decision making regarding the use of IGE-mediated sensitizations

Future research is needed:
- Need standardized provocation and avoidance testing to determine the clinical relevance of obtaining a positive APT result

Top Ten Allergens as Identified by The North American Contact Dermatitis Group

<table>
<thead>
<tr>
<th>Test Substance</th>
<th>Allergic Reactions (%)</th>
<th>Common Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neomycin sulfate</td>
<td>13.1</td>
<td>Most commonly used topical antibiotic</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>10.9</td>
<td>Used in paints, powders, rubrics</td>
</tr>
<tr>
<td>Sodium thiosulfate</td>
<td>9.5</td>
<td>Used in bleaching, hair care products</td>
</tr>
<tr>
<td>Aluminium powder</td>
<td>9.0</td>
<td>Used in cosmetics, toothpaste</td>
</tr>
<tr>
<td>Nickel sulfate</td>
<td>8.7</td>
<td>Found in some jewelry, belt buckles</td>
</tr>
<tr>
<td>Fragrance mixes</td>
<td>8.7</td>
<td>Used in detergents, cosmetics</td>
</tr>
<tr>
<td>Balsam of Peru</td>
<td>8.8</td>
<td>Fragrance material</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>9.3</td>
<td>Used in adhesives, resins, glues</td>
</tr>
<tr>
<td>Quaternium-15</td>
<td>9.0</td>
<td>Used in soaps, detergents, hair care products</td>
</tr>
<tr>
<td>Cobalt chloride</td>
<td>9.0</td>
<td>Used in paints, dyes, adhesives</td>
</tr>
<tr>
<td>Bicarbonate of soda</td>
<td>8.5</td>
<td>Used in toothpaste, deodorants, cleansers</td>
</tr>
</tbody>
</table>

To ronto Notes 2014

- one of the main ingredients in Polysporin®
**Dyshidrotic Dermatitis**

**Clinical Presentation**
- “tapioca pudding” papulovesicular dermatitis of hands and feet that coalesce into plaques, followed by painful fissuring
- acute stage often very pruritic
- secondary infection common
- lesions heal with desquamation and may lead to chronic lichenification
- sites: palms and soles ± dorsal surfaces of hands and feet

**Pathophysiology**
- NOT caused by hyperhidrosis (excessive sweating)
- emotional stress may precipitate the dermatitis

**Management**
- topical: high potency corticosteroid with plastic cling wrap occlusion to increase penetration
- intralesional triamcinolone injection
- systemic:
  - prednisone in severe cases
  - antibiotics for secondary *S. aureus* infection

**Nummular Dermatitis**

**Clinical Presentation**
- annular, coin-shaped, pruritic, dry, scaly, erythematous plaques, can become lichenified
- often associated with atopic and dyshidrotic dermatitis
- secondary infection common

**Management**
- moisturization
- mid to high potency corticosteroid ointment bid

**Seborrheic Dermatitis**

**Clinical Presentation**
- greasy, erythematous, yellow, scaling, minimally elevated papules and plaques in areas rich in sebaceous glands, can look moist and superficially eroded in flexural regions
- infants: cause of “cradle cap”
- children: may be generalized with flexural and scalp involvement
- adults: diffuse involvement of scalp margin with yellow to white flakes, pruritus, and underlying erythema
- sites: scalp, eyebrows, eyelashes, beard, glabella, post-auricular, over sternum, trunk, body folds, genitalia

**Pathophysiology**
- possible etiologic association with *Malassezia* spp. (yeast)

**Epidemiology**
- common in infants and at puberty
- increased incidence and severity in immunocompromised patients (e.g. HIV)
- in adults, can cause dandruff (pityriasis sicca)

**Management**
- face: ketoconazole (Nizoral®) cream daily or bid + mild steroid cream daily or bid
- scalp: salicylic acid in olive oil or Derma-Smoothe FS® lotion (peanut oil, mineral oil, fluocinolone acetonide 0.01%) to remove dense scales, 2% ketoconazole shampoo (Nizoral®), ciclopirox (Stieprox®) shampoo, selenium sulfide (e.g. Selsun®) or zinc pyrithione (e.g. Head and Shoulders®) shampoo, steroid lotion (e.g. betamethasone valerate 0.1% lotion bid)
**Stasis Dermatitis**

**Clinical Presentation**
- persistent inflammation of the lower legs with erythema, xerosis, scaling, and brownish pigmentation in late stages
- associated with venous insufficiency

**Management**
- compression stockings
- rest and elevate legs (above the level of the heart)
- moisturizer to treat xerosis
- mid-high potency topical corticosteroids to control inflammation

**Complications**
- ulceration (common at medial malleolus), secondary bacterial infections

**Lichen Simplex Chronicus**

**Clinical Presentation**
- chronic dermatitis resulting from continued rubbing/scratching of skin → lichenified skin
- may develop secondarily to another pruritic skin disease

**Management**
- treat pruritus to break the itch-scratch cycle: antihistamines, topical antipruritics
- topical high-potency corticosteroids

**Papulosquamous Diseases**

**Lichen Planus**

**Clinical Presentation**
- acute or chronic inflammation of mucous membranes or skin characterized by violaceous papules, especially on flexural surfaces
- small, polygonal, flat-topped, shiny, violet papules; resolves into hyperpigmented macules
- sites: wrists, ankles, mucous membranes in 60% (mouth, vulva, glans), nails, scalp
- distribution: symmetrical and bilateral
- Wickham's striae: reticulate white-grey lines over surface; pathognomonic
- mucous membrane lesions: lacy, whitish reticular network, milky-white plaques/papules; increased risk of SCC in erosions and ulcers
- nails: longitudinal ridging; dystrophic; pterygium formation
- scalp: scarring alopecia with perifollicular hyperkeratosis
- spontaneously resolves but may last for weeks, months or years (mouth and skin lesions)
- rarely associated with hepatitis C
- Koebner phenomenon
- may be triggered by severe emotional stress

**Management**
- topical corticosteroids with occlusion or intradermal steroid injections
- short courses of oral prednisone (rarely)
- photochemotherapy for generalized or resistant cases
- oral retinoids for erosive lichen planus in mouth
- systemic immunosuppression/modulation e.g. azathioprine, methotrexate, cyclosporine, metronidazole

**Pityriasis Rosea**

**Clinical Presentation**
- acute, self-limiting eruption characterized by red, oval plaques/patches with central scale that does not extend to edge of lesion
- long axis of lesions follows skin tension lines (aka Langer's Lines) parallel to ribs producing “Christmas tree” pattern on back
- varied degree of pruritus
- most start with a “herald” patch which precedes other lesions by 1-2 wk
- sites: trunk, proximal aspects of arms and legs
Etiology
• suspected HHV7

Management
• none required; clears spontaneously in 6-12 wk, reassurance
• topical corticosteroids when post-inflammatory pigmentation is a concern or if patient is uncomfortable
• oral erythromycin or oral acyclovir may expedite healing

Psoriasis

Classification
1. plaque psoriasis  
2. guttate psoriasis  
3. erythrodermic psoriasis  
4. pustular psoriasis  
5. psoriatic arthritis

Differential Diagnosis
• atopic dermatitis, mycosis fungoides (cutaneous T-cell lymphoma), seborrheic dermatitis, tinea

Diagnosis
• usually clinical, biopsy to confirm
• psoriasis area and severity index (PASI)
  ▪ score is based on: percentage of surface area involved and the severity of symptoms (erythema, infiltration, desquamation)

1. PLAQUE PSORIASIS

Clinical Presentation
• chronic and recurrent disease characterized by well-circumscribed erythematous papules/plaques with silvery-white scales
• often worse in winter (lack of sun and humidity)
• Koebner phenomenon
• Auspitz sign: bleeds from minute points when scale is removed
• usually non-pruritic
• exacerbating factors: drugs (lithium, ethanol, chloroquine, β-blockers), stress
• sites: scalp, extensor surfaces of elbows and knees, trunk (especially buttocks), nails, pressure areas

Pathophysiology
• decreased epidermal transit time from stratum basale to stratum corneum
• shortened cell cycle of psoriatic compared to normal skin
• Th1-mediated inflammatory response

Management
Table 11. Topical Treatment of Psoriasis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lubricants</td>
<td>Reduce fissure formation</td>
<td>Petrolatum is effective</td>
</tr>
<tr>
<td>Salicylic acid 1-12%</td>
<td>Remove scales</td>
<td></td>
</tr>
<tr>
<td>Tar (LCD: Liquor carbonis detergens 20% coal tar solution)</td>
<td>Inhibits DNA synthesis, increases cell turnover</td>
<td>Poor long term compliance</td>
</tr>
<tr>
<td>Calciptorine /calcitriol (Dovonex®, Vectical®)</td>
<td>Binds to skin 1,25-dihydroxyvitamin D3 to inhibit keratinocyte proliferation</td>
<td>Can be used on face and skin folds</td>
</tr>
<tr>
<td>Betamethasone + calcipotriene (Dovobet®, Taclonex®)</td>
<td>See above</td>
<td>Sold as Dovobet® in Canada and Europe, sold as Taclonex® in US</td>
</tr>
<tr>
<td>Corticosteroid ointment</td>
<td>Reduce scaling and thickness</td>
<td>Use appropriate potency steroid in different areas for degree of psoriasis</td>
</tr>
<tr>
<td>Tazarotene (Tazorac®) (gel/cream)</td>
<td>Retinoid derivative, decreased scaling</td>
<td>Use on nails</td>
</tr>
</tbody>
</table>

Table 12. Systemic Treatment of Psoriasis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Bone marrow toxicity, hepatic cirrhosis</td>
</tr>
<tr>
<td>PUVA</td>
<td>Pruritus, burning, cutaneous, skin cancer</td>
</tr>
<tr>
<td>Acitretin</td>
<td>Alopecia, chelitis, keratodermatitis, xerosis, hypertiglyceridemia</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Renal toxicity, hypertension, immunosuppression</td>
</tr>
<tr>
<td>UVB and “Narrow band” UVB (311-312 nm)</td>
<td>Well tolerated</td>
</tr>
</tbody>
</table>

Table 13. Biologics Approved in Canada

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Route</th>
<th>Dosing Schedule</th>
<th>Effectiveness</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>etanercept (Enbrel®)*</td>
<td>SC</td>
<td>Twice weekly initially</td>
<td>+++</td>
<td>Anti-TNF</td>
</tr>
<tr>
<td>adalimumab (Humira®)*</td>
<td>SC</td>
<td>Every 2 wk</td>
<td>++++</td>
<td>Anti-TNF</td>
</tr>
<tr>
<td>infliximab (Remicade®)*</td>
<td>IV</td>
<td>Every 2 mo</td>
<td>++++++</td>
<td>Anti-TNF</td>
</tr>
<tr>
<td>ustekinumab (Stelara®)</td>
<td>SC</td>
<td>Every 12 wk during maintenance</td>
<td>++++</td>
<td>Anti-IL 12/23</td>
</tr>
</tbody>
</table>

*Can also be used to treat psoriatic arthritis

2. GUTTATE PSORIASIS (“DROP-LIKE”)

Clinical Presentation
- discrete, scattered salmon-pink scaling papules
- sites: generalized, sparing palms and soles
- often antecedent streptococcal pharyngitis

Management
- UVB phototherapy, sunlight, lubricants
- penicillin V or erythromycin if Group A β-hemolytic Streptococcus on throat culture

3. ERYTHRODERMIC PSORIASIS

Clinical Presentation
- generalized erythema with fine desquamative scale on surface
- associated symptoms: arthralgia, severe pruritus
- may present in patient with previous mild plaque psoriasis
- aggravating factors: lithium, β-blockers, NSAIDs, antimalarials, phototoxic reaction, infection

Management
- hospitalization, bed rest, IV fluids, monitor fluid and electrolytes
- treat underlying aggravating condition, sun avoidance
- methotrexate, cyclosporine, UV, oral retinoids, biologics

Mechanism of Biologics
- “-mab” = monoclonal antibody
- “-cept” = receptor
4. PUSTULAR PSORIASIS

Clinical Presentation
- sudden onset of erythematous macules and papules which evolve rapidly into pustules, very painful
- can be generalized or localized to palms/soles
- patient usually has history of psoriasis; may occur with sudden withdrawal from steroid therapy

Management
- methotrexate, oral retinoids, biologics

5. PSORIATIC ARTHRITIS

- 5 categories
  - asymmetric oligoarthropathy
  - DIP joint involvement (predominant)
  - rheumatoid pattern (symmetric polyarthropathy)
  - psoriatic arthritis mutilans (most severe form)
  - predominant spondylitis or sacroiliitis
- see Rheumatology RH23

Vesiculobullous Diseases

Bullous Pemphigoid

Clinical Presentation
- chronic autoimmune bullous eruption characterized by pruritic, tense, subepidermal bullae on an erythematous or normal skin base
- sites: flexor aspect of forearms, axillae, medial thighs, groin, abdomen, mouth (33%)

Pathophysiology
- IgG produced against dermal-epidermal basement membrane proteins (hemidesmosomes) leads to subepidermal bullae

Epidemiology
- 60-80 yr old
- there are case reports of association with internal malignancy, but this is exceedingly rare

Investigations
- immunofluorescence shows linear deposition of IgG and C3 along the basement membrane
- anti-basement membrane antibody (IgG) (pemphigoid antibody detectable in serum)

Prognosis
- generalized bullous eruption heals without scarring
- rarely fatal

Management
- prednisone ± steroid-sparing agents (e.g. azathioprine, methotrexate)
- topical potent steroids (clobetasol) may be as effective as systemic steroids
- tetracycline ± nicotinamide is effective for some cases
- dapsone for milder cases

Pemphigus Vulgaris

Clinical Presentation
- autoimmune blistering disease characterized by flaccid, non-pruritic epidermal bullae/vesicles on an erythematous or normal skin base
- may present with erosions and secondary bacterial infection
- sites: mouth (90%), scalp, face, chest, axillae, groin, umbilicus
- Nikolsky’s sign: sliding or rubbing pressure on skin ⇒ separation of epidermis
- Asboe-Hansen sign: pressure applied to bulla causes it to extend laterally

Pathophysiology
- IgG produced against epidermal desmoglein-1 and -3 leads to intraepidermal bullae

Epidemiology
- 40-60 yr old, higher prevalence in Jewish, Mediterranean, Asian populations
- paraneoplastic pemphigus may be associated with thymoma, myasthenia gravis, malignancy, and use of D-penicillamine
**Investigations**
- immunofluorescence: shows IgG and C3 deposition intraepidermally
- circulating serum anti-desmoglein IgG antibodies

**Prognosis and Clinical Course**
- begins with mouth lesions, followed by skin lesions
- first localized (6-12 mo) then generalized
- lesions heal with hyperpigmentation but no scar
- may be fatal unless treated with immunosuppressive agents

**Management**
- prednisone 1-3 mg/kg until no new blisters, then 1-1.5 mg/kg until clear, then taper
- steroid-sparing agents: azathioprine, methotrexate, gold, cyclophosphamide, cyclosporine, intravenous immunoglobulin (IVIG), mycophenolate mofetil, rituximab
- plasmapheresis for acutely high antibody levels

**Table 14. Summary of Vesiculobullous Diseases**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Bullous Pemphigoid</th>
<th>Dermatitis Herpetiformis</th>
<th>Pemphigus Vulgaris</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Basement membrane</td>
<td>Dermal</td>
<td>Intraepidermal</td>
</tr>
<tr>
<td>Infiltrate</td>
<td>Eosinophils</td>
<td>Neutrophils</td>
<td>Eosinophils and neutrophils</td>
</tr>
<tr>
<td>Management</td>
<td>Systemic steroids</td>
<td>Gluten-free diet</td>
<td>High dose steroids</td>
</tr>
<tr>
<td></td>
<td>Tetracycline</td>
<td>Dapsone</td>
<td>Immunosuppressive agent (e.g. Imuran®, mycophenolic acid)</td>
</tr>
<tr>
<td></td>
<td>Clobetasol cream</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Association</td>
<td>Malignancy (rarely)</td>
<td>Gluten enteropathy</td>
<td>Malignancy with paraneoplastic pemphigus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thyroid disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intestinal lymphoma</td>
<td></td>
</tr>
</tbody>
</table>

**Dermatitis Herpetiformis**

**Clinical Presentation**
- grouped papules/vesicles/urticarial wheals on an erythematous base, associated with intense pruritus, burning, stinging
- almost always excoriated, rarely seen as blisters
- lesions grouped, bilaterally symmetrical
- sites: extensor surfaces of elbows/knees, sacrum, buttocks, scalp

**Pathophysiology**
- 90% have HLA B8, DR3, DQWZ
- 90% associated with an often subclinical gluten-sensitive enteropathy (celiac)
- 30% have thyroid disease; increased risk of intestinal lymphoma in untreated comorbid celiac disease; iron/folate deficiency is common

**Epidemiology**
- 20-60 yr old, M:F = 2:1

**Management**
- dapsone for pruritus
- gluten-free diet for life

**Porphyria Cutanea Tarda**

**Clinical Presentation**
- tense vesicles/bullae in photoexposed areas subjected to trauma
- facial hypertrichosis, brown hypermelanosis vesicles, and bullae in photodistribution (dorsum of hands and feet)
- sites: light-exposed areas subjected to trauma, dorsum of hands and feet, nose, and upper trunk

**Pathophysiology**
- autosomal dominant or sporadic skin disorder associated with the presence of excess heme precursors
- associated with hemochromatosis, alcohol abuse, DM, drugs (estrogen therapy, NSAIDs), HIV, hepatitis C, increased iron indices

**Epidemiology**
- 30-40 yr old, M>F
**Investigations**
- urine + 5% HCl shows orange-red fluorescence under Wood's lamp (UV rays)
- 24 hour urine for uroporphyrins (elevated)
- stool contains elevated coproporphyrins
- immunofluorescence shows IgE at dermal-epidermal junctions

**Management**
- discontinue aggravating substances (alcohol, estrogen therapy)
- phlebotomy to decrease body iron load
- low dose hydroxychloroquine

---

**Drug Hypersensitivity Syndrome**
- fever followed by symmetrical bright red exanthematous eruption that may lead to internal organ involvement (hepatitis, arthralgia, nephritis, pneumonitis, lymphadenopathy, hematologic abnormalities, thyroid abnormalities)
- classically occurs approximately 7-10 d after first exposure to the drug
- may be elevated incidence of similar reactions in siblings
- most common causes: sulfonamides, allopurinol, and anticonvulsants (phenytoin, phenobarbital, carbamazepine, lamotrigine)
- 10% mortality if severe, undiagnosed, and untreated

**Erythema Multiforme (EM), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)**
- disorders with varying presence of characteristic skin lesions, blistering and mucous membrane involvement

### Table 15. Comparison of Erythema Multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis

<table>
<thead>
<tr>
<th></th>
<th>Erythema Multiforme (EM)</th>
<th>Stevens-Johnson Syndrome (SJS)</th>
<th>Toxic Epidermal Necrolysis (TEN)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lesion</strong></td>
<td>Macules/papules with central vesicles</td>
<td>Cutaneous blistering with mucous membrane involvement (especially lips)</td>
<td>Mucous membrane involvement, and severe blistering <em>Atypical lesions</em>: 50% have no target lesions Diffuse erythema then necrosis and sheet-like epidermal detachment in &gt;30% of BSA</td>
</tr>
<tr>
<td><strong>Sites</strong></td>
<td>Dorsa of hands and forearms</td>
<td>Prominent face and trunk involvement Palms and soles may be spared &gt;30% BSA</td>
<td>Nails may also shed</td>
</tr>
<tr>
<td><strong>Other Complications</strong></td>
<td>Burning and stinging Recurrences Secondary bacterial infection</td>
<td>Infection, scarring, contractures, eruptive nevomelanocytic nevi, corneal scarring, blindness, phimosis and vaginal symphysis</td>
<td>Same as SJS’s PLUS electrolyte imbalance, dehydration, tubular necrosis and acute kidney injury, epithelial erosions of trachea, death</td>
</tr>
<tr>
<td><strong>Constitutional Symptoms</strong></td>
<td>Weakness, malaise</td>
<td>Prodrome 1-14 d prior to eruption with fever and flu-like illness</td>
<td>High fever &gt;38°C</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Infection: HSV, or <em>Mycoplasma pneumoniae</em></td>
<td>Frequently drug-related (NSAIDs, anticonvulsants, sulfonamides, penicillins)</td>
<td>Same as SJS</td>
</tr>
<tr>
<td><strong>Differential Diagnosis</strong></td>
<td>Urticaria, granuloma annulare, mycosis fungoides, vasculitis</td>
<td>Scarlet fever, phototoxic, eruption, GVHD, SSSS, exfoliative dermatitis, Kawasaki disease, paraneoplastic pemphigus</td>
<td>Same as SJS</td>
</tr>
<tr>
<td><strong>Course and Prognosis</strong></td>
<td>Lesions last 2 wk and heal without complications 4-6 wk course 5% mortality</td>
<td>30% mortality due to fluid loss, regrowth of epidermis by 3 wk, secondary infection</td>
<td>As for Stevens-Johnson syndrome Admit to burn unit Debride frankly necrotic tissue Consider IVIG vs. cyclosporine</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Symptomatic treatment (oral antihistamines, oral antacids) Corticosteroids in severely ill (controversial) Prophylactic oral acyclovir for 6-12 mo for HSV-associated EM with frequent recurrences</td>
<td>Prolonged hospitalization Withdraw suspect drug Intravenous fluids Infection prophylaxis Consider IVIG vs. cyclosporine (corticosteroids controversial)</td>
<td>As for Stevens-Johnson syndrome Admit to burn unit Debride frankly necrotic tissue Consider IVIG vs. cyclosporine</td>
</tr>
</tbody>
</table>
Exanthematous Eruptions (Maculopapular Eruptions/Morbilliform)

- symmetrical, widespread, erythematous patches or plaques ± scales
- the "classic" and most common adverse drug reaction
- often starts on trunk
- may progress to generalized exfoliative dermatitis especially if the drug is continued
- most common causes: penicillin, sulfonamides, phenytoin

Fixed Drug Eruptions

- sharply demarcated erythematous oval patches on the skin or mucous membranes
  - sites: face, mucosa, genitalia, acral
  - reoccurs in same location upon subsequent exposure to the drug (fixed location)
- most common causes: antimicrobials (tetracycline, sulfonamides), anti-inflammatories, psychoactive agents (barbiturates), phenolphthalein

Photosensitivity Eruptions

- phototoxic reaction: "an exaggerated sunburn" confined to sun-exposed areas
- photoallergic reaction: an eczematous eruption that may spread to areas not exposed to light
- most common causes: chlorpromazine, doxycycline, thiazide diuretics, procainamide

Serum Sickness-Like Reaction

- a symmetric drug eruption resulting in fever, arthralgia, lymphadenopathy, and skin rash (urticaria)
- usually appears 5-10 d after drug exposure
- most common causes: cefaclor in kids; buproprion (Zyban®, Wellbutrin®) in adults

Heritable Disorders

Ichthyosis Vulgaris

Clinical Presentation
- generalized hyperkeratosis leading to dry skin
- genetic deficiency in filaggrin protein
- “fish-scale” appearance especially on extremities with sparing of flexural creases, palms and soles

Pathophysiology
- abnormal retention of keratinocytes (hyperkeratosis)
- scaling without inflammation

Epidemiology
- 1:300 incidence
- autosomal dominant inheritance
- associated with atopic dermatitis and keratosis pilaris

Management
- immersion in bath and oils
- emollient or humectant creams, and creams or oils containing urea or α- or β-hydroxy acids
**Neurofibromatosis (Type I; von Recklinghausen’s Disease)**

**Clinical Presentation**
- diagnostic criteria includes 2 or more of the following:
  1. more than 5 café-au-lait patches >1.5 cm in an adult or more than 5 café-au-lait macules >0.5 cm in a child under age 5
  2. axillary or inguinal freckling
  3. iris hamartomas (Lisch nodules)
  4. optic gliomas
  5. neurofibromas
  6. distinctive bony lesion (sphenoid wing dysplasia or thinning of long bone cortex)
  7. first degree relative with neurofibromatosis type I
- associated with pheochromocytoma, astrocytoma, bilateral acoustic neuromas, bone cysts, scoliosis, precocious puberty, developmental delay, and renal artery stenosis
- skin lesions less prominent in neurofibromatosis Type II (see Pediatrics, P91)

**Pathophysiology**
- autosomal dominant disorder with excessive and abnormal proliferation of neural crest elements (Schwann cells, melanocytes), high incidence of spontaneous mutation
- linked to absence of neurofibromin (a tumour suppressor gene)

**Epidemiology**
- incidence 1:3,000

**Management**
- watch for brain tumors such as astrocytoma
- excise suspicious or painful lesions
- see Pediatrics, P92

---

**Vitiligo**

**Clinical Presentation**
- primary pigmentary disorder characterized by depigmentation
- acquired destruction of melanocytes characterized by sharply margined white patches
- associated with streaks of depigmented hair, chorioretinitis
- sites: extensor surfaces and periorificial areas (mouth, eyes, anus, genitalia)
- Koebner phenomenon, may be precipitated by trauma

**Pathophysiology**
- acquired autoimmune destruction of melanocytes

**Epidemiology**
- 1% incidence, polygenic
- 30% with positive family history

**Investigations**
- rule out associated autoimmune diseases: thyroid disease, pernicious anemia, Addison’s disease, Type I DM
- Wood’s lamp to detect lesions: illuminates UV light onto skin to detect patches of amelanosis

**Management**
- sun avoidance and protection
- topical immunomodulator (i.e. tacrolimus, pimecrolimus) or a topical steroid
- PUVA or Narrow band UVB
- make-up
- “bleaching” normal pigmented areas (i.e. monobenzyl ether of hydroquinone 20%) if widespread loss of pigmentation

---

**Interventions for Vitiligo**
Cochrane DB Syst Rev 2010;1:CD003263

**Study:** Systematic review of randomized controlled trials.

**Patients:** 3139 participants with vitiligo.

**Intervention:** Topical treatments, light therapies, oral treatments, surgical methods, and psychological therapies

**Outcome:** >75% repigmentation, adverse effects

**Results:** Moderate evidence exists for the use of topical corticosteroids to induce repigmentation. However, adverse effects are observed with long-term use. Topical use of non-steroidal immunomodulators (i.e. tacrolimus), especially in combination with light therapies, has also been shown to induce repigmentation. However, long-term use may theoretically increase the risk for skin cancer. In general, combination therapy including some form of light therapy had the most significant improvement. Sustained repigmentation (>2 yr) has not been reported and thus results should be treated with caution.
Infections

Bacterial Infections

- often involve the epidermis, dermis, hair follicles or periungual region ± systemic

EPIDERMIS

IMPETIGO

Clinical Presentation
- acute purulent infection which appears vesicular; progresses to golden yellow “honey-crusted” lesions surrounded by erythema
- can present with bullae
- sites: commonly face, arms, legs and buttocks

Etiology
- GAS, S. aureus, or both

Epidemiology
- preschool and young adults living in crowded conditions, poor hygiene, neglected minor trauma

Differential Diagnosis
- infected eczema, HSV, Varicella virus

Investigations
- Gram stain and culture of lesion fluid or biopsy

Management
- remove crusts, use saline compresses and topical antiseptic soaks bid
- topical antibacterials such as 2% mupirocin or fusidic acid (Canada only) tid; continue for 7-10 d after resolution
- systemic antibiotics such as cloxacillin or cephalexin for 7-10 d

DERMIS

Table 16. Comparison of Erysipelas and Cellulitis

<table>
<thead>
<tr>
<th></th>
<th>Erysipelas</th>
<th>Cellulitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Presentation</strong></td>
<td>Involves upper dermis</td>
<td>Involves lower dermis/subcutaneous fat</td>
</tr>
<tr>
<td></td>
<td>Confluent, erythematous, sharp raised edge, warm plaque, well demarcated</td>
<td>Tender, vesicles poorly demarcated, not uniformly raised</td>
</tr>
<tr>
<td></td>
<td>Very painful (“St. Anthony’s fire”)</td>
<td>Tender</td>
</tr>
<tr>
<td></td>
<td>Sites: face and legs</td>
<td>Sites: commonly on legs</td>
</tr>
<tr>
<td></td>
<td>Systemic symptoms: fever, chills, headache, weakness (if present, sign of more serious infection)</td>
<td>Systemic symptoms (uncommon): fever, leukocytosis, lymphadenopathy</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>GAS, GAS, S. aureus (large sized wounds), H. influenzae (periorbital), Pasteurella multocida (dog/cat bite)</td>
<td>GAS, S. aureus (large sized wounds), H. influenzae (periorbital), Pasteurella multocida (dog/cat bite)</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Scarlet fever, streptococcal gangrene, fat necrosis, coagulopathy, spreads via lymphatics</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Differential Diagnosis</strong></td>
<td>DVT (less red, less hot, smoother), superficial phlebitis, contact dermatitis, photosensitivity reaction, stasis dermatitis, panniculitis, vasculitis</td>
<td>Same as erysipelas</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Clinical diagnosis: rarely do skin/blood culture</td>
<td>Same as erysipelas</td>
</tr>
<tr>
<td></td>
<td>If suspect necrotizing fasciitis: do immediate biopsy and frozen section, histopathology</td>
<td>Same as erysipelas</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>1st line: penicillin, cloxacillin or cefazolin</td>
<td>1st line: cloxacillin or cefazolin/cephalexin</td>
</tr>
<tr>
<td></td>
<td>2nd line: clindamycin or cephalexin</td>
<td>2nd line: erythromycin or clindamycin</td>
</tr>
<tr>
<td></td>
<td>If allergic to penicillin, use erythromycin</td>
<td>Children: cefuroxime</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If diabetes mellitus (foot infections): TMP/SMX and metronidazole</td>
</tr>
</tbody>
</table>
## COMMON HAIR FOLLICLE INFECTIONS

### Table 17. Comparison of Superficial Folliculitis, Furuncles and Carbuncles

<table>
<thead>
<tr>
<th></th>
<th>Superficial Folliculitis</th>
<th>Furuncles (Boils)</th>
<th>Carbuncles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Presentation</td>
<td>Superficial infection of the hair follicle (versus pseudofolliculitis: inflammation of follicle due to friction, irritation, or occlusion) Acute lesion consists of a dome-shaped pustule at the mouth of hair follicle Pustule ruptures to form a small crust Sites: primarily scalp, shoulders, anterior chest, upper back, other hair-bearing areas</td>
<td>Red, hot, tender, inflammatory nodules with central yellowish point, which forms over summit and ruptures Involves subcutaneous tissue that arises from a hair follicle Sites: hair-bearing skin (thigh, neck, face, axillae, perineum, buttocks)</td>
<td>Deep-seated abscess formed by multiple coalescing furuncles Usually in areas of thicker skin Occasionally ulcerates Lesions drain through multiple openings to the surface Systemic symptoms may be associated</td>
</tr>
<tr>
<td>Etiology</td>
<td>Normal non-pathogenic bacteria (Staphylococcus – most common; Pseudomonas – hot tub)</td>
<td>S. aureus</td>
<td>S. aureus</td>
</tr>
<tr>
<td>Management</td>
<td>Antiseptic (Hibiclens®) Topical antibacterial (fusidic acid, mupirocin, or erythromycin) Oral cloxacillin for 7-10 d</td>
<td>Incise and drain large carbuncles to relieve pressure and pain If afebrile: hot wet packs, topical antibiotic If febrile/cellulitis: culture blood and aspirate pustules (Gram stain and C&amp;S) Cloxacillin for 1-2 wk (especially for lesions near external auditory canal/rose, with surrounding cellulitis, and not responsive to topical therapy)</td>
<td>Same as for furuncles</td>
</tr>
</tbody>
</table>

### Dermatophytoses

#### Clinical Presentation
- infection of skin, hair and nails caused by dermatophytes (fungi that live within the epidermal keratin or hair follicle and do not penetrate into deeper structures)

#### Pathophysiology
- digestion of keratin by dermatophytes results in scaly skin, broken hairs, crumbling nails/onycholysis

#### Etiology
- *Trichophyton, Microsporum, Epidermophyton* species (*Pityrosporum* is a superficial yeast and not a dermatophyte)

#### Investigations
- skin scrapings, hair, and/or nail clippings analyzed with potassium hydroxide (KOH) prep to look for hyphae and mycelia

#### Management
- topicals as first line agents for tinea corporis/cruris and tinea pedis (interdigital type):
  - e.g. clotrimazole or terbinafine cream applied bid, until one week after complete resolution of lesions
- oral therapy is indicated for onychomycosis or tinea capitis:
  - e.g. terbinafine (Lamisil® – liver toxicity, CYP 2D6 inhibitor) or itraconazole (Sporanox® – CYP 3A4 inhibitor, liver toxicity)

### Table 18. Different Manifestations of Dermatophyte Infection

<table>
<thead>
<tr>
<th></th>
<th>Clinical Presentation</th>
<th>Differential Diagnosis</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea Capitis</td>
<td>Round, scaly patches of alopecia, possibly with broken off hairs; pruritic Sites: scalp, eyelashes, and eyebrows; involving hair shafts and follicles Kerion (boggy, elevated, purulent inflamed nodule/plaque) may form secondary to infection by bacteria and result in scarring May have occipital lymphadenopathy Affects children (mainly black), immunocompromised adults Very contagious and may be transmitted from barber, hats, theatre seats, pets</td>
<td>Alopeica areata, psoriasis, seborrheic dermatitis, trichotillomania</td>
<td>Wood’s light examination of hair; green fluorescence only for Microsporum infection Culture of scales/hair shaft Microscopic examination of KOH preparation of scales or hair shafts</td>
<td>Terbinafine (Lamisil®) x 4 wk NB: oral agents are required to penetrate the hair root where dermatophyte resides Adjunctive antifungal shampoos or lotions may be helpful, and may prevent spread (e.g. selenium sulfide, ketoconazole, ciclopirox)</td>
</tr>
<tr>
<td>Tinea Corporis (Ringworm)</td>
<td>Pruritic, scaly, round/oval plaque with active erythematous margin and central clearing Site: trunk, limbs, face</td>
<td>Granuloma annulare, pityriasis rosea, psoriasis, seborrheic dermatitis</td>
<td>Microscopic examinations of KOH prep of scales shows hyphae Culture of scales</td>
<td>Topicals: 1% clotrimazole, 2% ketoconazole 2% miconazole, terbinafine or ciclopirox olamine cream bid for 2-4 wk Oral terbinafine, or itraconazole, or fluconazole, or ketoconazole if extensive</td>
</tr>
</tbody>
</table>
### Parasitic Infections

#### SCABIES

**Clinical Presentation**
- A transmissible parasitic skin infection due to *Sarcoptes scabiei*, a mite, characterized by superficial burrows, intense pruritus (especially nocturnal), and secondary infection
- Primary lesion: superficial linear burrows; inflammatory papules and nodules in the axilla and groin
- Secondary lesion: small urticarial crusted papules, eczematous plaques, excoriations
- Sites: axillae, groin, buttocks, hands/feet (especially web spaces), sparing of head and neck (except in infants)

**Pathogenesis**
- Scabies mite remains alive 2-3 d on clothing/sheets
- Incubation of 1 mo, then pruritus begins
- Re-infection followed by hypersensitivity in 24 h

**Etiology**
- *Sarcoptes scabiei*
- Risk factors: sexual promiscuity, crowding, poverty, nosocomial, immunocompromised

**Differential Diagnosis**
- Asteatotic eczema, dermatitis herpetiformis, lichen simplex chronicus (neurodermatitis)

**Investigations**
- Microscopic examination of root and content of burrow and mineral oil mount for mite, eggs, feces

**Management**
- Bathe, then apply permethrin 5% cream (i.e. Nix®) from neck down to soles of feet (must be left on for 8-14 h and requires second treatment 7 d after first treatment)
- Change underwear and linens; wash with detergent in hot water cycle then machine dry
- Treat family and close contacts
- Pruritus may persist for 2-3 wk after effective treatment due to prolonged hypersensitivity reaction
- Mid potency topical steroids and antihistamines for symptom management
LICE (Pediculosis)

Clinical Presentation
- Intensely pruritic red excoriations, morbilliform rash, caused by louse (a parasite)
- Scalp lice: nits (i.e., louse eggs) on hairs
  - Red excoriated skin with secondary bacterial infection, lymphadenopathy
- Pubic lice: nits on hairs
  - Excoriations
- Body lice: nits and lice in seams of clothing
  - Excoriations and secondary infection mainly on shoulders, belt-line and buttocks

Differential Diagnosis
- Bacterial infection of scalp, seborrheic dermatitis

Management
- Permethrin 1% (Nix® cream rinse) (ovicidal) or permethrin 1% (RC & Cor®, Kwellada-P® shampoo)
- Comb hair with fine-toothed comb using dilute vinegar solution to remove nits
- Repeat in 7 d after first treatment
- Shave hair if feasible, change clothing and linens; wash with detergent in hot water cycle then machine dry

Bed bugs (Hemiptera)

Clinical Presentation
- Burning wheals, turning to firm papules, often in groups of three – “breakfast, lunch and dinner” in areas with easy access (face, neck, arms, legs, hands)

Etiology
- Caused by Cimex lectularius, a small insect that feeds mainly at night
- During day bedbugs hide in crevices in walls and furniture

Differential Diagnosis
- Dermatitis herpetiformis, drug eruptions, ecthyma, other insect bites, scabies

Management
- Professional fumigation of home
- Topical steroids and oral H1-antagonists for symptomatic relief
- Definitive treatment is removal of clutter in home and application of insecticides to walls and furniture

Viral Infections

Herpes Simplex

Clinical Presentation
- Herpetiform (i.e., grouped) vesicles on an erythematous base on skin or mucous membranes
- Transmitted via contact with erupted vesicles or via asymptomatic viral shedding
- Primary
  - Children and young adults
  - Usually asymptomatic; may have high fever, regional lymphadenopathy, malaise
  - Followed by antibody formation and latency of virus in dorsal nerve root ganglion
- Secondary
  - Recurrent form seen in adults; much more common than primary
  - Prodrome: tingling, pruritus, pain
  - Triggers for recurrence: fever, excess sun exposure, physical trauma, menstruation, emotional stress, URTI
- Potential complications
  - Dendritic corneal ulcer
  - EM
  - Herpes simplex encephalitis (infants at risk)
  - HSV infection on atopic dermatitis causing Kaposi’s varicelliform eruption (eczema herpeticum)
- Two biologically and immunologically different subtypes: HSV-1 and HSV-2
HSV-1
- typically “cold sores” (grouped vesicles at the mucocutaneous junction which quickly burst)
- recurrent on face, lips and hard palate, but NOT on soft, non-keratinized mucous membranes (unlike aphthous ulcers)

Management
- treat during prodrome to prevent vesicle formation
- topical antiviral (Zovirax®) cream, apply 5-6x/d x 4-7 d for facial/genital lesions
- oral antivirals are far more effective and have an easier dosing schedule

HSV-2
- sexually transmitted; incubation 2-20 d
- gingivostomatitis: entire buccal mucosa involved with erythema and edema of gingiva
- vulvovaginitis: edematous, erythematous, extremely tender, profuse vaginal discharge
- urethritis: watery discharge in males
- recurrent on vulva, vagina, penis for 5-7 d
- diagnosis
  - negative dark field, negative serology for syphilis, negative bacterial cultures
  - Tzanck smear with Giemsa stain shows multinucleated giant epithelial cells
  - tissue culture and electron microscopy of vesicular fluid
  - skin biopsy
  - antibody titres increase one week after primary infection only (no increase with recurrent lesions)
- ddx of genital ulcers: Candida balanitis, chancroid, syphilitic chancres

Management
- rupture vesicle with sterile needle if you wish to culture it
- wet dressing with aluminum subacetate solution, Burow’s compression, or betadine solution
- 1st episode: acyclovir 200 mg PO 5 times a day x 10 d
  - maintenance: acyclovir 400 mg PO bid
- famciclovir or valacyclovir may be substituted and have better enteric absorption and less frequent dosing
- in case of herpes genitalis, look for and treat any other sexually-transmitted infections
- for active lesions in pregnancy, see Obstetrics, OB21

HERPES ZOSTER (SHINGLES)

Clinical Presentation
- unilateral dermatomal eruption occurring 3-5 d after pain and paresthesia of that dermatome
- vesicles, bullae, and pustules on an erythematous, edematous base
- lesions may become eroded/ulcerated and last days – weeks
- pain is pre-herpetic, synchronous with rash, or post-herpetic
- severe post-herpetic neuralgia often occurs in elderly
- Hutchinson’s sign: involvement of tip of nose suggests eye involvement
- distribution: thoracic (50%), trigeminal (10-20%), cervical (10-20%); disseminated in HIV

Etiology
- caused by reactivation of VZV
- risk factors: immunosuppression, old age, occasionally associated with hematologic malignancy

Differential Diagnosis
- before thoracic skin lesions occur, must consider other causes of chest pain
- contact dermatitis, localized bacterial infection, zosteriform HSV (more pathogenic for the eyes than VZV)

Management
- compress with normal saline, Burow’s, or betadine solution
- analgesics (NSAIDs, amitriptyline)
- famciclovir or valacyclovir or acyclovir for 7 d; must initiate within 72 h to be of benefit
- gabapentin 300-600 mg PO tid for post-herpetic neuralgia

MOLLUSCUM CONTAGIOSUM

Clinical Presentation
- discrete dome-shaped and umbilicated pearly, white papules caused by DNA Pox virus
  - Molluscum contagiosum virus (MCV)
- sites: eyelids, beard (likely spread by shaving), neck, axillae, trunk, perineum, buttocks

Etiology
- MCV is spread via direct contact, auto-inoculation, sexual contact
- common in children and sexually active young adults (giant molluscum and severe cases can be seen in the setting of HIV)
Management
- topical cantharidin (a vesicant)
- cryotherapy
- curettage
- Aldara™ (imiquimod): immune modulator that produces a cytokine inflammation

**WARTS (VERRUCA VULGARIS) [HUMAN PAPILLOMAVIRUS (HPV) INFECTIONS]**

### Table 19. Different Manifestations of HPV Infection

<table>
<thead>
<tr>
<th>Wart Type</th>
<th>Definition and Clinical Features</th>
<th>Differential Diagnosis</th>
<th>Distribution</th>
<th>HPV Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verruca Vulgaris</strong> (Common Warts)</td>
<td>Hyperkeratotic, elevated discrete epidermal growths with papillated surface caused by HPV. Paring of surface reveals punctate, red-brown specks (thrombosed capillaries)</td>
<td>Molluscum contagiosum, seborheic keratosis</td>
<td>Located at trauma sites: fingers, hands, knees of children and teens</td>
<td>At least 80 types are known</td>
</tr>
<tr>
<td><strong>Verruca Plantaris</strong> (Plantar Warts) and <strong>Verruca Palmaris</strong> (Palmar Warts)</td>
<td>Hyperkeratotic, shiny, sharply marginated growths. Paring of surface reveals red-brown specks (capillaries), interruption of epidermal ridges</td>
<td>May need to scrape (&quot;pare&quot;) lesions to differentiate wart from callus and corn (see sidebar, D7)</td>
<td>Located at pressure sites: metatarsal heads, heels, toes</td>
<td>Commonly HPV 1, 2, 4, 10</td>
</tr>
<tr>
<td><strong>Verruca Planae</strong> (Flat Warts)</td>
<td>Multiple discrete, skin coloured, flat topped papules grouped or in linear configuration</td>
<td>Syringoma, seborheic keratosis, molluscum contagiosum, lichen planus</td>
<td>Sites: face, dorsa of hands, shins, knees</td>
<td>Commonly HPV 3, 10</td>
</tr>
<tr>
<td><strong>Condyloma Acuminata</strong> (Genital Warts)</td>
<td>Skin coloured pinhead papules to soft cauliflower like masses in clusters. Often occurs in young adults, infants, children</td>
<td>Condyloma lata (secondary syphilitic lesion, dark field strongly +ve), Molluscum contagiosum</td>
<td>Sites: genitalia and perianal areas</td>
<td>Commonly HPV 6 and 11, HPV 16, 18, 31, 33 cause cervical dysplasia, SCC and invasive cancer</td>
</tr>
</tbody>
</table>

### Table 20. Management of Warts

<table>
<thead>
<tr>
<th>Management</th>
<th>Type of Wart</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Destructive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryotherapy/electrodesiccation</td>
<td>All</td>
<td>Dyschromia, pain, blisters</td>
</tr>
<tr>
<td>Surgery</td>
<td>Resistant</td>
<td>Scar, recurrence</td>
</tr>
<tr>
<td>Laser</td>
<td>Resistant</td>
<td>CO₂ laser</td>
</tr>
<tr>
<td><strong>Caustic Acids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cantharidin (topical)</td>
<td>Small, common</td>
<td>Keratolytic irritation, blisters, hyperpigmentation</td>
</tr>
<tr>
<td>Mono-, di-, or tri-chloracetic acid</td>
<td>Common</td>
<td>Irritation, blisters, scar</td>
</tr>
<tr>
<td><strong>Chemotherapeutic Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Podophyllotoxin*</td>
<td>Genital</td>
<td>Erythema, erosions, ulcers, pain</td>
</tr>
<tr>
<td>Bleomycin (intraleisonal)*</td>
<td>Common</td>
<td>Pain, nail loss/dystrophy, Raynaud’s phenomenon</td>
</tr>
<tr>
<td><strong>Hypersensitivity Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dinotrichrobenzene (DNdB), diphenylcyprone</td>
<td>Common, planar</td>
<td>Causes an allergic/hypersensitivity reaction</td>
</tr>
<tr>
<td>Candida antigen (intraleisonal)</td>
<td>Genital</td>
<td>Erythema, burning, erosion</td>
</tr>
<tr>
<td>Immune Response Modifiers</td>
<td>All</td>
<td></td>
</tr>
<tr>
<td>5% imiquimod cream (Aldara®)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>Common</td>
<td>65-90% resolve spontaneously over several years</td>
</tr>
<tr>
<td>Salicylic acid 40% minimum</td>
<td>Common, planar</td>
<td>OTC, use with occlusion</td>
</tr>
<tr>
<td>Tretinoin (topical)*</td>
<td>Flat</td>
<td>Irritation</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Resistant</td>
<td>Best in children</td>
</tr>
<tr>
<td>Cantharidin + podophyllin + salicylic acid</td>
<td>Common, planar</td>
<td></td>
</tr>
</tbody>
</table>

*Avoid in pregnancy

- other viruses associated with skin changes, e.g. measles, roseola, fifth disease, etc.
- see Pediatric Exanthems, D40

**Treatment for Skin Warts**

**First Line Therapies**
- Salicylic acid preparations (patches, solutions, creams, ointments)
- Cryotherapy
- Topical cantharidin

**Second Line Therapies**
- Topical imiquimod
- Topical 5-Fluorouracil
- Topical tretinoin
- Podophyllotoxin

**Third Line Therapies**
- Curettage
- Caution
- Surgery
- Laser
- Oral cimetidine (particularly children)
- Topical 5-Fluorouracil
- Topical tretinoin (flat warts)
- Localized heat therapy
- Intralesional bleomycin (plantar warts)

**Treatment for Anogenital Warts**

**First line therapies**
- Imiquimod cream
- Podophyllotoxin (solution, cream, or gel)
- Cryotherapy

**Second line therapies**
- Trichloroacetic acid
- Topical 5-Fluorouracil
- Topical tretinoin
- Electrodesiccation
- Surgical excision (with cold steel or scissors)
- CO₂ laser
Yeast Infections

CANDIDIASIS

Candidal Paronychia
• painful red swellings of periungual skin
• management: topical agents not as effective; oral antifungals recommended

Candidal Intertrigo
• macerated/eroded erythematous patches that may be covered with papules and pustules, located in intertriginous areas often under breast, groin, or interdigitally
• peripheral “satellite” pustules
• predisposing factors: obesity, diabetes, systemic antibiotics, immunosuppression, malignancy
• starts as non-infectious maceration from heat, moisture and friction
• management: keep area dry, miconazole, ketoconazole/clotrimazole cream bid until rash clears

PITYRIASIS (TINEA) VERSICOLOR

Clinical Presentation
• chronic asymptomatic superficial fungal infection with brown/white scaling macules
• affected skin darker than surrounding skin in winter, lighter in summer (does not tan)
• sites: upper trunk most common

Pathophysiology
• microbe produces carboxylic acid → inflammatory reaction inhibiting melanin synthesis yielding variable pigmentation
• affinity for sebaceous glands; require fatty acids to survive

Etiology
• Pityrosporum ovale (Malassezia furfur)
• also associated with folliculitis and seborrheic dermatitis
• predisposing factors: summer, tropical climates, Cushing's syndrome, prolonged corticosteroid use

Investigations
• microscopic examination, KOH prep of scales for hyphae and spores

Management
• ketoconazole shampoo or cream PO daily for 7 d if more extensive
• topical terbinafine or ciclopirox olamine
• systemic fluconazole or itraconazole for 7 d

Sexually Transmitted Infections

SYPHILIS

Clinical Presentation
• characterized initially by a painless ulcer (chancre)
• following inoculation, systemic infection with secondary and tertiary stages

Etiology
• Treponema pallidum
• transmitted sexually, congenitally, or rarely by transfusion

Natural History of Untreated Syphilis
• Inoculation
• Primary syphilis (10-90 d after infection)
• Secondary syphilis (simultaneous to primary syphilis or up to 6 mo after healing of primary lesion)
• Latent syphilis
• Tertiary syphilis (2-20 yr)

Latent Syphilis
70% of untreated patients will remain in this stage for the rest of their lives and are immune to new primary infection.
Table 21. Stages of Syphilis

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Primary Syphilis</th>
<th>Secondary Syphilis</th>
<th>Tertiary Syphilis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single red, indurated, painless chancre, that develops into painless ulcer with raised border and scanty serous exudate</td>
<td>Presents 2-6 mo after primary infection (patient may not recall presence of primary chancre)</td>
<td>Extremely rare</td>
</tr>
<tr>
<td></td>
<td>Chancre develops at site of inoculation after 3 wk of incubation and heals in 4-6 wk; chancre may also develop on lips or anus</td>
<td>Associated with generalized lymphadenopathy, splenomegaly, headache, chills, fever, arthralgias, myalgias, malaise, photophobia</td>
<td>3-7 yr after secondary</td>
</tr>
<tr>
<td></td>
<td>Regional non-tender lymphadenopathy appears &lt;1 wk after onset of chancre</td>
<td>Lesions heal in 1-6 wk and may recur for 1 yr</td>
<td>Main skin lesion: ‘Gumma’ – a granulomatous non-tender nodule</td>
</tr>
<tr>
<td></td>
<td>DDx: chancroid (painful), HSV (multiple lesions)</td>
<td>3 types of lesions: 1. Macules and papules: flat top, scaling, non-pruritic, sharply defined, circular/annular rash (DDx: pityriasis rosea, tinea corporis, drug eruptions, lichen planus) 2. Condyloma lata: wart-like moist papules around genital/perianal region 3. Mucous patches: macerated patches mainly found in oral mucosa</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAN NOT be based on clinical presentation alone</td>
<td>VDRL positive</td>
<td>As in primary syphilis</td>
</tr>
<tr>
<td></td>
<td>VDRL negative – repeat weekly for 1 mo</td>
<td>FTA-ABS +ve; +ve after 1 yr following appearance of chancre</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluorescent treponemal antibody-syphilis (FTA-ABS) test has greater sensitivity and may detect disease earlier in course</td>
<td>Dark field +ve in all secondary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dark field examination – spirochete in chancre fluid or lymph node aspirate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Management</th>
<th>Penicillin G, 2.4 million units IM, single dose</th>
<th>As for primary syphilis</th>
<th>Treatment: penicillin G, 2.4 million units IM weekly x 3 wk</th>
</tr>
</thead>
</table>

GONOCOCCEMIA

Clinical Presentation
- disseminated gonococcal infection
- hemorrhagic, tender, pustules on a purpuric/petechial background
- sites: distal aspects of extremities
- associated with fever, arthritis, urethritis, proctitis, pharyngitis and tenosynovitis
- neonatal conjunctivitis if infected via birth canal

Etiology
- Neisseria gonorrhoeae

Management
- notify Public Health authorities
- screen for other sexually transmitted infections (STIs)
- cefixime 400 mg PO (drug of choice) or ceftriaxone 125 mg IM

HSV
- see Viral Infections, D29

HPV
- see Viral Infections, D30

Pre-Malignant Skin Conditions

Actinic Keratosis (Solar Keratosis)

Clinical Presentation
- ill-defined, scaly erythematous papules or plaques on a background of sun-damaged skin (solar heliosis)
- sandpaper-like, gritty sensation felt on palpation, often easier to appreciate on palpation rather than inspection
- sites: areas of sun exposure (face, ears, scalp if bald, neck, sun-exposed limbs)

Pathophysiology
- UV radiation damage to keratinocytes from repeated sun exposure (especially UVB)
- risk of transformation of actinic keratosis (AK) to SCC (~1/1000), but higher likelihood if AK is persistent

Types of Actinic Keratosis (AK)
- Erythematous: typical AK lesion
- Hypertrophic: thicker, rough papule/plaque
- Cutaneous horn: firm hyperkeratotic outgrowth
- Actinic cheilitis: confluent AKs on the lip
- Pigmented: flat, tan-brown, scaly plaque
- Spreading pigmented
- Proliferative
- Conjunctival: pinguecula, pterygium
Epidemiology
- common with increasing age, outdoor occupation, M>F
- skin phototypes I-III (see sidebar, D3), rare in darker skin as melanin is protective

Differential Diagnosis
- SCC in situ, superficial BCC, seborrheic keratosis, cutaneous lupus erythematosus

Investigations
- biopsy lesions that are refractory to treatment

Management
- destructive: cryotherapy, electrodessication and curettage
- pharmacotherapy: 5-fluorouracil cream for 2-3 wk, imiquimod cream for 8-10 wk, photodynamic therapy
- excision

Leukoplakia

Clinical Presentation
- a morphologic term describing homogenous or speckled white plaques with sharply demarcated borders
- sites: oropharynx, most often floor of the mouth, soft palate, and ventral/lateral surfaces of the tongue

Pathophysiology
- precancerous or premalignant condition
- oral form is strongly associated with tobacco use and alcohol consumption

Epidemiology
- 1-5% prevalence in adult population after 30 yr of age; peak at age 50
- M>F, fair-skinned
- most common oral mucosal premalignant lesion

Differential Diagnosis
- lichen planus, oral hairy leukoplakia

Investigations
- biopsy is mandatory because it is premalignant

Management
- low risk sites on buccal/labial mucosal or hard palate: eliminate carcinogenic habits, follow-up
- moderate/dysplastic lesions: excision, cryotherapy

Malignant Skin Tumours

Non-Melanoma Skin Cancers

BASAL CELL CARCINOMA (BCC)

Subtypes
- noduloulcerative (typical)
  - skin-coloured papule/nodule with rolled, translucent ("pearly") telangiectatic border and depressed/eroded/ulcerated centre
- pigmented variant
  - flecks of pigment in translucent lesion with surface telangiectasia
  - may mimic malignant melanoma
- superficial variant
  - flat, tan to red-brown plaque, often with scaly, pearly border and fine telangiectasia at margin
  - least aggressive subtype
- sclerosing (morphaform) variant
  - flesh/yellowish-coloured, shiny papule/plaque with indistinct borders, indurated
Pathophysiology
- malignant proliferation of basal keratinocytes of the epidermis
  - low grade cutaneous malignancy, locally aggressive (primarily tangential growth), rarely metastatic
  - usually due to UVB light exposure, therefore >80% on face
  - may also occur in previous scars, radiation, trauma, arsenic exposure, or genetic predisposition (Gorlin syndrome)

Epidemiology
- most common malignancy in humans
- 75% of all malignant skin tumours >40 yr, increased prevalence in the elderly
- M>F, skin phototypes I and II, chronic cumulative sun exposure

Differential Diagnosis
- benign: sebaceous hyperplasia, intradermal melanocytic nevus, dermatofibroma
- malignant: nodular malignant melanoma, SCC

Management
- imiquimod 5% cream (Aldara®) or cryotherapy is indicated for superficial BCCs on the trunk
- shave excision + electrodessication and curettage for most types of BCCs, not including morpheiform
- Mohs surgery: microscopically controlled, minimally invasive, stepwise excision for lesions on the face or in areas that are difficult to reconstruct
- radiotherapy used in advanced cases of BCC where surgical intervention is not an option
- life-long follow-up
- 95% cure rate if lesion <2 cm in diameter or if treated early

SQUAMOUS CELL CARCINOMA (SCC)

Clinical Presentation
- indurated erythematous nodule/plaque with surface scale/crust ± ulceration
- more rapid enlargement than BCC
- sites: face, ears, scalp, forearms, dorsum of hands

Pathophysiology
- malignant neoplasm of keratinocytes (primarily vertical growth)
- predisposing factors include: UV radiation, PUVA, ionizing radiation therapy/exposure, chemical carcinogens (such as arsenic, tar and nitrogen mustards), HPV 16, 18, immunosuppression
- may occur in previous scar (SCC more commonly than BCC)

Epidemiology
- second most common type of cutaneous neoplasm
- primarily on sun-exposed skin in the elderly, M>F, skin phototypes I and II, chronic sun exposure
- in organ transplant recipients SCC is most common cutaneous malignancy, with increased mortality as compared to non-immunocompromised population

Differential Diagnosis
- benign: nummular eczema, psoriasis, irritated seborrheic keratosis
- malignant: keratoacanthoma, Bowen's disease, BCC

Management
- surgical excision with primary closure, skin flaps or grafting
- Mohs surgery
- lifelong follow-up (more aggressive treatment than BCC)

Prognosis
- good prognostic factors: early treatment, negative margins, and small size of lesion
- SCCs that arise from actinic keratosis metastasize less frequently (~1%) than other SCCs (e.g. arising de novo in old burns) (2-5% of cases)
- overall control is 75% over 5 yr, 5-10% metastasize
OTHER FORMS OF SQUAMOUS CELL CARCINOMA (SCC)

BOWEN’S DISEASE (SQUAMOUS CELL CARCINOMA IN SITU)

Clinical Presentation
• erythematous plaque with a sharply demarcated red and scaly border
• often 1-3 cm in diameter and found on the skin and mucous membranes
• evolves to SCC in 10-20% of cutaneous lesions and >20% of mucosal lesions

Management
• same as for BCC
• biopsy required for diagnosis
• topical 5-fluorouracil (Efudex®) or imiquimod (Aldara®) used if extensive and as a tool to identify margins of poorly defined tumours
• cryosurgery
• shave excision with electrodessication and curettage

KERATOACANTHOMA

Clinical Presentation
• rapidly growing, firm, dome-shaped, erythematous or skin-coloured nodule with central keratin-filled crater, resembling an erupting volcano
• may spontaneously regress within a year, leaving a scar
• sites: sun-exposed skin

Pathophysiology
• epithelial neoplasm with atypical keratinocytes in epidermis
• low grade variant of SCC

Etiology
• HPV, UV radiation, chemical carcinogens (tar, mineral oil)

Epidemiology
• >50 yr, rare <20 yr

Differential Diagnosis
• treat as SCC until proven otherwise
• hypertrophic solar keratosis, verruca vulgaris

Management
• surgical excision, treated similarly to SCC

Malignant Melanoma (MM)

Clinical Presentation
• malignant characteristics of a mole: see mnemonic “ABCDE”
• sites: skin, mucous membranes, eyes, CNS

Clinical Subtypes of Malignant Melanoma
• lentigo maligna
  • malignant melanoma in situ (normal and malignant melanocytes confined to the epidermis)
  • 2-6 cm, tan/brown/black uniformly flat macule or patch with irregular borders
  • lesion grows radially and produces complex colours
  • often seen in the elderly
  • 10% evolve to lentigo maligna melanoma
• lentigo maligna melanoma (15% of all melanomas)
  • malignant melanocytes invading into the dermis
  • associated with pre-existing solar lentigo, not pre-existing nevi
  • flat, brown, stain-like, gradually enlarging with loss of skin surface markings
  • with time, colour changes from uniform brown to dark brown with black and blue
  • found on all skin surfaces, especially those often exposed to sun, such as the face and hands
• superficial spreading melanoma (60-70% of all melanomas)
  • atypical melanocytes initially spread laterally in epidermis then invade the dermis
  • irregular, indurated, enlarging plaques with red/white/blue discolouration, focal papules or nodules
  • ulcerate and bleed with growth

Does this Patient have a Mole or Melanoma?

ABCDE checklist

A  symmetry
B  border (irregular and/or indistinct)
C  colour (varied)
D  diameter (increasing or > 6 mm)
E  enlargement, elevation, evolution (i.e., change in colour, size or shape)

Sensitivity 92% (CI 82-98%)
Specificity 100% (CI 54-100%)
JAMA 1998;279:696-701
• nodular melanoma (30% of all melanomas)
  ▪ atypical melanocytes that initially grow vertically with little lateral spread
  ▪ uniformly ulcerated, blue-black, and sharply delineated plaque or nodule
  ▪ rapidly fatal
  ▪ may be pink or have no colour at all, this is called an amelanotic melanoma
  ▪ “EFG” Elevated, Firm, Growing

• acro lentiginous melanoma (5% of all melanomas)
  ▪ ill-defined dark brown, blue-black macule
  ▪ palmar, plantar, subungual skin
  ▪ melanomas on mucous membranes have poor prognosis

Pathophysiology
• malignant neoplasm of pigment forming cells (melanocytes and nevus cells)

Epidemiology
• incidence 1/75 (Canada) 1/50 (US)
• risk factors: numerous moles, fair skin, red hair, positive personal/family history, large congenital nevi, familial dysplastic nevus syndrome, multiple dysplastic nevi
• most common sites: back (M), calves (F)
• worse prognosis if: male, on scalp, hands, feet, late lesion, no pre-existing nevus present

Differential Diagnosis
• benign: nevi, solar lentigo, seborrheic keratosis
• malignant: pigmented BCC

Management
• excisional biopsy preferable, otherwise incisional biopsy
• remove full depth of dermis and extend beyond edges of lesion only after histologic diagnosis
• beware of lesions that regress – tumour is usually deeper than anticipated
• high dose IFN for stage II (regional), chemotherapy (cis-platinum, BCG) and high dose IFN for stage III (distant) disease
• never chemotherapeutic, gene therapies and vaccines starting to be used in metastatic melanoma
• radiotherapy may be used as adjunctive treatment

<table>
<thead>
<tr>
<th>Table 22. American Joint Committee on Cancer Staging System Based on Breslow’s Thickness of Invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 &lt; 1.0 mm</td>
</tr>
<tr>
<td>T2 1.01-2.0 mm</td>
</tr>
<tr>
<td>T3 2.01-4.0 mm</td>
</tr>
<tr>
<td>T4 &gt; 4.0 mm</td>
</tr>
</tbody>
</table>

a = no ulceration; b = ulceration

Other Cutaneous Cancers

CUTANEOUS T-CELL LYMPHOMA

Clinical Presentation
• Mycosis fungoides (limited superficial type)
  ▪ characterized by: erythematos patches/plaques/nodules/tumours, which may be pruritic and poikilodermic (atrophy, telangiectasia, hyperpigmentation)
  ▪ common sites include: trunk, buttocks, proximal limbs
  ▪ mildly symptomatic, usually excellent prognosis for early disease

• Sézary syndrome (widespread systemic type)
  ▪ rare variant characterized by: erythroderma, lymphadenopathy, WBC >20 x 10^9/L with Sézary cells
  ▪ associated with intense pruritus, alopecia, palmoplantar hyperkeratosis, and systemic symptoms (fatigue, fever)
  ▪ often fatal

Pathophysiology
• clonal proliferation of skin-homing CD4 T cells

Epidemiology
• >50 yr old, M:F 2:1
Differential Diagnosis
- tinea corporis, nummular dermatitis, psoriasis, discoid lupus erythematosus, Bowen’s disease

Investigations
- skin biopsy (histology, "lymphocyte antigen cell" markers, TcR gene arrangement)
- blood smear looking for Sézary cells or flow cytometry (e.g. CD4:CD8 >10 is Sézary)
- imaging (for systemic involvement)

Management
- Mycosis fungoides
  - treatment is dependent on stage of disease
  - topical steroids and/or PUVA, narrow band (311-313 nm), UVB (NBUVB)
- Sézary syndrome
  - oral retinoids and IFN
  - extra-corporeal photophoresis
  - may need radiotherapy for total skin electron beam radiation
  - may maintain on UV therapy
  - other chemotherapy agents

Alopecia (Hair Loss)

Hair Growth
- hair grows in a cyclic pattern that is defined in 3 stages
  1. growth stage = anagen phase
  2. transitional stage = catagen stage
  3. resting stage = telogen phase
- total duration of the growth stage reflects the type and location of hair: eyebrow, eyelash, and axillary hairs have a short growth stage in relation to the resting stage
- growth of the hair follicles is also based on the hormonal response to testosterone and DHT; this response is genetically controlled

Non-Scarring (Non-Cicatricial) Alopecia

ANDROGENETIC ALOPECIA

Clinical Presentation
- male-pattern or female-pattern alopecia
  - males: fronto-temporal areas progressing to vertex, entire scalp may be bald
  - females: widening of central part, “Christmas tree” pattern

Pathophysiology
- action of testosterone on hair follicles

Epidemiology
- males: early 20s-30s
- females: 40s-50s

Management
- minoxidil (Rogaine®) solution or foam to reduce rate of loss/partial restoration
- spironolactone in women (anti-androgenic effects), cyproterone acetate (Diane-35°)
- finasteride (Propecia®) (5-α-reductase inhibitor) 1 mg/d in men
- hair transplant

PHYSICAL
- trichotillomania: impulse-control disorder characterized by compulsive hair pulling with irregular patches of hair loss, and with remaining hairs broken at varying lengths
- traumatic (e.g. tight “corn-row” braiding of hair, wearing tight pony tails, tight tying of turbans)

TELOGEN EFFLUVIUM

Clinical Presentation
- uniform decrease in hair density secondary to hairs leaving the growth (anagen) stage and entering the resting (telogen) stage of the cycle
Pathophysiology
- precipitated by: malnutrition, Fe deficiency, thyroid dysfunction, post-partum/miscarriage, scalp diseases (seborrhoeic dermatitis, allergic contact dermatitis), medications (e.g. OCP), physical/mental stress
- hair loss typically occurs 2-4 mo after exposure to precipitant
- regrowth occurs within a few months but may not be complete

ANAGEN EFFLUVIUM

Clinical Presentation
- hair loss due to insult to hair follicle impairing its mitotic activity (growth stage)

Pathophysiology
- precipitated by chemotherapeutic agents (most common), other meds (bismuth, levodopa, colchicine, cyclosporine), exposure to chemicals (thallium, boron, arsenic)
- dose-dependent effect
- hair loss 7-14 d after single pulse of chemotherapy; most clinically apparent after 1-2 mo
- reversible effect; follicles resume normal mitotic activity few weeks after agent stopped

ALOPECIA AREATA

Clinical Presentation
- autoimmune disorder characterized by patches of complete hair loss often localized to scalp but can affect eyebrows, beard, eyelashes, etc.
- may be associated with dystrophic nail changes – fine stippling, pitting
- “exclamation mark” pattern (hairs fractured and have tapered shafts, i.e. looks like “!”)
- may be associated with pernicious anemia, vitiligo, thyroid disease, Addison’s disease
- spontaneous regrowth may occur within months of first attack (worse prognosis if young at age of onset and extensive loss)
- frequent recurrence often precipitated by emotional distress

Management
- generally unsatisfactory
- intralesional triamcinolone acetonide (corticosteroids) can be used for isolated patches
- UV or PUVA therapy
- immunomodulatory (diphencyprone)

Scarring (Cicatricial) Alopecia

Clinical Presentation
- irreversible loss of hair follicles with fibrosis

Etiology
- physical: radiation, burns
- infections: fungal, bacterial, TB, leprosy, viral (HZV)
- inflammatory
  - lichen planus (lichen planopilaris)
  - DLE (note that SLE can cause an alopecia unrelated to discoid lupus lesions which are non-scarring)
  - morphoea: “coup de sabre” with involvement of centre of scalp
- central centrifugal cicatricial alopecia: seen in up to 40% of black women, starting at central scalp; one of most commonly diagnosed scarring alopecias, may be associated with hair care practices in this population

Investigations
- biopsy from active border

Management
- infections: treat underlying infection
- inflammatory: topical/intralesional steroids, anti-inflammatory antibiotics, antimalarials

DDx of Scarring (cicatricial) Alopecia

Developmental/Hereditary Disorders
- Aplasia cutis congenita
- Epidermal nevi
- Romberg’s syndrome
- Generalized follicular hamartoma

Primary causes
- Group 1: Lymphocytic
  - Discoid lupus erythematosus
  - Lichen planopilaris
  - Central centrifugal cicatricial alopecia
  - Classic Pseudopelade
- Group 2: Neutrophilic
  - Folliculitis decalvans
  - Dissecting scalp cellulitis
- Group 3: Mixed
  - Acne keloidalis nuchae

Secondary causes
- Infectious agents
  - Bacterial (e.g. post-cellulitis)
  - Fungal (e.g. tinea capitis)
  - Neoplasms (e.g. BCC, SCC, lymphomas, and metastatic tumours)
- Physical agents
  - Mechanical trauma
  - Burns
  - Radiotherapy
  - Caustic chemicals
### Nails and Disorders of the Nail Apparatus

**Table 23. Nail Changes in Systemic and Dermatological Conditions**

<table>
<thead>
<tr>
<th>Nail Abnormality</th>
<th>Definition/Etiology</th>
<th>Associated Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NAIL PLATE CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clubbing</td>
<td>Proximal nail plate has greater than 180 degree angle to nail fold, watch-glass nails, bulbous digits</td>
<td>Cyanotic heart disease, bacterial endocarditis, pulmonary disorders, GI disorders, etc.</td>
</tr>
<tr>
<td>Koilonychia</td>
<td>Spoon shaped nails</td>
<td>Iron deficiency, malnutrition, diabetes</td>
</tr>
<tr>
<td>Onycholysis</td>
<td>Separation of nail plate from nail bed</td>
<td>Psoriasis, dermatophytes, thyroid disease</td>
</tr>
<tr>
<td>Onychogryphosis</td>
<td>Hypertrophy of the nail plate and subungual hyperkeratosis</td>
<td>Poor circulation, chronic inflammation, tinea</td>
</tr>
<tr>
<td>Onycholobroma</td>
<td>Subungual hematoma</td>
<td>Trauma to nail bed</td>
</tr>
<tr>
<td>Onychonuxosis</td>
<td>Fungal infection of nail (e.g. dermatophyte, yeast, mould)</td>
<td>HIV, DM, peripheral arterial disease</td>
</tr>
<tr>
<td>Onychocryptosis</td>
<td>Often hallux with congenital malalignment, painful inflammation, granulation tissue</td>
<td>Tight fitting shoes, excessive nail clipping</td>
</tr>
<tr>
<td><strong>SURFACE CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V-shaped nicking</td>
<td>Distal margin has v-shaped loss of the nail plate</td>
<td>Darier’s disease (follicular dyskeratosis)</td>
</tr>
<tr>
<td>Pterygium inversus unguum</td>
<td>Distal nail plate does not separate from underlying nail bed</td>
<td>Scleroderma</td>
</tr>
<tr>
<td>Pitting</td>
<td>Punctate depressions that migrate distally with growth</td>
<td>Psoriasis (random pattern), alopecia areata (geometric, gridshaped arrangement), eczema</td>
</tr>
<tr>
<td>Transverse ridging</td>
<td>Transverse depressions often more in central portion of nail plate</td>
<td>Serious acute illness slows nail growth (when present in all nails = Beau’s lines), eczema, chronic paronychia, trauma</td>
</tr>
<tr>
<td>Transverse white lines</td>
<td>Bands of white discoloration</td>
<td>Poisons, hypoalbuminemia (Muherke’s lines)</td>
</tr>
<tr>
<td><strong>COLOUR CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow</td>
<td>Tinea, jaundice, tetracycline, pityriasis rubra pilaris, yellow nail syndrome, psoriasis, tobacco use</td>
<td></td>
</tr>
<tr>
<td>Green</td>
<td>Pseudomonas</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>Melanoma, hematoma</td>
<td></td>
</tr>
<tr>
<td>Brown</td>
<td>Nicotine use, psoriasis, poisons, longitudinal melanonychia (ethnic)</td>
<td></td>
</tr>
<tr>
<td>Splinter hemorrhages</td>
<td>Extravasation of blood from longitudinal vessels of nail bed, blood attaches to overlying nail plate and moves distally as it grows</td>
<td>Trauma, bacterial endocarditis, blood dyscrasias, psoriasis</td>
</tr>
<tr>
<td>Oil spots</td>
<td>Brown-yellow discoloration</td>
<td>Psoriasis</td>
</tr>
<tr>
<td><strong>NAIL FOLD CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpetic whitlow</td>
<td>HSV infection of distal phalanx</td>
<td>HSV infection</td>
</tr>
<tr>
<td>Paronychia</td>
<td>Local inflammation of the nail fold around the nail bed</td>
<td>Acute: painful infection</td>
</tr>
<tr>
<td>Nail fold telangiectasias</td>
<td>Cuticular hemorrhages, roughness, capillary changes</td>
<td>Chronic: constant wetting (e.g. dishwashing, thumbsucking)</td>
</tr>
</tbody>
</table>

**Skin Manifestations of Systemic Disease**

**Table 24. Skin Manifestations of Internal Conditions**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Related Dermatoses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUTOIMMUNE DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td>Behçet’s disease</td>
<td>Painful aphthous ulcers in oral cavity ➝ genital mucous membranes, erythema nodosum, acral form papules</td>
</tr>
<tr>
<td>Buerger’s disease</td>
<td>Superficial migratory thrombophlebitis, pallor, cyanosis, gangrene, ulcerations, digital erosions</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Periorbital and extensor violaceous erythema, heliotrope with edema, Gottron’s papules (violarious flat-topped papules with atrophy), perungual erythema, telangiectasia, calcinosis cutis</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Subcutaneous nodules, stellate purpura, erythema, gangrene, splinter hemorrhages, livido reticularis, ulceration</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>Petechiae, urticaria, erythema nodosum, rheumatic nodules, evanscence rash</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Raynaud’s, nonpitting edema, wax/y/shiny/tense atrophic skin (morphea), ulcers, cutaneous calcification, perungual telangiectasia, acrosclerosis, salt-and-pepper pigmentation</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Malar erythema, discoid rash (erythematosus papules or plaques with keratotic scale, follicular plugging, atrophic scarring on face, hands, and arms), hemorrhagic bullae, palpable purpura, urticarial purpura, patchy/diffuse alpecia, mucosal ulcers, photosensitivity</td>
</tr>
<tr>
<td>Crohn’s Disease/Ulcerative colitis</td>
<td>Pyoderma gangrenosum, erythema nodosum, Sweet’s syndrome</td>
</tr>
</tbody>
</table>

**Raynaud’s Phenomenon DDx**

**COLD HAND**
- Cryoglobulins/Cryofibrinogens
- Obstruction/Occupational
- Lupus erythematosus, other connective tissue disease
- Diabetes mellitus/Drugs
- Hematologic problems (polycythemia, leukemia, etc)
- Arterial problems (atherosclerosis)
- Neurologic problems (vascular tone)
- Disease of unknown origin (idiopathic)
### Table 24. Skin Manifestations of Internal Conditions (continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Related Dermatoses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENDOCRINE DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>Generalized hyperpigmentation or limited to skin folds, buccal mucosa and scars</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Moon facies, purple striae, acne, hyperpigmentation, hirsutism, atrophic skin with telangiectasia</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Infections (boils, carbuncles, Candidiasis, S. aureus, dermatophytes, tinea pedis and cruris, infectious eczematoid dermatitis), pruritus, eruptive xanthomas, necrobiosis lipidica diabetorum, granuloma annulare, diabetic foot, diabetic bullae, acanthosis nigricans, calciphylaxis</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Most, warm skin, seborrhea, acne, nail atrophy, hyperpigmentation, toxic alopecia, pretibial myxedema, acropachy, ochronysiosis</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Cool, dry, scaly, thickened, hyperpigmented skin; toxic alopecia with dry, coarse hair, brittle nails, myxedema, loss of lateral 1/3 eyebrows</td>
</tr>
<tr>
<td>HIV-RELATED</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>Viral (HSV, HZV, HPV, CMV, molluscum contagiosum, oral hairy leukoplakia), bacterial (impetigo, acneiform folliculitis, dental caries, cellulitis, bacillary epithelioid angiomatosis, syphilis), fungal (candidiasis, histoplasmosis, cryptococcus, blastomycosis)</td>
</tr>
<tr>
<td>Inflammatory dermatoses</td>
<td>Seborrhea, psoriasis, pityriasis rosea, vasculitis</td>
</tr>
<tr>
<td>Malignancies</td>
<td>Kaposis sarcoma, lymphoma, BCC, SCC, MM</td>
</tr>
<tr>
<td><strong>MALIGNANCY</strong></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal (GI)</td>
<td>Peutz-Jeghers: pigmented macules on lips/oral mucosa</td>
</tr>
<tr>
<td>Colorectal/rectum</td>
<td>Pezet’s disease: eroding scaling plaques of perineum</td>
</tr>
<tr>
<td>Carcinoma</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>Palmoplantar keratoderma: thickened skin of palms/soles</td>
</tr>
<tr>
<td>GI</td>
<td>Pezet’s disease: eczematous and crusting lesions of breast</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Sipple’s syndrome: multiple mucosal neuromas</td>
</tr>
<tr>
<td>Breast/GU/lung/ovary</td>
<td>Dermatomyositis: heliotrope erythema of eyelids and violaceous plaques over knuckles</td>
</tr>
<tr>
<td>Lymphoma/Leukemia</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s</td>
<td>Ataxia Telangiectasia: telangiectasia on pinna, bulbar conjunctiva</td>
</tr>
<tr>
<td>Acute Leukemia</td>
<td>Ichthyosis: generalized scaling especially on extremities, Sweet’s syndrome</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>Bloom’s syndrome: butterfly erythema on face, associated with short stature</td>
</tr>
<tr>
<td><strong>OTHERS</strong></td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>Pruritus, hyperpigmentation, spider nevi, palmar erythema, white nails (Terry’s nails), porphyria cutanea tarda, xanthomas, hair loss, jaundice</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Pruritus, pigmentation, half and half nails, perforating dermatosis, calciphylaxis</td>
</tr>
<tr>
<td>Pruritic urticaria papules and plaques of pregnancy</td>
<td>Erythematous papules or urticarial plaques in distribution of striae distensae: buttocks, thighs, upper inner arms and lower backs</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>Palpable purpura in cold-exposed areas, Raynaud’s, cold urticaria, acral hemorrhagic necrosis, bleeding disorders, associated with hepatitis C infection</td>
</tr>
</tbody>
</table>

### Pediatric Exanthems

**Definitions**
- Exanthem: an eruption on the skin occurring as a symptom of a systemic disease typically with a fever.
- Exanthem: an eruption on a mucous membrane occurring in the context of an exanthem.

### Table 25. Common Pediatric Exanthems

<table>
<thead>
<tr>
<th>Exanthem</th>
<th>Etiology</th>
<th>Clinical Description</th>
<th>Important Complications</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicken Pox</td>
<td>HHV3</td>
<td>Diffuse itchy vesicular eruption beginning on thorax spreading to extremities</td>
<td>Secondary infection, necrotizing fasciitis, meningitis, encephalitis, cerebellar ataxia, pneumonitis, disseminated intravascular coagulation (DIC), hepatitis</td>
<td>Supportive treatment, acyclovir or valacyclovir; IV if severe; IF severe, Varicella Zoster immunoglobulin (within 96 h of contact), Varicella vaccine</td>
</tr>
<tr>
<td>Enteroviral</td>
<td>Enteroviruses</td>
<td>Polymorphic rash (macules, papules, vesicles, petechiae, urticaria)</td>
<td>None</td>
<td>Supportive treatment for majority of cases; immunosuppressed can be treated with pleconaril</td>
</tr>
<tr>
<td>Erythema Infectiosum</td>
<td>Parovirus B19</td>
<td>Slapped cheeks (red, flushed cheeks) then 1-4 d later lacy/reticulate maculo-papular rash of trunk/extremities</td>
<td>STAR complex (Sore Throat, Arthritis, Rash)</td>
<td>No treatment: children often feel well</td>
</tr>
</tbody>
</table>

*NSAIDs for symptomatic arthropathy.*
### Table 25. Common Pediatric Exanthems (continued)

<table>
<thead>
<tr>
<th>Exanthem</th>
<th>Etiology</th>
<th>Clinical Description</th>
<th>Important Complications</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gianotti-Crosti Syndrome</td>
<td>Epstein-Barr virus most common, hepatitis B, Coxsackie A and B viruses</td>
<td>Symmetric papular eruption of face, buttocks, and extremities, Sparing of trunk, Proceeded by viral prodrome</td>
<td>None</td>
<td>Supportive treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vesicular eruption of palms and soles with an erosive stomatitis, Enanthem: vesicles involving tongue and posterior pharynx</td>
<td>Pulmonary, dehydration, neurological death</td>
<td>Supportive treatment</td>
</tr>
<tr>
<td></td>
<td>Hand, Foot and Mouth Disease</td>
<td></td>
<td>Most common cause of vasculitis and acquired heart disease in children (coronary artery aneurysm)</td>
<td>ASA, IVIG, baseline echo and repeat in 6 wk</td>
</tr>
<tr>
<td></td>
<td>Kawasaki Disease</td>
<td>Fever &gt; 5 d and 4/5: unilateral lymphadenopathy; puffy/red palms and soles; red, cracked lips/strawberry tongue; skin rash; non-punulent bilateral conjunctivitis</td>
<td>十一神庙, pneumonia, encephalitis, SJS, glomerular nephritis, myocarditis/pericarditis</td>
<td>Vitamin A, immunoglobulin, MMR vaccine</td>
</tr>
<tr>
<td></td>
<td>Measles</td>
<td>Morbilliform rash starts at hairline and spreads down to face/neck/trunk, desquamates (no palm or sole involvement), Prodrome: cough, coryza, conjunctivitis (3 Cs)</td>
<td>Enanthem: Koplik spots (grey/white papules on buccal mucosa)</td>
<td>Supportive treatment</td>
</tr>
<tr>
<td></td>
<td>Meningococcemia</td>
<td>Purpuric and petechial rash (“stellate purpura with a central gummetal-grey hue”)</td>
<td>Hearing loss, intellectual disability, necrosis and loss of digits and/or limbs, septic shock, death</td>
<td>5-7 d course of 3rd generation cephalexin</td>
</tr>
<tr>
<td></td>
<td>Roseola</td>
<td>Pink macules and papules on neck/arms/trunk ± face, Eruption after high fever ends</td>
<td>Enanthem: Nagayama sign (red papules on soft palate)</td>
<td>Supportive treatment</td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
<td>1-5 d following mild prodrome (fever, headache, respiratory symptoms), a pink maculopapular rash erupts on face spreading down to neck/trunk, Occipital and retroauricular nodes</td>
<td>Enanthem: strawberry tongue, petechiae on palate</td>
<td>Supportive treatment</td>
</tr>
<tr>
<td></td>
<td>Scarlet Fever</td>
<td>Generalized rash, red papules, “sand-paper” texture, desquamation (palms and soles), flexural accentuation (Pastia’s lines)</td>
<td>Enanthem: strawberry tongue, petechiae on palate</td>
<td>Supportive treatment</td>
</tr>
</tbody>
</table>

### Miscellaneous Lesions

#### Angioedema and Urticaria

**Angioedema**
- Deeper swelling of the skin involving subcutaneous tissues; often involves the eyes, lips, and tongue
- May or may not accompany urticaria
- Hereditary or acquired forms
- Hereditary angioedema (does not occur with urticaria)
  - Onset in childhood; 80% have positive family history
  - Recurrent attacks; 25% die from laryngeal edema
  - Triggers: minor trauma, emotional upset, temperature changes
- Treatment
  - Prophylaxis with danazol or stanozolol for hereditary angioedema
  - Epinephrine pen to temporize until patient reaches hospital in acute attack

**Urticaria**
- Also known as “hives”; see Table 26 for classification
- Transient, red, pruritic well-demarcated wheals
- Each individual lesion lasts less than 24 h
- Second most common type of drug reaction
- Results from release of histamine from mast cells in dermis
- Can also result after physical contact with allergen
Table 26. Classification of Urticaria

<table>
<thead>
<tr>
<th>Type</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Urticaria</td>
<td>&gt;2/3 of cases&lt;br&gt;Attacks last &lt;6 wk&lt;br&gt;Individual lesions last &lt;24 h</td>
</tr>
<tr>
<td></td>
<td>Drugs: especially ASA, NSAIDs&lt;br&gt;Foods: nuts, shellfish, eggs, fruit&lt;br&gt;Idiopathic (vast majority)&lt;br&gt;Infection&lt;br&gt;Insect stings (bees, wasps, hornets)&lt;br&gt;Percutaneous absorption: cosmetics, work exposures&lt;br&gt;Stress&lt;br&gt;Systemic diseases: SLE, endocrinopathy, neoplasm</td>
</tr>
<tr>
<td>Chronic Urticaria</td>
<td>&lt;1/3 of cases&lt;br&gt;Attacks last &gt;6 wk&lt;br&gt;Individual lesion lasts &lt;24 h&lt;br&gt;Idiopathic (90% of chronic urticaria patients)&lt;br&gt;Aeroallergens&lt;br&gt;Drugs (antibiotics, hormones, local anesthetics)&lt;br&gt;Insect stings&lt;br&gt;Parasitic infections&lt;br&gt;Physical contact (animal saliva, plant resins, latex, metals, lotions, soap)&lt;br&gt;Direct mast cell release&lt;br&gt;Opiates, muscle relaxants, radio-contrast agents&lt;br&gt;Complement-mediated&lt;br&gt;Serum sickness, transfusion reactions&lt;br&gt;Infections, viral/bacterial (&gt;80% of urticaria in pediatric patients)&lt;br&gt;Urticarial vasculitis&lt;br&gt;Araachidonic acid metabolism&lt;br&gt;ASA, NSAIDs&lt;br&gt;Physical&lt;br&gt;Dermatographism (friction, rubbing skin), cold (ice cube, cold water), cholinergic (hot shower, exercise), solar, pressure (shoulder strap, buttocks), aquagenic (exposure to water), adrenergic (stress), heat&lt;br&gt;Other&lt;br&gt;Mastocytosis, urticaria pigmentosa</td>
</tr>
</tbody>
</table>

Urticarial Vasculitis

<table>
<thead>
<tr>
<th>Type</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual lesions last &gt;24 h</td>
<td>Idiopathic&lt;br&gt;Infections&lt;br&gt;Hepatitis&lt;br&gt;Autoimmune diseases&lt;br&gt;SLE&lt;br&gt;Drug hypersensitivity&lt;br&gt;cidetine and diltiazem</td>
</tr>
</tbody>
</table>

Erythema Nodosum

Clinical Presentation
- acute or chronic inflammation of subcutaneous fat (panniculitis)
- round, red, tender, poorly demarcated nodules
- sites: asymmetrical on extensor lower legs, knees, arms, (typically shins)
- associated with arthralgia, fever, malaise

Etiology
- 40% are idiopathic
- drugs: sulfonamides, oral contraceptives (also pregnancy), analgesics, trans retinoic acid
- infections: GAS, TB, histoplasmosis, Yersinia
- inflammation: sarcoidosis, Crohn's > UC
- malignancy: acute leukemia, Hodgkin's lymphoma

Epidemiology
- 15-30 yr old, F:M = 3:1
- lesions last for days and spontaneously resolve in 6 wk

Investigations
- chest x-ray (to rule out chest infection and sarcoidosis)
- throat culture, antistreptolysin (ASO) titre, purified protein derivative (PPD) skin test

Management
- symptomatic: bed rest, compressive bandages, wet dressings
- NSAIDs, intralesional steroids
- treat underlying cause

DDx of Erythema Nodosum

NODOSUMM
No cause (idiopathic) in 40%
Drugs (sulfonamides, OCP, etc.)
Other infections (GAS+)
Sarcoidosis
Ulcerative colitis and Crohn's
Malignancy (leukemia, Hodgkin's lymphoma)
Many Infections

DDx for Urticaria

DAM HIVES
Drugs and foods
Allergic
Malignancy
Hereditary
Infection
Vasculitis
Emotions
Stings

Approach to Urticaria
- Thorough Hx and P/E
- Acute: if individual lesions last <24 h, but attacks last <6 wk; no immediate investigations needed; consider referral for allergy testing
- Chronic: if individual lesions last <24 h but attacks last >6 wk; further investigations required: CBC and differential, urinalysis, ESR, TSH, LFTs to help identify underlying cause
- Vasculitic: if individual lesions last >24 h; biopsy of lesion and referral to dermatology

Mastocytosis (Urticaria Pigmentosa)
Rare disease due to excessive infiltration of the skin by mast cells. It manifests as many reddish-brown elevated plaques and macules. Friction to a lesion produces a wheal surrounded by intense erythema (Barter’s sign), due to mast cell degranulation. This occurs within minutes.
**Pruritus**

**Clinical Presentation**
- a sensation provoking a desire to scratch
- pruritus can present with or without skin lesions
- lesions may arise from the underlying disease, or from excoriation causing crusts, lichenified plaques, or wheals

**Etiology**
- dermatologic – generalized
  - atopic and contact dermatitis, lichen planus, urticaria, insect bites, dermatitis herpetiformis
  - infection: varicella, candidiasis
  - lichen simplex chronicus
  - prurigo nodularis
- systemic disease – usually generalized
  - hepatic: obstructive biliary disease, cholestatic liver disease of pregnancy
  - renal: chronic renal failure, uremia secondary to hemodialysis
  - hematologic: Hodgkin’s lymphoma, multiple myeloma, leukemia, polycythemia vera, hemochromatosis, Fe deficiency anemia, cutaneous T-cell lymphoma
  - neoplastic: lung, breast, gastric (internal solid tumours), non-Hodgkin’s lymphoma
  - endocrine: carcinoid, DM, hypothyroid/thyrotoxicosis
  - infectious: HIV, trichinosis, echinococcosis, hepatitis C
  - psychiatric: depression, psychosis
  - neurologic: post-herpetic neuralgia, multiple sclerosis

**Investigations**
- detailed history
- complete physical, including rectal and pelvic examination
- bloodwork: CBC, ESR, Cr/BUN, LFT, TSH, fasting blood sugar, stool culture and serology for parasites

**Management**
- treat underlying cause
- cool water compresses to relieve pruritus
- bath oil and emollient ointment (especially if xerosis is present)
- topical corticosteroid and antipruritics (e.g. menthol, camphor, phenol, mirtazapine, capsaicin)
- systemic antihistamines: H1 blockers are most effective, most useful for urticaria
- phototherapy with UVB or PUV A
- doxepin, amitryptyline
- immunosuppressive agents if severe: steroids and steroid sparing

**Wounds and Ulcers**
- see Plastic Surgery: PS8, PS15

**Common Medications**

**Sunscreens and Preventative Therapy**

**Sunburn**
- erythema 2-6 h post UV exposure often associated with edema, pain and blistering with subsequent desquamation of the dermis, and subsequent hyperpigmentation
- chronic UVA, UVB exposure leads to photoaging, immunosuppression, photocarcinogenesis
- prevention: avoid peak UVR (10 am to 4 pm), wear appropriate clothing, wide-brimmed hat, sunglasses, and broad-spectrum sunscreen
- clothing with UV protection expressed as UV protection factor (UPF) is analogous to SPF of sunscreen
Sunscreens
- under ideal conditions an SPF of 10 means that a person who normally burns in 20 min will burn in 200 min following the application of the sunscreen
- topical chemical: absorbs UV light
  - requires application at least 15-60 min prior to exposure, should be reapplied every 2 h
    (more often if sweating, swimming)
  - UVB absorbers: PABA, salicylates, cinnamates, benzylidine camphor derivatives
  - UVA absorbers: benzophenones, anthranilates, dibenzoylmethanes, benzylidine camphor derivatives
- topical physical: reflects and scatters UV light
  - titanium dioxide, zinc oxide, kaolin, talc, ferric chloride and melanin
- all are effective against the UVA and UVB spectrum
- less risk of sensitization than chemical sunscreens and waterproof, but may cause folliculitis or miliaria
- some sunscreen ingredients may cause contact or photocontact allergic reactions, but are uncommon

Management
- sunburn: if significant blistering present, consider treatment in hospital; otherwise, symptomatic treatment (cool wet compresses, oral anti-inflammatory, topical corticosteroids)
- antioxidants, both oral and topical are being studied for their abilities to protect the skin; topical agents are limited by their ability to penetrate the skin

### Topical Steroids

#### Table 27. Potency Ranking of Topical Steroids

<table>
<thead>
<tr>
<th>Relative Potency</th>
<th>Relative Strength</th>
<th>Generic Names</th>
<th>Trade Names</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak</td>
<td>x1</td>
<td>hydrocortisone 2.5% (1% available over-the-counter)</td>
<td>Emo Cort®</td>
<td>Intertinginos areas, children, face, thin skin</td>
</tr>
<tr>
<td>Moderate</td>
<td>x3</td>
<td>hydrocortisone 17-valerate – 0.2% desonide mometasone furoate</td>
<td>Westcort®, Tridesilon®, Elocom®</td>
<td>Arm, leg, trunk</td>
</tr>
<tr>
<td>Potent</td>
<td>x6</td>
<td>betamethasone – 0.1% 17-valerate – 0.1% amcinonide</td>
<td>Betnovate®, Celestoderm – V®, Cyclorcort®</td>
<td>Body</td>
</tr>
<tr>
<td>Very Potent</td>
<td>x9</td>
<td>betamethasone dipropionate – 0.05% fluocinolone – 0.05% halcinonide</td>
<td>Diprosone®, Lidex, Tipsyn gel®, Lyderm®, Halog®</td>
<td>Palms and soles</td>
</tr>
<tr>
<td>Extremely Potent</td>
<td>x12</td>
<td>clobetasol propionate -0.05% (most potent) betamethasone dipropionate ointment halobetasol propionate -0.05%</td>
<td>Dermovate®, Diprolene®, Ultravate®</td>
<td>Palms and soles</td>
</tr>
</tbody>
</table>

#### Body Site: Relative Percutaneous Absorption

<table>
<thead>
<tr>
<th>Body Site</th>
<th>Relative Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forearm</td>
<td>1.0</td>
</tr>
<tr>
<td>Plantar foot</td>
<td>0.14</td>
</tr>
<tr>
<td>Palm</td>
<td>0.83</td>
</tr>
<tr>
<td>Back</td>
<td>1.7</td>
</tr>
<tr>
<td>Scalp</td>
<td>3.7</td>
</tr>
<tr>
<td>Forehead</td>
<td>6.0</td>
</tr>
<tr>
<td>Cheeks</td>
<td>13.0</td>
</tr>
<tr>
<td>Scrotum</td>
<td>42.0</td>
</tr>
</tbody>
</table>

Calculation of strength of steroid compared to hydrocortisone on forearm: relative strength of steroid x relative percutaneous absorption

#### Side Effects of Topical Steroids

- Local: Atrophy
- Percutaneous dermatitis
- Steroid acne
- Rosacea
- Contact dermatitis
- Tachyphylaxis (tolerance)
- Systemic: Suppression of HPA axis

#### Dermatologic Therapies

#### Table 28. Common Topical Therapies

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcipotriol (Dovonex®)</td>
<td>0.005% cream, ointment, scalp solution, apply bid For maintenance therapy apply OD</td>
<td>Psoriasis</td>
<td>Burning, itching, skin irritation, worsening of psoriasis Avoid face, mucous membranes, eyes; wash hands after application Maximum weekly dosage of cream by age: 2.5 yr – 25 g/wk 6-10 yr – 50 g/wk 11-14 yr – 75 g/wk &gt;14 yr – 100 g/wk Inactivated by light (do not apply before phototherapy)</td>
</tr>
<tr>
<td>Imiquimod (Aldara®)</td>
<td>5% cream applied 3x/wk Apply at bedtime, leave on 6-10 h, then wash off with mild soap and water Max duration 16 wk</td>
<td>Genital warts Cutaneous warts Actinic keratosis Superficial BCC</td>
<td>Avoid natural/artificial sun exposure Local skin and application site reactions Works best for warts on mucosal surfaces May induce inflammation and erosion</td>
</tr>
</tbody>
</table>

#### Vehicles

- Ointment (water in oil): hydrate, greasy
- Cream (oil in water): hydrate, variable
- Lotion (powder in water): drying, cosmesis
- Solutions (water, alcohol, propylene glycol)
- Gel (solution that melts on contact with skin, alcohol): drying
**Table 28. Common Topical Therapies (continued)**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Permethrin</strong>&lt;br&gt;(Kwellada® P Lotion and Nix® Dermal Cream)</td>
<td>5% cream, applied once overnight to all skin areas from neck down, repeated one week later</td>
<td>Scabies (Kwellada-P Lotion, Nix® Dermal Cream) Pediculosis (Kwellada-P Crème Rinse®, Nix Crème Rinse®)</td>
<td>Do not use in children &lt;2 yr old&lt;br&gt;Hypersensitivity to drug, or known sensitivity to chrysanthemums&lt;br&gt;Local reactions only (resolve rapidly); including burning, pruritus&lt;br&gt;Low toxicity, excellent results&lt;br&gt;Consider 2nd application after 7 d</td>
</tr>
<tr>
<td><strong>Pimecrolimus</strong>&lt;br&gt;(Elidel®)</td>
<td>1.0% cream bid&lt;br&gt;Use for as long as lesions persist and discontinue upon resolution of symptoms</td>
<td>AD (mild to moderate)</td>
<td>Burning&lt;br&gt;Lacks adverse effects of steroids&lt;br&gt;May be used on all skin surfaces including head, neck, and intertriginous areas&lt;br&gt;Expensive</td>
</tr>
<tr>
<td><strong>Tacrolimus topical</strong>&lt;br&gt;(Protopic®)</td>
<td>0.03% (children) or 0.1% (adults) ointment bid&lt;br&gt;Continue for duration of disease PLUS x 1 wk after clearing</td>
<td>AD (mild to moderate)</td>
<td>Burning&lt;br&gt;Lacks adverse effects of steroids&lt;br&gt;May be used on all skin surfaces including head, neck, and intertriginous areas&lt;br&gt;Expensive</td>
</tr>
</tbody>
</table>

**Table 29. Common Oral Therapies**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acitretin</strong>&lt;br&gt;(Soriatane®)</td>
<td>25-50 mg PO OD; maximum 75 mg/d</td>
<td>Severe psoriasis&lt;br&gt;Other disorders of hyperkeratinization (ichthyosis, Darier’s disease)</td>
<td>Monitoring strategies:&lt;br&gt;Monitor lipids, LFTs at baseline and q1-2wk until stable&lt;br&gt;Contraindications:&lt;br&gt;Women of childbearing potential unless strict contraceptive requirements are met&lt;br&gt;Drug interactions:&lt;br&gt;Other systemic retinoids, methotrexate, tetracyclines, certain contraceptives&lt;br&gt;May be combined with PUVA phototherapy (known as re-PUVA)</td>
</tr>
<tr>
<td><strong>Antivirals</strong>&lt;br&gt;Famcyclovir (Famvir®)</td>
<td>250 mg PO tid x 7-10 d&lt;br&gt;(for 1st episode of genital herpes)&lt;br&gt;125 mg PO bid x 5d&lt;br&gt;(for recurrent genital herpes)</td>
<td>Chickenpox&lt;br&gt;Herpes zoster&lt;br&gt;Genital herpes&lt;br&gt;Acute and prophylactic to reduce transmission in infected patients&lt;br&gt;Herpes labialis</td>
<td>Side effects:&lt;br&gt;Headache, nausea, diarrhea, abdominal pain&lt;br&gt;Reduce dose if impaired renal function</td>
</tr>
<tr>
<td>Valacyclovir (Valtrex®)</td>
<td>1000 mg PO bid x 7-10 d&lt;br&gt;(for 1st episode of genital herpes)&lt;br&gt;500 mg PO bid x 5 d&lt;br&gt;(for recurrent genital herpes)</td>
<td></td>
<td>Side effects:&lt;br&gt;Dizziness, depression, abdominal pain&lt;br&gt;Reduce dose if impaired renal function&lt;br&gt;Drug interactions:&lt;br&gt;cimetidine</td>
</tr>
<tr>
<td><strong>Cyclosporin</strong>&lt;br&gt;(Neoral®)</td>
<td>2.5-4 mg/kg/d PO div bid&lt;br&gt;Max 4 mg/kg/d&lt;br&gt;After 4 wk may increase by 0.5 mg/kg/d q2wks&lt;br&gt;Concomitant dose of magnesium may protect the kidneys</td>
<td>Psoriasis&lt;br&gt;May also be effective in: Lichen planus&lt;br&gt;EM&lt;br&gt;Recalcitrant urticaria&lt;br&gt;Recalcitrant AD</td>
<td>Monitoring strategies:&lt;br&gt;Blood pressure, renal function&lt;br&gt;Contraindications:&lt;br&gt;Abnormal renal function, uncontrolled hypertension, malignancy (except non-melanoma skin cancer), uncontrolled infection, immunodeficiency (excluding autoimmune disease), hypersensitivity to drug&lt;br&gt;Long term effects preclude use of cyclosporin for &gt;2 yr; discontinue earlier if possible&lt;br&gt;May consider rotating therapy with other drugs to minimize adverse effects of each drug</td>
</tr>
<tr>
<td><strong>Dapsone</strong></td>
<td>50-100-150 mg PO OD tapering to 25-50 mg PO OD to as low as 50 mg 2x/wk</td>
<td>Dermatitis herpetiformis, neutrophilic dermatoses</td>
<td>Monitoring strategies:&lt;br&gt;Obtain GSPD levels before initiating; in the initial two wk obtain methemoglobin levels and follow the blood counts carefully for the first few months&lt;br&gt;Side effects:&lt;br&gt;Neuropathy&lt;br&gt;Hemolysis (Vitamin C and E supplementation can help prevent this)&lt;br&gt;Drug interactions:&lt;br&gt;Substrate of CYP2C8/9 (minor), 2C19 (minor), 2E1 (minor), 3A4 (major)&lt;br&gt;Often a dramatic response within hours</td>
</tr>
</tbody>
</table>
### Table 29. Common Oral Therapies (continued)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isotretinoin</strong> (Accutane®)</td>
<td>0.5-1 mg/kg/d given OD, to achieve a total dose of 120 mg/kg (20-24 wk)</td>
<td>Severe nodular and/or inflammatory acne</td>
<td>Monitoring strategies: Baseline lipid profile and LFTs before treatment, β-HCG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acne conglobata</td>
<td>Contraindications: Teratogenic – in sexually active females, 2 forms of reliable contraception necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recalcitrant acne</td>
<td>Generally regarded as unsafe in lactation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Widespread comedonal acne</td>
<td>Side effects: Night blindness, decreased tolerance to contact lenses, dry mucous membranes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>May transiently exacerbate acne, dry skin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Depression, myalgia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug interactions:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Do not use at the same time as tetracycline or minocycline – both may cause pseudotumour cerebri</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug may be discontinued at 16-20 wk when nodule count has dropped by &gt;70%. A second course may be initiated after 2 mo pm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Refractory cases may require &gt;3 courses</td>
</tr>
<tr>
<td><strong>Itraconazole</strong> (Sporanox®)</td>
<td>100-400 mg PO OD, depending on infection treated</td>
<td>Onychomycosis Tinea corporis, cruris, pedis, versicolor, capsitis</td>
<td>Contraindications: CHF</td>
</tr>
<tr>
<td></td>
<td>Tinea corporis/cruris: 200 mg PO OD x 7 d</td>
<td></td>
<td>Side effects: Serious hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Tinea pedis: 200 mg PO bid x 7 d</td>
<td></td>
<td>Drug Interactions: Inhibits CYP 3A4. Increases concentration of some drugs metabolized by this enzyme (i.e. statins, diabetic drugs)</td>
</tr>
<tr>
<td></td>
<td>Tinea versicolor: 200 mg PO OD x 7 d</td>
<td></td>
<td>Give capsules with food, capsules must be swallowed whole</td>
</tr>
<tr>
<td></td>
<td>Toenails with or without fingernail involvement: 200 mg PO bid x 7 d once per month, repeated 3x</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fingernail involvement only: 200 mg bid PO x 7 d once per month, repeated 2x</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ivermectin</strong> (Mectizan®, Stromectol®)</td>
<td>200-250 µg/kg PO qweekly x 2</td>
<td>Onchocerciasis (USA only) Not licensed for use in Canada Also effective for: Scabies</td>
<td>No significant serious side effects</td>
</tr>
<tr>
<td></td>
<td>Take once as directed; repeat one wk later</td>
<td></td>
<td>Efficacious</td>
</tr>
<tr>
<td><strong>Methotrexate</strong> (Trexall®)</td>
<td>10-25 mg qwk, PO, IM, or IV Max: 30 mg/ivk</td>
<td>Psoriasis AD Lymphomatoid papulosis May also be effective in: Cutaneous sarcoidosis</td>
<td>Monitoring strategies: Baseline renal, liver, and hematological studies</td>
</tr>
<tr>
<td></td>
<td>To minimize side effects, administer with folic acid supplementation: 1-5 mg OD</td>
<td></td>
<td>Contraindications: Pregnancy, lactation, alcohol abuse, liver dysfunction, immunodeficiency syndrome, blood dyscrasias, hypersensitivity to drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Restricted to severe, recalcitrant or disabling psoriasis not adequately responsive to other forms of therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be combined with cyclosporine to allow lower doses of both drugs</td>
<td></td>
</tr>
<tr>
<td><strong>Minocycline</strong> (Minocin®)</td>
<td>50-100 mg PO bid Taper to 50 mg PO OD as acne lessens</td>
<td>Acne vulgaris Rosacea</td>
<td>Contraindications: Caution if impaired renal or liver function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug interactions: Do not use with isotretinoin (Accutane®)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Side effects: Extensive; affects multiple organ systems including CNS, teeth, eyes, bones, renal, and skin (photosensitivity, and blue pigmentation) Drug-induced lupus (check p-ANCA) Alternative to tetracycline</td>
</tr>
<tr>
<td><strong>Terbinafine</strong> (Lamisil®)</td>
<td>250 mg PO OD x 2 wk Finger nails x 6 wk Toenails x 12 wk Confirm diagnosis prior to treatment</td>
<td>Onychomycosis Tinea corporis, cruris, pedis, capsitis</td>
<td>Contraindications: Pregnancy, chronic or active liver disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug interactions: Potent inhibitor of CYP 2D6; use with caution when also taking β-blockers, certain anti-arrhythmic agents, MAOI type B, and/or antipsychotics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug concentrates rapidly in skin, hair and nails at levels associated with fungicidal activity</td>
</tr>
<tr>
<td><strong>Tetracycline</strong></td>
<td>250-500 mg PO bid to tid Taken 1 h before or 2 h after a meal</td>
<td>Acne vulgaris Rosacea Bullous pemphigoid</td>
<td>Contraindications: Severe renal or hepatic dysfunction</td>
</tr>
</tbody>
</table>
Dermatology

References

Textbooks
Kraft J, Ing C, Betsuci U. University of Toronto pharmacology handbook. dermatology. (publication pending).

Articles
Wihite JD et al. Does this patient have a mole or a melanoma? JAMA 1999;279:696-701.
Acronyms ........................................ 2
Initial Patient Assessment/Management .... 2
Rapid Primary Survey (RPS)
Resuscitation
Secondary Survey
Ethical Considerations

Traumatology ................................. 6
Considerations for Traumatic Injury
Head Trauma
Mild Traumatic Brain Injury
Spine and Spinal Cord Trauma
Chest Trauma
Abdominal Trauma
Genitourinary Tract Injuries
Orthopedic Injuries
  Life and Limb Threatening Injuries
  Upper Extremity Injuries
  Lower Extremity Injuries
Wound Management
Trauma in Pregnancy

Approach to Common ER Presentations .... 19
Abdominal Pain
Acute Pelvic Pain
Altered Level of Consciousness (LOC)
Chest Pain
Epistaxis
Headache
Joint Pain
Otalgia
Seizures
Shortness of Breath
Syncope
Sexual Assault

Medical Emergencies ..................... 30
Anaphylaxis and Allergic Reactions
Asthma
Cardiac Dysrhythmias
Chronic Obstructive Pulmonary Disease (COPD)
Congestive Heart Failure
DVT and Pulmonary Embolism
Diabetic Emergencies
Electrolyte Disturbances
Hypertensive Emergencies
Stroke

Gynecology/Urology Emergencies ........ 39
Vaginal Bleed
Pregnant Patient in the ER
Nephrolithiasis (Renal Colic)

Ophthalmology Emergencies .......... 41

Dermatologic Emergencies ............ 42
Life Threatening Dermatoses

Environmental Injuries ................. 43
Heat Exhaustion and Heat Stroke
Hypothermia and Cold Injuries
Burns
Inhalation Injury
Bites
Near Drowning

Toxicology ................................. 48
Alcohol Related Emergencies
Approach to the Overdose Patient
ABCs of Toxicology
D1 – Universal Antidotes
D2 – Draw Bloods
D3 – Decontamination and Enhanced Elimination
E – Expose and Examine the Patient
F – Full Vitals, ECG Monitor, Foley, X-rays
G – Give specific Antidotes and Treatments
Disposition from the Emergency Department

Psychiatric Emergencies .......... 55
Approach to Common Psychiatric Presentations
Acute Psychosis
Suicidal Patient
Violent Patient

Common Pediatric ER Presentations .... 56
Modified Glasgow Coma Score
Respiratory Distress
Febrile Infant and Febrile Seizures
Abdominal Pain
Common Infections
Child Abuse and Neglect

Procedural Sedation .................... 60

Common Medications .................... 60

References ............................... 61
## Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA</td>
<td>abdominal aortic aneurysm</td>
</tr>
<tr>
<td>ABG</td>
<td>arterial blood gas</td>
</tr>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
</tr>
<tr>
<td>AVN</td>
<td>avascular necrosis</td>
</tr>
<tr>
<td>AVPU</td>
<td>alert, voice, pain, unresponsive</td>
</tr>
<tr>
<td>AXR</td>
<td>abdominal x-ray</td>
</tr>
<tr>
<td>Bi-PAP</td>
<td>bilevel positive airway pressure</td>
</tr>
<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
</tr>
<tr>
<td>CPP</td>
<td>cerebral perfusion pressure</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CVA</td>
<td>costovertebral angle</td>
</tr>
<tr>
<td>CXR</td>
<td>chest x-ray</td>
</tr>
<tr>
<td>D&amp;C</td>
<td>dilatation and curettage</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>DRE</td>
<td>digital rectal exam</td>
</tr>
<tr>
<td>DVT</td>
<td>deep venous thrombosis</td>
</tr>
<tr>
<td>ED</td>
<td>emergency department</td>
</tr>
<tr>
<td>ETT</td>
<td>endotracheal tube</td>
</tr>
<tr>
<td>FAST</td>
<td>focused abdominal sonogram for trauma</td>
</tr>
<tr>
<td>FFP</td>
<td>fresh frozen plasma</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow coma scale</td>
</tr>
<tr>
<td>IBG</td>
<td>inflammatory bowel disease</td>
</tr>
<tr>
<td>ICS</td>
<td>intercostal space</td>
</tr>
<tr>
<td>IVP</td>
<td>intravascular pressure</td>
</tr>
<tr>
<td>LOC</td>
<td>level of consciousness</td>
</tr>
<tr>
<td>LVM</td>
<td>left ventricular hypertrophy</td>
</tr>
<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
</tr>
<tr>
<td>MDI</td>
<td>metered dose inhaler</td>
</tr>
<tr>
<td>MVC</td>
<td>motor vehicle collision</td>
</tr>
<tr>
<td>NG</td>
<td>nasogastric</td>
</tr>
<tr>
<td>NS</td>
<td>normal saline</td>
</tr>
<tr>
<td>OD</td>
<td>overdose</td>
</tr>
<tr>
<td>PE</td>
<td>pulmonary embolism</td>
</tr>
<tr>
<td>PNS</td>
<td>parasympathetic nervous system</td>
</tr>
<tr>
<td>PRA</td>
<td>packed red blood cells</td>
</tr>
<tr>
<td>RCM</td>
<td>range of motion</td>
</tr>
<tr>
<td>RSI</td>
<td>rapid sequence induction</td>
</tr>
<tr>
<td>SNS</td>
<td>sympathetic nervous system</td>
</tr>
<tr>
<td>SOT</td>
<td>shortness of breath</td>
</tr>
<tr>
<td>SOB</td>
<td>urine toxicology screen</td>
</tr>
<tr>
<td>U/S</td>
<td>ultrasound</td>
</tr>
<tr>
<td>UTox</td>
<td>urine toxicology screen</td>
</tr>
<tr>
<td>VBG</td>
<td>venous blood gas</td>
</tr>
</tbody>
</table>

## Initial Patient Assessment/Management

### 1. Rapid Primary Survey (RPS)

- Airway maintenance with cervical spine (C-spine) control
- Breathing and ventilation
- Circulation (pulses, hemorrhage control)
- Disability (neurological status)
- Exposure (complete) and Environment (temperature control)
- Continually reassessed during secondary survey

**IMPORTANT:** always watch for signs of shock while doing primary survey (see Table 1)

#### A. AIRWAY

- First priority is to secure airway
- Assume a cervical injury in every trauma patient and immobilize with collar
- Assess ability to breathe and speak
- Can change rapidly, therefore reassess frequently

**Airway Management**

- Permit adequate oxygenation and ventilation

1. **Basic Airway Management (Temporizing Measures)**
   - Protect the C-spine
   - Head-tilt (if C-spine injury not suspected) or jaw thrust to open the airway
   - Sweep and suction to clear mouth of foreign material

2. **Temporizing Measures**
   - Nasopharyngeal airway (if gag reflex present, i.e. conscious)
   - Oropharyngeal airway (if gag reflex absent, i.e. unconscious)
   - "Rescue" airway devices [e.g. laryngeal mask airway (LMA); Combitube™]
   - Transtracheal jet ventilation through cricothyroid membrane (last resort)

3. **Definitive Airway Management**
   - ETT intubation with in-line stabilization of C-spine (Figure 1)
     - Orotracheal ± RSI preferred
     - Nasotracheal – may be better tolerated in conscious patient
       - Relatively contraindicated with basal skull fracture
     - Does not provide 100% protection against aspiration
   - Surgical airway (if unable to intubate using oral/nasal route and unable to ventilate)
     - Cricothyroidotomy

**Contraindications to Intubation**

- Supraglottic/glottic pathology that would preclude successful intubation
B. BREATHING

- Look
  - mental status (anxiety, agitation, decreased LOC), colour, chest movement (bilateral vs. asymmetrical), respiratory rate/effort, nasal flaring
- Listen
  - auscultate for signs of obstruction (e.g. stridor), breath sounds, symmetry of air entry, air escaping
- Feel
  - tracheal shift, chest wall for crepitus, flail segments, sucking chest wounds, subcutaneous emphysema

Breathing Assessment
- objective measures of respiratory function: rate, oximetry, arterial blood gas (ABG), A-a gradient

Management of Breathing
- nasal prongs → simple face mask → non-rebreather mask → CPAP/BiPAP (in order of increasing FiO2)
- Venturi mask: used to precisely control O2 delivery
- Bag-Valve mask and CPAP to supplement inadequate ventilation

C. CIRCULATION

Definition of Shock
- inadequate organ and tissue perfusion with oxygenated blood (brain, kidney, extremities) (see Table 2)

Table 1. Major Types of Shock

<table>
<thead>
<tr>
<th>Hypovolemic</th>
<th>Cardiogenic</th>
<th>Distributive (vasodilation)</th>
<th>Obstructive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage (external and internal)</td>
<td>Myocardial ischemia</td>
<td>Septic</td>
<td>Cardiac tamponade</td>
</tr>
<tr>
<td>Severe burns</td>
<td>Dysrhythmias</td>
<td>Tension pneumonia</td>
<td>Tension pneumonia</td>
</tr>
<tr>
<td>High output fistulas</td>
<td>Congestive heart failure</td>
<td>Anaphylactic</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Dehydration (diarrhea, DKA)</td>
<td>Cardiomyopathies</td>
<td>Neurogenic (spinal cord injury)</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Constrictive periarteritis</td>
</tr>
</tbody>
</table>

Clinical Evaluation
- early: tachypnea, tachycardia, narrow pulse pressure, reduced capillary refill, cool extremities and reduced central venous pressure (CVP)
- late: hypotension and altered mental status, reduced urine output

Table 2. Estimation of Degree of Hemorrhagic Shock

<table>
<thead>
<tr>
<th>Class</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss</td>
<td>&lt;750 cc</td>
<td>750-1500 cc</td>
<td>1500-2000 cc</td>
<td>&gt;2000 cc</td>
</tr>
<tr>
<td>% of blood volume</td>
<td>&lt;15%</td>
<td>15-30%</td>
<td>30-40%</td>
<td>&gt;40%</td>
</tr>
<tr>
<td>Pulse</td>
<td>&lt;100</td>
<td>&gt;100</td>
<td>&gt;120</td>
<td>&gt;140</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>20</td>
<td>30</td>
<td>35</td>
<td>&gt;45</td>
</tr>
<tr>
<td>Capillary refill</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
<td>None</td>
</tr>
<tr>
<td>Urinary output</td>
<td>30 cc/h</td>
<td>20 cc/h</td>
<td>10 cc/h</td>
<td>None</td>
</tr>
<tr>
<td>Fluid replacement</td>
<td>Crystalloid</td>
<td>Crystalloid</td>
<td>Crystalloid + blood</td>
<td>Crystalloid + blood</td>
</tr>
</tbody>
</table>

Shock in a trauma patient is hemorrhagic until proven otherwise.

Signs of Fluid Depletion
- Increased heart rate
- Postural changes in vital signs
- Decreased urine output
- Hypotensive
- Decreased skin turgor
- Sunken eyes
- Decreased capillary refill

Causes of Shock

SHOCKED
- Sepsis (spinal/neurogenic, Hemorrhagic
- Obstructive (e.g. tension pneumonia, cardiac tamponade, pulmonary embolism)
- Cardiogenic (e.g. blunt myocardial injury, dysrhythmia, MI)
- Anaphylactic
- Endocrine (e.g. Addison’s, myxedema, coma)
- Drugs

Estimated Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Based on Position of Most Distal Palpable Pulse</th>
<th>sBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial</td>
<td>&gt;80</td>
</tr>
<tr>
<td>Femoral</td>
<td>&gt;70</td>
</tr>
<tr>
<td>Carotid</td>
<td>&gt;60</td>
</tr>
</tbody>
</table>
Management of Hemorrhagic Shock

- ABCs
  - diagnose and manage underlying cause
  - if bleeding externally, apply direct pressure and elevate extremities if possible
  - do not remove impaled objects as they tamponade hemorrhage
  - tourniquet as a last resort
- resuscitation
  - infuse 1-2 L of crystalloid with large bore IVs (warmed if possible)
  - if inadequate response, consider acute internal bleeding (e.g., chest, abdomen, pelvis, femurs), will likely require surgical intervention
  - if severely hypotensive on arrival or if shock persists, consider pRBC transfusion
  - transfuse crossmatched (ideally) or type-specific blood if available
  - if unavailable, transfuse O-negative in children/women of child bearing age or O-positive in all others
- with significant blood loss, early transfusion of platelets and FFP may improve outcomes

D. DISABILITY
- assess level of consciousness by AVPU method or GCS (Table 3)

Glasgow Coma Scale (GCS)
- for use in trauma patients with decreased LOC; good indicator of severity of injury and neurosurgical prognosis
- most useful if repeated and used for monitoring of trend
- change in GCS with time is more relevant than the absolute number
- less meaningful for metabolic coma
- patient with deteriorating GCS needs immediate attention
- prognosis based on best post-resuscitation GCS
- reported as a 3 part score: Eyes + Verbal + Motor = Total (see Table 3)
- if patient intubated, GCS score reported out of 10 + T (T= tubed, i.e. no verbal component)

Table 3. Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Eyes Open</th>
<th>Best Verbal Response</th>
<th>Best Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneously</td>
<td>Answers questions appropriately</td>
<td>Obey commands</td>
</tr>
<tr>
<td>To voice</td>
<td>Confused, disoriented</td>
<td>Localizes to pain</td>
</tr>
<tr>
<td>To pain</td>
<td>Inappropriate words</td>
<td>Withdraws from pain</td>
</tr>
<tr>
<td>No response</td>
<td>Incomprehensible sounds</td>
<td>Decorticate (flexion)</td>
</tr>
<tr>
<td>No verbal response</td>
<td></td>
<td>Decerebrate (extension)</td>
</tr>
</tbody>
</table>

13-15 = mild injury, 9-12 = moderate injury, ≤8 = severe injury
See Table 30 for modified GCS for infants and children

E. EXPOSURE/ENVIRONMENT
- undress patient completely and assess entire body for injury; logroll to examine back
- digital rectal exam
- keep patient warm with a blanket ± radiant heaters; avoid hypothermia
- warm IV fluids/blood
- keep providers safe (contamination, combative patient)

2. Resuscitation

- done concurrently with primary survey
- attend to ABCs (see Table 4)
- manage life-threatening problems as they are identified
- vital signs q5-15 min
- ECG, BP and O₂ monitors
- Foley catheter and NG tube if indicated
- tests and investigations: CBC, electrolytes, BUN, Cr, glucose, amylase, INR/PTT, β-hCG, toxicology screen, cross and type

Fluid Resuscitation
- Give bolus until HR decreases, urine output increases, and patient stabilizes
- Maintenance: 4:2:1 rule
- 0-10 kg: 4 cc/kg/h
- 10-20 kg: 2 cc/kg/h
- Remaining weight: 1 cc/kg/h
- Replace ongoing losses and deficits (assume 10% of body weight)

3:1 Rule
Since only 30% of infused isotonic crystalloids remains in intravascular space, you must give 3x estimated blood loss.

Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock
NEJM 2008;358:877-87
Study: Multicentre, randomized, double-blind trial
Patients: 778 patients with septic shock
Intervention: Low-dose vasopressin (0.01 to 0.03 U per minute) or norepinephrine (5 to 15 ug per minute) in addition to open-label vasopressors and a minimum of 5 ug of norepinephrine.
Outcome: Mortality rate 28 d after start of infusions.
Results: No significant difference between the vasopressin and the norepinephrine groups at 28 d or 90 d. However, in patients with less severe septic shock, mortality rate was lower in the vasopressin group.

Contraindications to Foley insertion
- Blood at urethral meatus
- Scrotal hematoma
- High-riding prostate on DRE
Table 4. 2010 AHA CPR Guidelines

<table>
<thead>
<tr>
<th>Step/Action</th>
<th>Adult: &gt;8 years</th>
<th>Child: 1-8 years</th>
<th>Infant: &lt;1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway</td>
<td>Head tilt-chin lift</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breaths</td>
<td>2 breaths at 1 second/breath – stop once see chest rise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foreign-body airway obstruction</td>
<td>Abdominal thrust</td>
<td>Back slaps and chest thrusts</td>
<td></td>
</tr>
<tr>
<td><strong>Compressions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compression landmarks</td>
<td>In the centre of the chest, between nipples</td>
<td>Just below nipple line</td>
<td></td>
</tr>
<tr>
<td>Compression method: push hard and fast and allow for complete recoil</td>
<td>2 hands: heel of 1 hand with second hand on top</td>
<td>2 hands: heel of 1 hand with second on top, or 1 hand: heel of 1 hand only</td>
<td>2 fingers, or thumbs</td>
</tr>
<tr>
<td>Compression depth</td>
<td>At least 2 inches</td>
<td>About 1/3 to 1/2 the depth of the chest</td>
<td></td>
</tr>
<tr>
<td>Compression rate</td>
<td>100/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compression-ventilation ratio</td>
<td>30 compressions to 2 ventilations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compression-only CPR</td>
<td>Hands-only CPR is preferred if the bystander is not trained or does not feel confident in their ability to provide conventional CPR or if the bystander is trained but chooses to use compressions only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defibrillation</td>
<td>Immediate defibrillation for all rescuers responding to a sudden witnessed collapse</td>
<td>Compressions (5 cycles/2 min) before AED is considered if unwitnessed arrest</td>
<td>Manual defibrillators are preferred for children and infants but can use adult dose AED if a manual defibrillator is not available</td>
</tr>
</tbody>
</table>

3. Secondary Survey

- done after rapid primary survey problems have been addressed
- identifies major injuries or areas of concern
- full physical exam and x-rays (C-spine, chest, pelvis – required in blunt trauma, consider T-spine and L-spine)

**HISTORY**

- “SAMPLE”: Signs and symptoms, Allergies, Medications, Past medical history, Last meal, Events related to injury

**PHYSICAL EXAMINATION**

**Head and Neck**

- pupils
  - assess equality, size, symmetry, reactivity to light
  - inequality/sugglish suggests local eye problem or lateralizing CNS lesion
  - relative afferent pupillary defect (swinging light test) – optic nerve damage
  - extraocular movements and nystagmus
  - fundoscopy (papilledema, hemorrhages)
  - reactive pupils + decreased LOC \(\rightarrow\) metabolic or structural cause
  - non-reactive pupils + decreased LOC \(\rightarrow\) structural cause (especially if asymmetric)
  - palpation of facial bones, scalp

**Chest**

- inspect for midline trachea, flail segment: \(\geq 2\) rib fractures in \(\geq 2\) places; if present look for associated hemothorax, pneumothorax, and contusions
- auscultate lung fields
- palpate for subcutaneous emphysema
- CXR

**Abdomen**

- assess for peritonitis, abdominal distention, and evidence of intra-abdominal bleeding
- FAST or CT (if stable)
- rectal exam for GI bleed, high riding prostate and anal tone (best to do during the log roll)
- bimanual exam in females as appropriate

**Musculoskeletal (MSK)**

- examine all extremities for swelling, deformity, contusion, tenderness, ROM
- check for pulses and sensation in all injured limbs
- log roll and palpate thoracic and lumbar spines
- palpate iliac crests and pubic symphysis, pelvic stability (lateral, AP, vertical)
- pelvic x-ray

---

**NG Tube Contraindications**

- Significant mid-face trauma
- Basal skull fracture

See Anesthesia, A28 for 2012 ACLS Guidelines.
Neurological
- GCS
- full cranial nerve exam
- alterations of rate and rhythm of breathing are signs of structural or metabolic abnormalities
  ▪ progressive deterioration of breathing pattern implies a failing CNS
- assess spinal cord integrity
  ▪ conscious patient: assess distal sensation and motor
  ▪ unconscious patient: response to painful or noxious stimulus applied to extremities

Ethical Considerations

Consent to Treatment: Adults
- see Ethical, Legal and Organizational Aspects of Medicine, ELOAM5
- Emergency Rule: consent is not needed when a patient is at imminent risk from a serious injury
  AND obtaining consent is either: a) not possible OR b) would increase risk to the patient
  ▪ assumes that most people would want to be saved in an emergency
- any capable and informed patient can refuse treatment or part of treatment, even if it is life-saving
- exceptions to the Emergency Rule: treatment cannot be initiated if
  ▪ a competent patient has previously refused the same or similar treatment and there is no evidence to suggest the patient's wishes have changed
  ▪ an advanced directive is available – e.g. do not resuscitate (DNR) order
  ▪ NOTE: refusal of help in a suicide situation is NOT an exception; care must be given
- if in doubt, initiate treatment
  ▪ care can be withdrawn if necessary at a later time or if wishes are clarified by family

Consent to Treatment: Children
- treat immediately if patient is at imminent risk
- parents/guardians have the right to make treatment decisions
- if parents refuse treatment that is life-saving or will potentially alter the child's quality of life, Children's Aid Society (CAS) must be contacted – consent of CAS is needed to treat

Other Issues of Consent
- need consent for HIV testing, as well as for administration of blood products
- however, if delay in substitute consent for blood transfusions puts patient at risk, transfusions can be given

Duty to Report
- law may vary depending on province and/or state
- examples: gunshot wounds, potential drunken drivers, suspected child abuse, various communicable diseases, medical unsuitability to drive, risk of substantial harm to others

Traumatology

- epidemiology
  ▪ leading cause of death in patients <45 yr
  ▪ 4th highest cause of death in North America
  ▪ causes more deaths in children/adolescents than all diseases combined
- trimodal distribution of death
  ▪ minutes: lethal injuries, death usually at the scene
  ▪ early: death within 4-6 h – “golden hour” (decreased mortality with trauma care)
  ▪ days-weeks: death from multiple organ dysfunction, sepsis, etc.
- injuries fall into two categories
  ▪ blunt (most common): motor vehicle collision (MVC), pedestrian-automobile impact, motorcycle collision, fall, assault, sports
  ▪ penetrating (increasing in incidence): gunshot wound, stabbing, impalement

Jehovah’s Witnesses
- Capable adults have the right to refuse medical treatment
- May refuse whole blood, pRBCs, platelets and plasma even if life-saving
- Should be questioned directly about the use of albumin, immunoglobulins, hemophilic preparations
- Do not allow autologous transfusion unless there is uninterrupted extracorporeal circulation
- Usually ask for the highest possible quality of care without the use of the above interventions (e.g. crystalloids for volume expansion, attempts at bloodless surgery)
- Patient will generally sign hospital forms releasing medical staff from liability
- Most legal cases involve children of Jehovah’s Witnesses; if life-saving treatment is refused contact CAS
Considerations for Traumatic Injury

• important to know the mechanism of injury in order to anticipate traumatic injuries
• always look for an underlying cause (alcohol, medications, illicit substances, seizure, suicide attempt, medical problem)
• always inquire about head injury, loss of consciousness, amnesia, vomiting, headache and seizure activity

Table 5. Mechanisms and Considerations of Traumatic Injuries

<table>
<thead>
<tr>
<th>Mechanism of Injury</th>
<th>Special Considerations</th>
<th>Associated Injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor Vehicle Collision</td>
<td>Vehicle(s) involved: weight, size, speed, damage, Location of patient in vehicle</td>
<td>Head-on collision: head/facial, thoracic (aortic), lower extremity, lateral/T-bone</td>
</tr>
<tr>
<td></td>
<td>Use and type of seatbelt, Ejection of patient from vehicle, Entrapment of patient under vehicle</td>
<td>collision: head, cervical spine, thoracic, abdominal, pelvic and lower extremity.</td>
</tr>
<tr>
<td></td>
<td>Airbag deployment, Helmet use in motorcycle collision</td>
<td>Rear-end collision: hyper-extension of cervical spine (whiplash injury) Rollover</td>
</tr>
<tr>
<td>Pedestrian-Automobile Impact</td>
<td>High morbidity and mortality, Vehicle speed is an important factor, Site of impact on car</td>
<td>Children at increased risk of being run over (multisystem injuries) Adults tend to be struck in lower legs (lower extremity injuries), impacted against car (truncal injuries) and thrown to ground (head injuries)</td>
</tr>
<tr>
<td>Falls</td>
<td>1 storey = 12 feet = 3.6 m, Distance of fall: 50% mortality at 4 stories and 95% mortality at 7 stories, Landing position (vertical vs. horizontal)</td>
<td>Vertical: lower extremity, pelvic and spine fractures, Head injuries Horizontal: facial, upper extremity and rib fractures, Abdominal, thoracic and head injuries</td>
</tr>
<tr>
<td>Gunshot Wounds (GSW)</td>
<td>Type of gun, Type of ammunition, Range of shot, Characterize route of entry, even or odd number of wounds and site of exit wound (if any) KE = 1/2 mv^2</td>
<td>Injuries dependent on location of GSW and underlying structures Hand gun: low/medium velocity, extent of injury may be limited to small area Hunting rifle: high velocity, widespread injury Shotgun: widespread tissue destruction at close range, massive tissue destruction, deposition of wadding into wound</td>
</tr>
<tr>
<td>Stab Wounds (SW)</td>
<td>Route/direction of entry, Length of blade, Type of penetration (stab, slash, impalement), If blade in-situ, DO NOT REMOVE – may be tamponading vessel (to be removed in OR)</td>
<td>Injuries dependent on location of SW and underlying structures</td>
</tr>
</tbody>
</table>

Head Trauma

• see Neurosurgery, NS30
• 60% of trauma admissions have head injuries
• 60% of MVC-related deaths are due to head injury

Specific Injuries

• fractures
  • Dx: non-contrast head CT and physical exam
  A. skull fractures
    • vault fractures
      • linear, non-depressed
        – most common
        – typically occur over temporal bone, in area of middle meningeal artery (commonest cause of epidural hematoma)
      • depressed
        – open (associated overlying scalp laceration and torn dura), skull fracture disrupting paranasal sinuses or middle ear) vs. closed
    • basal skull
      • typically occur through floor of anterior cranial fossa (longitudinal more common than transverse)
      • clinical diagnosis superior as poorly visualized on CT (Battle’s sign, raccoon eyes, CSF rhinorrhea/otorrhea, hemotympanum)
  B. facial fractures (see Plastic Surgery, PL28)
    • neuronal injury
    • beware of open fracture or sinus fractures (risk of infection)
    • unstable or displaced fractures (need semi-urgent plastics referral)
    • severe facial fractures may pose risk to airway from profuse bleeding

Cardiac box: sternal notch, nipples and xiphoid process; injuries inside this area should increase suspicion of cardiac injury.

Always completely expose and count the number of wounds.
• **scalp laceration**  
  ▪ can be a source of significant bleeding  
  ▪ achieve hemostasis, inspect and palpate for skull bone defects ± CT head (rule-out skull fracture)

• **neuronal injury**
  A. **diffuse**  
  ▪ mild traumatic brain injury = concussion  
  ▪ transient alteration in mental status that may involve loss of consciousness  
  ▪ hallmarks of concussion: confusion and amnesia, which may occur immediately after the trauma or minutes later  
  ▪ loss of consciousness (if present) must be less than 30 min, initial GCS must be between 13-15 and post-traumatic amnesia must be less than 24 h
  ▪ diffuse axonal injury  
  ▪ mild: coma 6-24 h, possibly lasting deficit
  ▪ moderate: coma >24 h, little or no signs of brainstem dysfunction
  ▪ severe: coma >24 h, frequent signs of brainstem dysfunction
  B. **focal injuries**  
  ▪ contusions
  ▪ intracranial hemorrhage (epidural, subdural, intracerebral)

### ASSESSMENT OF BRAIN INJURY

#### History
• pre-hospital status  
• mechanism of injury

#### Physical Examination
• assume C-spine injury until ruled out  
• vital signs  
  ▪ shock (not likely due to isolated brain injury, except in infants)
  ▪ Cushing's response to increasing ICP (bradycardia, hypertension, irregular respirations)
• severity of injury determined by  
  1. LOC  
     ▪ GCS ≤8 intubate, any change in score of 3 or more = serious injury  
     ▪ mild TBI = 13-15, moderate = 9-12, severe = 3-8
  2. pupils: size, anisocoria >1 mm (in patient with altered LOC), response to light
  3. lateralizing signs (motor/sensory)  
     ▪ may become more subtle with increasing severity of injury
• reassess frequently

#### Investigations
• labs: CBC, electrolytes, PT/PTT or INR/PTT, glucose, toxicology screen  
• CT scan (non-contrast) to exclude intracranial mass lesions  
• C-spine imaging, often with CT head and neck to exclude intracranial mass lesions

#### Management
• goal in ED: reduce secondary injury by avoiding hypoxia, ischemia, decreased CPP, seizure

  general
  ▪ ABCs
  ▪ ensure oxygen delivery to brain through intubation and prevent hypercarbia
  ▪ maintain BP (sBP >90)
• treat other injuries
• early neurosurgical consultation for acute and subsequent patient management

  medical management
  ▪ seizure treatment/prophylaxis  
    ▪ benzodiazepines, phenytoin, phenobarbital
    ▪ steroids are of no proven value
  ▪ treat suspected raised ICP  
    ▪ consider if head injury with signs of increased ICP:  
      ▪ raise head of stretcher 20° if patient hemodynamically stable  
      ▪ intubate and hyperventilate (100% O₂) to a pCO₂ of 30-35 mmHg
      ▪ mannitol 1g/kg infused as rapidly as possible (contraindicated in shock and renal failure/anuria)
      ▪ consider paralyzing medications if agitated/high airway pressures
      ▪ maintenance of CPP is critical (CPP=MAP-ICP)

#### Disposition
• neurosurgical ICU admission for severe head injuries (HI)
• in hemodynamically unstable patient with other injuries, prioritize most life-threatening injuries and maintain cerebral perfusion
• for minor head injury not requiring admission, provide 24 h HI protocol to competent caregiver, follow-up with neurology as even seemingly minor HI may cause lasting deficits
Mild Traumatic Brain Injury

Epidemiology
- traumatic brain injury results in 1.7 million deaths, hospitalizations and ED visits each year (US)
- 75% are estimated to be mild TBI; remainder are moderate or severe (see Neurosurgery, NS31)
- highest rates in children 0-4 yr, adolescents 15-19 yr and elderly >65 yr

Clinical Features
- somatic: headache, sleep disturbance, nausea, vomiting, blurred vision
- cognitive dysfunction: attentional impairment, reduced processing speed, drowsiness, amnesia
- emotion and behaviour: impulsivity, irritability, depression
- severe concussion: may precipitate seizure, bradycardia, hypotension, sluggish pupils

Etiology
- falls, motor vehicle and traffic accidents, struck by an object, assault, sports

Investigations
- neuro exam
- concussion recognition tool (see thinkfirst.ca)
- imaging – CT as per Canadian CT Head Rules, or MRI if worsening symptoms despite normal CT

Treatment
- close observation and follow-up; patients at risk of intracranial complications [give appropriate discharge instructions to patient and family] watch for changes to clinical features above, and if change, return to ER
- hospitalization with normal CT (GCS <15, seizures, bleeding diathesis), or with abnormal CT
- early rehabilitation to maximize outcomes
- pharmacological management of pain, depression, headache
- follow Return to Play guidelines: Cantu, Colorado Medical Society, American Academy of Neurology, 2008 Consensus Statement on Concussion in Sports – no data on superiority

Prognosis
- most recover with minimal treatment
  - athletes with previous concussion are at increased risk of cumulative brain injury
- repeat TBI can lead to life threatening cerebral edema or permanent impairment

Spine and Spinal Cord Trauma

- assume cord injury with significant falls (>12 ft), deceleration injuries, blunt trauma to head, neck or back
- spinal immobilization (cervical collar, spine board during patient transport only) must be maintained until spinal injury has been ruled out (Figure 2)
- vertebral injuries may be present without spinal cord injury; normal neurologic exam does not exclude spinal injury
- cord may be injured despite normal C-spine x-ray (SCIWORA = spinal cord injury without radiologic abnormality)
- injuries can include: complete/incomplete transection, cord edema, spinal shock

History
- mechanism of injury, previous deficits, SAMPLE
- neck pain, paralysis/weakness, paresthesia

Physical Exam
- ABCs
- abdo: ecchymosis, tenderness
- neuro: complete exam, including mental status
- spine: maintain neutral position, palpate C-spine; logroll, then palpate T-spine and L-spine spine; assess rectal tone
  - when palpating assess for tenderness, muscle spasm, bony deformities, step-off and spinous process mal-alignment
- extremities: check cap refill, suspect thoracolumbar injury with calcaneal fractures

Investigations
- labs: CBC, electrolytes, creatinine, glucose, coagulation profile, cross and type, toxicology screen
- imaging
  - full C-spine x-ray series for trauma (AP, lateral, odontoid)
  - thoracolumbar x-rays
  - AP and lateral views
  - indications:
    - patients with C-spine injury
    - unconscious patients (with appropriate mechanism of injury)
    - patients with neurological symptoms or findings

Epidemiology

- falls, motor vehicle and traffic accidents, struck by an object, assault, sports

Investigations

- neuro exam
- concussion recognition tool (see thinkfirst.ca)
- imaging – CT as per Canadian CT Head Rules, or MRI if worsening symptoms despite normal CT

Treatment

- close observation and follow-up; patients at risk of intracranial complications [give appropriate discharge instructions to patient and family] watch for changes to clinical features above, and if change, return to ER
- hospitalization with normal CT (GCS <15, seizures, bleeding diathesis), or with abnormal CT
- early rehabilitation to maximize outcomes
- pharmacological management of pain, depression, headache
- follow Return to Play guidelines: Cantu, Colorado Medical Society, American Academy of Neurology, 2008 Consensus Statement on Concussion in Sports – no data on superiority

Prognosis

- most recover with minimal treatment
  - athletes with previous concussion are at increased risk of cumulative brain injury
- repeat TBI can lead to life threatening cerebral edema or permanent impairment

Spine and Spinal Cord Trauma

- assume cord injury with significant falls (>12 ft), deceleration injuries, blunt trauma to head, neck or back
- spinal immobilization (cervical collar, spine board during patient transport only) must be maintained until spinal injury has been ruled out (Figure 2)
- vertebral injuries may be present without spinal cord injury; normal neurologic exam does not exclude spinal injury
- cord may be injured despite normal C-spine x-ray (SCIWORA = spinal cord injury without radiologic abnormality)
- injuries can include: complete/incomplete transection, cord edema, spinal shock

History

- mechanism of injury, previous deficits, SAMPLE
- neck pain, paralysis/weakness, paresthesia

Physical Exam

- ABCs
- abdo: ecchymosis, tenderness
- neuro: complete exam, including mental status
- spine: maintain neutral position, palpate C-spine; logroll, then palpate T-spine and L-spine spine; assess rectal tone
  - when palpating assess for tenderness, muscle spasm, bony deformities, step-off and spinous process mal-alignment
- extremities: check cap refill, suspect thoracolumbar injury with calcaneal fractures

Investigations

- labs: CBC, electrolytes, creatinine, glucose, coagulation profile, cross and type, toxicology screen
- imaging
  - full C-spine x-ray series for trauma (AP, lateral, odontoid)
  - thoracolumbar x-rays
  - AP and lateral views
  - indications:
    - patients with C-spine injury
    - unconscious patients (with appropriate mechanism of injury)
    - patients with neurological symptoms or findings
• patients with deformities that are palpable when patient logroll
• patients with back pain
• patients with bilateral calcaneal fractures (due to fall from height)
• concurrent burst fractures of the lumbar or thoracic spine in 10% (T11-L2)
• consider CT (for subtle bony injuries), MRI (for soft tissue injuries) if appropriate

Management of Cord Injury
• immobilize
• evaluate ABCs
• treat shock (maintain SBP >100 mmHg)
• insert NG and Foley catheter
• high dose steroids: methylprednisolone 30 mg/kg bolus, then 5.4 mg/kg/h drip, start within 6-8 h of injury (controversial and recently has less support)
• complete imaging of spine and consult spine service if available
• continually reassess high cord injuries as edema can travel up cord
• if cervical cord lesion, watch for respiratory insufficiency
  • low cervical transection (C5-T1) produces abdominal breathing (phrenic innervation of diaphragm still intact)
  • high cervical cord injury (above C4) may require intubation and ventilation
• beware of hypotension (neurogenic shock)
• treatment: warm blanket, Trendelenberg position (occasionally), volume infusion, consider vasopressors

Approach to C-Spine X-Rays
• 3-view C-spine series is the screening modality of choice
  1. lateral C1-T1 ± swimmer’s view (Figure 3, see Table 6 for interpretation)
  • lateral view is best, identifies 90-95% of injuries
  2. odontoid view (open mouth or oblique submental view) (see Figure 4)
  • examine the dens for fractures
  • if unable to rule out fracture, repeat view or consider CT or plain film tomography
  • examine lateral aspects of C1 and spacing relative to C2
  3. AP view
  • alignment of spinous processes in the midline
  • spacing of spinous processes should be equal
  • check vertebral bodies and facet dislocations

Figure 2. Approach to clearing the C-spine

Can Clear C-spine if:
• no posterior midline cervical tenderness
• no evidence of intoxication
• oriented to person, place, time and event
• no focal neurological deficits
• no painful distracting injuries (e.g. long bone fracture)

Figure 3. Lines of contour on a lateral C-spine x-ray

Prevertebral soft tissue swelling is only 49% sensitive for injury.
Supine Oblique Views
- rarely used
- better visualization of posterior element fractures (lamina, pedicle, facet joint)
- good to assess patency of neural foramina
- can be used to visualize the C7-T1 junction

Table 6. Interpretation of Lateral View: The ABCS

A Adequacy and Alignment
- Must see C1 to C7-T1 junction; if not, downward traction of shoulders, swimmer’s view, bilateral supine obliques, or CT scan needed
- Lines of contour – in children < 8 yr of age: can see physiologic subluxation of C2 on C3, and C3 on C4, but the spino-laminar line is maintained
- Fanning of spinous processes – suggests posterior ligamentous disruption
- Widening of facet joints
- Check atlanto-occipital joint:
  - Line extending inferiorly from clivus should transect odontoid
  - Atlanto-axial articulation – widening of predental space (normal: < 3 mm in adults, < 5 mm in children) indicates injury of C1 or C2
  - Spino-laminal line is maintained

B Bones
- Height, width and shape of each vertebral body
- Pedicles, facets, and laminae should appear as one – doubling suggests rotation

C Cartilage
- Intervertebral disc spaces – wedging anteriorly or posteriorly suggests vertebral compression

S Soft Tissues
- Widening of retropharyngeal (normal: < 7 mm at C1-4, may be wide in children < 2 yr on expiration) or retrotracheal spaces (normal: < 22 mm at C6-T1, < 14 mm in children < 5 yr)

Sequelles of C-spine Fractures
- see Neurosurgery. NS 32
- acute phase of SCI
  - spinal shock: absence of all voluntary and reflex activity below level of injury
  - decreased reflexes, no sensation, flaccid paralysis below level of injury, lasting days to months
- neurogenic shock: loss of vasomotor tone, SNS tone
  - watch for: hypotension (lacking SNS), bradycardia (unopposed PNS), poikilothermia (lacking SNS so no shunting of blood from extremities to core)
  - occurs within 30 min of SCI at level T6 or above, lasting up to 6 wk
  - provide airway support, fluids, atropine (for bradycardia), vasopressors for BP support
- chronic phase of SCI
  - autonomic dysreflexia: in patients with an SCI at level T6 or above
  - signs and symptoms: pounding headache, nasal congestion, feeling of apprehension or anxiety, visual changes, dangerously increased sBP and dBP
  - common triggers
    - GU causes: bladder distention, urinary tract infection, and kidney stones
    - GI causes: fecal impaction or bowel distension
  - treatment: monitoring and controlling BP, prior to addressing causative issue

Chest Trauma
- two types: those found and managed in 1º survey and those found and managed in 2º survey (see Tables 7 and 8)

Table 7. Life-Threatening Chest Injuries Found in 1º Survey

<table>
<thead>
<tr>
<th>Physical Exam</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Airway Obstruction</strong></td>
<td>Anxiety, stridor, hoarseness, altered mental status, Aprexia, cyanosis</td>
<td>Do not wait for ABG to intubate</td>
</tr>
<tr>
<td><strong>Tension Pneumothorax</strong></td>
<td>Respiratory distress, tachycardia, distended neck veins, cyanosis, asymmetry of chest wall motion</td>
<td>Non-radiographic diagnosis</td>
</tr>
</tbody>
</table>

Figure 4. C-spine x-ray; odontoid view
- In contrast to neurogenic shock, hypovolemic shock has hypotension and tachycardia.
- Autonomic dysreflexia – a life threatening elevation of BP with SCI at or above T6.
- 20% of C-spine fractures are accompanied by other spinal fractures, so ensure thoracic and lumbar spine x-rays are normal before proceeding to OR.
- Trauma to the chest accounts for 50% of trauma deaths.
- 80% of all chest injuries can be managed non-surgically with simple measures such as intubation, chest tubes, and pain control.
- 3-way Seal for Open Pneumothorax (i.e. sucking chest wound): Allows air to escape during the expiratory phase (so that you don’t get a tension pneumothorax) but seals itself to allow adequate breaths during the inspiratory phase.
- Pulsus Paradoxus: a drop in BP of > 10 mmHg with inspiration. Recall that BP normally drops with inspiration, but what’s “paradoxical” about this is that it drops more than it should.
Airway Injuries

- Penetrating Neck Trauma
  - DON'T: Clamp structures (can damage nerves)
  - Probe
  - Insert NG tube (leads to bleeding)
  - Remove weapon/impaled object

Ruptured diaphragm is more often diagnosed on the left side, as liver conceals right side defect.

Aortic Tear: ABC WHITE
- x-ray features of Aortic tear depressed left mainstem Bronchus pleural
- Wide mediastinum (most consistent)
- Hemorrhage
- Indirect aortic knuckle
- Tracheal deviation to right side
- Esophagus (NG tube) deviated to right

(Note: present in 85% of cases, but cannot rule out)

If Penetrating Neck Trauma Present, DON'T:
- Clamp structures (can damage nerves)
- Probe
- Insert NG tube (leads to bleeding)
- Remove weapon/impaled object

Other Potentially Life-Threatening Injuries Related to the Chest

Penetrating Neck Trauma
- includes all penetrating trauma to the three zones of the neck (Figure 5)
- management: injuries deep to platysma require further evaluation by angiography, contrast CT or surgery
- do not explore penetrating neck wounds except in the OR

Airway Injuries
- always maintain a high index of suspicion

Table 7. Life-Threatening Chest Injuries Found in 1st Survey (continued)

<table>
<thead>
<tr>
<th>Physical Exam</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open Pneumothorax</td>
<td>• Air entering chest from wound rather than trachea</td>
<td>• Gunshot or other wound (hole &gt; 2/3 tracheal diameter) ± exit wound</td>
</tr>
<tr>
<td>Massive Hemothorax</td>
<td>• &gt; 1500 cc blood loss in chest cavity</td>
<td>• Pallor, flat neck veins, shock</td>
</tr>
<tr>
<td>Flail Chest</td>
<td>• Free-floating segment of chest wall due to &gt;2 rib fractures, each at 2 sites</td>
<td>• Paradoxic movement of flail segment</td>
</tr>
<tr>
<td>Cardiac Tamponade</td>
<td>• Clinical diagnosis</td>
<td>• Penetrating wound (usually)</td>
</tr>
</tbody>
</table>

Table 8. Potentially Life-Threatening Chest Injuries Found in 2nd Survey

<table>
<thead>
<tr>
<th>Physical Exam</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Contusion</td>
<td>• Blunt trauma to chest</td>
<td>• Intersitial edema impairs compliance and gas exchange</td>
</tr>
<tr>
<td>Ruptured Diaphragm</td>
<td>• Blunt trauma to chest or abdomen (e.g. high lap belt in MVC)</td>
<td>• CXR: abnormality of diaphragm/lower lung fields/NG tube placement</td>
</tr>
<tr>
<td>Esophageal Injury</td>
<td>• Usually penetrating trauma (pain out of proportion to degree of injury)</td>
<td>• CXR: mediastinal air (not always)</td>
</tr>
<tr>
<td>Aortic Tear</td>
<td>• 90% tear at subclavian (near ligamentum arteriosum), most die at scene</td>
<td>• Sudden high speed deceleration (e.g. MVC, fall, airplane crash), complaints of chest pain, dyspnea, hoarseness (frequently absent)</td>
</tr>
<tr>
<td>Blunt Myocardial Injury (rare)</td>
<td>• Blunt trauma to chest (usually in setting of multi-system trauma and therefore difficult to diagnose)</td>
<td>• Physical examination: overlying injury, e.g. fractures, chest wall contusion</td>
</tr>
</tbody>
</table>

HOT and FAT CHEST
- Hemothorax*
- Open pneumothorax
- Tension pneumothorax*
- Flail chest
- Airway obstruction
- Tamponade*

Contusion: pulmonary, myocardial
Hernia: traumatic, diaphragmatic
Esophageal perforation
Tracheobronchial disruption/ Traumatic injury/Thoracic Aorta Rupture* *Rapidly Life Threatening

DDx of Life Threatening Chest Injuries

Zone III: Superior aspect of neck
Zone II: Midportion of neck (cricord to the angle of mandible)
Zone I: Base of neck (thoracic inlet to cricoid cartilage)
larynx
- history: strangulation, direct blow, blunt trauma, any penetrating injury involving platysma
- triad: hoarseness, subcutaneous emphysema, palpable fracture crepitus
- other symptoms: hemothysis, dyspnea, dysphonia
- investigations: CXR, CT scan, arteriography (if penetrating)
- management
  - airway: manage early because of edema
  - C-spine may also be injured, consider mechanism of injury
  - surgical: tracheotomy vs. repair

trachea/bronchus
- frequently missed
- history: deceleration, penetration, increased intra-thoracic pressure; complaints of dyspnea, hemothysis
- examination: subcutaneous air, Hamman’s sign (crunching sound synchronous with heart beat)
- CXR: mediastinal air, persistent pneumothorax or persistent air leak after chest tube inserted for pneumothorax
- management: surgical repair if >1/3 circumference

Abdominal Trauma
- two mechanisms
  - blunt: usually causes solid organ injury (spleen = most common, liver = 2nd)
  - penetrating: usually causes hollow organ injury or liver injury (most common)

BLUNT TRAUMA
- results in two types of hemorrhage: intra-abdominal and retroperitoneal
- adopt high clinical suspicion of bleeding in multi-system trauma

History
- mechanism of injury, SAMPLE history

Physical Exam
- often unreliable in multi-system trauma, wide spectrum of presentations
  - slow blood loss not immediately apparent
  - other injuries may mask symptoms
  - serial examinations are required
- abdomen
  - inspect: contusions, abrasions, seatbelt sign, distention
  - auscultate: bruits, bowel sounds
  - palpate: tenderness, rebound tenderness, rigidity, guarding
  - DRE: rectal tone, blood, bone fragments, prostate location
  - placement of NG, Foley catheter should be considered part of the abdominal exam
- other systems to assess: cardiovascular, respiratory (possibility of diaphragm rupture), genitourinary, pelvis, back/neurological

Investigations
- labs: CBC, electrolytes, coagulation, cross and type, glucose, creatinine, CK, lipase, amylase, liver enzymes, ABG, blood EtOH, β-hCG, U/A, toxicology screen
- imaging: see Table 9

<table>
<thead>
<tr>
<th>Table 9. Imaging in Abdominal Trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging</td>
</tr>
<tr>
<td>X-Ray</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>CT scan</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Diagnostic Peritoneal Lavage (DPL)</td>
</tr>
<tr>
<td>(rarely used)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Ultrasound: FAST</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
imaging must be done if
- equivocal abdominal examination, suspected intra-abdominal injury or distracting injuries
- multiple trauma patient resulting in unreliable physical exam (altered sensorium, secondary to drugs, alcohol, head trauma, or distracting injury; spinal cord injury resulting in abdominal anesthesia)
- unexplained shock/hypotension
- multiple trauma patients who must undergo general anesthesia for orthopedic, neurosurgical, or other injuries
- fractures of lower ribs, pelvis, spine
- positive FAST

**Management**
- general: ABCs, fluid resuscitation and stabilization
- surgical: watchful waiting vs. laparotomy
- solid organ injuries: decision based on hemodynamic stability, not the specific injuries
- hemodynamically unstable or persistently high transfusion requirements: laparotomy
- hollow organ injuries: laparotomy
- even if low suspicion of injury: admit and observe for 24 h

**Penetrating Trauma**
- high risk of gastrointestinal perforation and sepsis
- history: size of blade, calibre/distance from gun, route of entry
- local wound exploration under direct vision may determine lack of peritoneal penetration (not reliable in inexperienced hands) with the following exceptions:
  - thoracoabdominal region (may cause pneumothorax)
  - back or flanks (muscles too thick)

**Management**
- general: ABCs, fluid resuscitation and stabilization
- gunshot wounds ➔ always require laparotomy

**Genitourinary Tract Injuries**

- see Urology, U32

**Etiology**
- blunt trauma: often associated with pelvic fractures
  - upper tract
    - renal
      - contusions (minor injury – parenchymal ecchymoses with intact renal capsule)
      - parenchymal tears/laceration: non-communicating (hematoma) vs. communicating (urine extravasation, hematuria)
    - ureter: rare, at uretero-pelvic junction
  - lower tract
    - bladder
      - extraperitoneal rupture of bladder from pelvic fracture fragments
      - intraperitoneal rupture of bladder from trauma and full bladder
    - urethra
      - posterior urethral injuries: MVCs, falls, pelvic fractures
      - anterior urethral injuries: blunt trauma to perineum, straddle injuries/direct strikes
  - external genitalia
  - penetrating trauma
    - damage to: kidney, bladder, ureter (rare), external genitalia
  - acceleration/deceleration injury
    - renal pedicle injury: high mortality rate (laceration and thrombosis of renal artery, renal vein, and their branches)
  - iatrogenic
    - ureter and urethra (from instrumentation)

**History**
- mechanism of injury
- hematuria (microscopic or gross), blood on underwear
- dysuria, urinary retention
- history of hypotension
Physical Examination
- abdominal pain, flank pain, costovertebral angle (CVA) tenderness, upper quadrant mass, perineal lacerations
- DRE: sphincter tone, position of prostate, presence of blood
- scrotum: ecchymoses, lacerations, testicular disruption, hematomas
- bimanual exam, speculum exam
- extraperitoneal bladder rupture: pelvic instability, suprapubic tenderness from mass of urine or extravasated blood
- intraperitoneal bladder rupture: acute abdomen
- urethral injury: perineal ecchymosis, scrotal hematoma, blood at penile meatus, high riding prostate, pelvic fractures

Investigations
- urethra: retrograde urethrography
- bladder: urinalysis, CT scan, urethrogram, ± retrograde cystoscopy, ± cystogram (distended bladder + post-void)
- ureter: retrograde ureterogram
- renal: CT scan (best, if hemodynamically stable), intravenous pyelogram (IVP)

Management
- urology consult
- renal
  - minor injuries: conservative management
    - bedrest, hydration, analgesia, antibiotics
  - major injuries: admit
    - conservative management with frequent reassessments, serial urinalysis, ± re-imaging
    - surgical repair (exploration, nephrectomy): e.g. hemodynamically unstable or continuing to bleed >48 h, major urine extravasation, renal pedicle injury, all penetrating wounds and major lacerations, infections, renal artery thrombosis
- ureter
  - uretero-uretostomy
- bladder
  - extraperitoneal
    - minor rupture: Foley drainage x 10-14 d
  - major rupture: surgical repair
  - intraperitoneal
    - drain abdomen and surgical repair
- urethra
  - anterior: conservative, if cannot void → Foley or suprapubic cystostomy and antibiotics
  - posterior: suprapubic cystostomy (avoid catheterization) ± surgical repair

Orthopedic Injuries
- see Orthopedics (Shoulder OR10, Knee, OR29 Wrist OR19, Ankle OR35)

Goals of ED Treatment
- diagnose potentially life/limb threatening injuries
- reduce and immobilize fractures (cast/splint) as appropriate
- provide adequate pain relief
- arrange proper follow-up if necessary

History
- use SAMPLE
- mechanism of injury may be very important

Physical Examination
- look (inspection): "SEADS" Swelling, Erythema, Atrophy, Deformity, Skin changes (e.g. bruises)
- feel (palpation): all joints/bones – local tenderness, swelling, warmth, crepitus, joint effusions, subtle deformity
- move: joints affected plus those above and below injury – active ROM preferred to passive
- neurovascular status: distal to injury (before and after reduction)
LIFE AND LIMB THREATENING INJURIES

Table 10. Life and Limb Threatening Orthopedic Injuries

<table>
<thead>
<tr>
<th>Life Threatening Injuries (usually blood loss)</th>
<th>Limb Threatening Injuries (usually interruption of blood supply)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major pelvic fractures</td>
<td>Fracture/dislocation of ankle (talar AVN)</td>
</tr>
<tr>
<td>Traumatic amputations</td>
<td>Crush injuries</td>
</tr>
<tr>
<td>Massive long bone injuries (beware of fat emboli)</td>
<td>Compartment syndrome</td>
</tr>
<tr>
<td>Vascular injury proximal to knee/elbow</td>
<td>Open fractures</td>
</tr>
<tr>
<td></td>
<td>Dislocations of knee/hip</td>
</tr>
<tr>
<td></td>
<td>Fractures above knee/elbow</td>
</tr>
</tbody>
</table>

Open Fractures
- communication between fracture site and external surface of skin – increased risk of osteomyelitis
- remove gross debris, irrigate, cover with sterile dressing – formal irrigation and debridement often done in the OR
- control bleeding with pressure (no clamping)
- splint
- antibiotics (1st generation cephalosporin and aminoglycoside) and tetanus prophylaxis
- must secure definitive surgical care within 6-8 h

Vascular Injuries
- realign limb/apply longitudinal traction and reassess pulses (e.g. Doppler probe)
- surgical consult
- direct pressure if external bleeding

Compartment Syndrome
- increased interstitial pressure in an anatomical “compartment” (forearm, calf) with little room for expansion, resulting in decreased perfusion and potential muscle/nerve necrosis
- clinical diagnosis: maintain a high index of suspicion
  - pain out of proportion to the injury
  - pain worse with passive stretch
  - look for “the 6 Ps” (see side bar)
- requires prompt decompression: remove constrictive casts, dressings; fasciotomy may be needed emergently

UPPER EXTREMITY INJURIES
- anterior shoulder dislocation
  - axillary nerve (lateral aspect of shoulder) and musculocutaneous nerve (extensor aspect of forearm) at risk
  - seen on lateral view: humeral head anterior to glenoid
    - reduce (traction, scapular manipulation), immobilize in internal rotation, repeat x-ray, out-patient follow-up with ortho
    - with forceful injury, look for fracture
  - Colles’ fracture (Figure 6)
    - distal radius fracture with dorsal displacement from Fall On an Outstretched Hand (FOOSH)
    - AP film: shortening, radial deviation, radial displacement
    - lateral film: dorsal displacement, volar angulation
    - reduce, immobilize with splint, out-patient follow-up with ortho or immediate orthopedic referral if complicated fracture
    - if involvement of articular surface, emergent orthopedic referral
  - scaphoid fracture (see Figure 7 for review of carpal bones)
    - tenderness in anatomical snuff box, pain on scaphoid tubercle, pain on axial loading of thumb
    - negative x-ray; thumb spica splint, re-x-ray in 1 wk ± bone scan
    - positive x-ray; thumb spica splint x 6-8 wk, re-x-ray in 2 wk
    - risk of AVN of scaphoid if not immobilized
    - outpatient ortho follow-up

LOWER EXTREMITY INJURIES
- ankle and foot fractures
  - see Ottawa Ankle and Foot Rules (Figure 8)
- knee injuries
  - see Ottawa Knee Rules (Figure 9)
• avulsion of the base of 5th metatarsal
  - occurs with inversion injury
  - supportive tensor or below knee walking cast for 3 wk
• calcaneal fracture
  - associated with fall from height
  - associated injuries may involve ankles, knees, hips, pelvis, lumbar spine

A knee x-ray examination is required only for acute injury patients with one or more of:
- Age 55 yrs or older
- Tenderness at head of fibula
- Isolated tenderness of patella
- Inability to flex to 90°
- Inability to bear weight both immediately and in the emergency department

Wound Management

Goals of ED Treatment
- identify injuries and stop any active bleeding – direct pressure
- manage pain
- wound examination and exploration (history and physical)
- cleansing ± antibiotic and tetanus prophylaxis
- closure and dressing

Tetanus Prophylaxis
- both tetanus toxoid (Td) and immunoglobulin (TIG) are safe in pregnancy

<table>
<thead>
<tr>
<th>Table 11. Guidelines for Tetanus Prophylaxis for Wounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunization History</td>
</tr>
<tr>
<td>Td²</td>
</tr>
<tr>
<td>Uncertain or &lt; 3 doses</td>
</tr>
<tr>
<td>3 or more, none for &gt;10 yr</td>
</tr>
<tr>
<td>3 or more, 5 to 10 yr ago</td>
</tr>
<tr>
<td>3 or more, &lt; 4 yr ago</td>
</tr>
</tbody>
</table>

¹ wounds >6 h old, >1 cm deep, puncture wounds, avulsions, wounds resulting from missiles, crush wounds, burns, frostbite, wounds contaminated with dirt, feces, soil, or saliva
² 0.5 mL IM tetanus and diphtheria toxoids (Td), adsorbed
³ tetanus immune globulin (TIG), 250 units deep IM

Source: MMWR 2001;50;418-427; MMWR 1991;40:1-52
Bruises

- non-palpable = ecchymosis
- palpable collection (not swelling) = hematoma following blunt trauma
- assess for coagulopathy (e.g. liver disease), anticoagulant use

Abrasions

- partial to full thickness break in skin
- management
  - clean thoroughly, ± local anesthetic, with brush to prevent foreign body impregnation
  - antiseptic ointment (Polysporin® or Vaseline®) for 7 d for facial and complex abrasions
  - tetanus prophylaxis (Table 11)

Lacerations

- see also Plastic Surgery, PL8
- consider every structure deep to a laceration injured until proven otherwise
- in hand injury patients, include the following in history: handedness, occupation, mechanism of injury, previous history of injury
- physical exam
  - think about underlying anatomy
  - examine tendon function actively against resistance and neurovascular status distally
  - clean and explore under local anesthetic; look for partial tendon injuries
  - x-ray or ultrasound wounds if a foreign body is suspected (e.g. shattered glass) and not found when exploring wound (remember: not all foreign bodies are radiopaque), or if suspect intra-articular involvement
- management
  - disinfect skin/use sterile techniques
  - irrigate copiously with normal saline
  - analgesia ± anesthesia
  - maximum dose of lidocaine:
    - 7 mg/kg with epinephrine
    - 5 mg/kg without epinephrine
  - in children, topical anesthetics such as LET (lidocaine, epinephrine and tetracaine) and in selected cases a short-acting benzodiazepine (midazolam or other agents) for sedation and amnesia are useful
  - secure hemostasis
  - evacuate hematomas, debride non-viable tissue, remove hair and foreign bodies
  - ± prophylactic antibiotics (consider for animal/human bites, intraoral lesion or puncture wounds to the foot)
  - take into account patient and wound factors when considering suturing
  - secure hemostasis
  - evacuate hematomas, debride non-viable tissue, remove hair and foreign bodies
  - ± prophylactic antibiotics (consider for animal/human bites, intraoral lesion or puncture wounds to the foot)
  - x-ray or ultrasound wounds if a foreign body is suspected (e.g. shattered glass) and not found when exploring wound (remember: not all foreign bodies are radiopaque), or if suspect intra-articular involvement
  - advise patient when to have sutures removed
  - cellulitis and necrotising fasciitis, see Plastic Surgery, PL14

Trauma in Pregnancy

- priorities: airway, breathing, circulation

Hemodynamic Considerations (changes that mimic shock)

- near term, inferior vena cava compression in the supine position can decrease cardiac output by 30-40% (see Maternal Physiology, Obstetrics, OB3)
  - use left lateral decubitus (LLD) positioning or hip bolster to alleviate compression and increase blood return if BP is low
- BP drops 5-15 mmHg systolic in 2nd trimester, increases to normal by term
- HR increases 15-20 beats per minute by 3rd trimester

Blood Considerations

- physiologic macrocytic anemia of pregnancy (Hb 100-120 g/L)
- WBC increases to a high of 20,000
- blood volume increase in pregnancy up to 45% (change can mask hypovolemic shock)

Shock

- pregnant patients may lose 35% of blood volume without typical signs of shock (i.e. tachycardia, hypotension)
- the fetus may be in “shock” due to contraction of the uteroplacental circulation
- fetal HR changes are an early warning of maternal circulatory compromise

Management Differences

- place bolster under right hip to stop inferior vena cava compression
- fetal monitoring (HR and fetal movements, continuous tocographic monitoring if viable fetus (>20 wk)
- early obstetrical consult
- do not avoid necessary imaging, but shield as much as possible
- consider need for RhoGAM® if mother Rh negative

High Risk Factors for Infection

- Puncture wounds
- Crush injuries
- Wounds greater than 12 h old
- Hand or foot wounds, wounds near joints
- Immune compromised patient
- Patient age greater than 50 yr
- Prosthetic joints or valves (risk of endocarditis)

Early wound irrigation and debridement are the most important factors in decreasing infection.

Since cellulitis can cause edema, remember to elevate the leg to decrease discomfort. Treat with antibiotics, analgesics and close follow-up.

The best treatment for the fetus is effective treatment of the mother.

- Primary survey: focus on mother
- Secondary survey: detailed assessment of mother + acquire info about fetus (Hx, fetal monitoring, etc.)
Approach to Common ER Presentations

Abdominal Pain

Rule Out Life-Threatening Causes
- CVS: MI, aortic dissection (tearing pain), ruptured AAA
- GI: perforated viscus, hepatic/splenic injury, ischemic bowel (diffuse pain)
- gynecologic: ectopic pregnancy

Additional Differential Diagnosis
- GI: appendicitis, diverticulitis, bowel obstruction, hepatitis, cholecystitis, pancreatitis
- urinary: pyelonephritis, ureteral calculi, cystitis
- gynecal:
  - female: tubo-ovarian abscess, ovarian torsion, ovarian cyst, salpingitis, pelvic inflammatory disease (PID), endometriosis
  - male: testicular torsion, epididymitis, prostatitis
- other: diabetic ketoacidosis (DKA), herpes zoster virus (HZV), intra-abdominal abscess, pneumonia, lead poisoning, porphyria, sickle cell crisis, psychiatric

History
- pain: OPQRST
- broad differential, including GU, gyn, GI, respiratory, and CV systems
- recent/remote abdominal trauma/surgeries

Physical Examination
- vitals, abdominal (including DRE, CVA tenderness), pelvic/genital, respiratory, and CVS as indicated by history

Investigations
- do not delay consultation if patient unstable
- CBC, electrolytes, glucose, BUN/creatinine, U/A, ± LFTs, lipase (if upper abdominal pain)
- ± others if indicated: β-hCG, ECG, troponins
- AXR: look for calcifications, free air, gas pattern, air fluid levels
- CXR upright: look for pneumoperitoneum (free air under diaphragm)
- U/S: biliary tract, ectopic pregnancy, AAA, free fluid
- CT: trauma, AAA, pancreatitis, nephro/uro lithiasis, appendicitis and diverticulitis

Management
- NPO, IV, NG tube, analgesics, consider antibiotics and anti-emetics
- growing evidence that small amounts of opioid analgesics improve diagnostic accuracy of physical exam of surgical abdomen
- consult as necessary: general surgery, vascular, gynecology, etc.

Disposition
- admission: surgical abdomen, workup of significant abnormal findings, need for IV antibiotics or pain control
- discharge: patients with a negative lab and imaging workup who improve clinically during their stay; instruct the patient to return if severe pain, fever, or persistent vomiting develop

Acute Pelvic Pain

Etiology
- gynecological
  - ovaries: ruptured ovarian cysts (most common cause of pelvic pain), ovarian abscess, ovarian torsion (rare, 50% will have ovarian mass)
  - fallopian tubes: salpingitis (STI), tubal abscess, hydrosalpinx
  - uterus: leiomyomas (uterine fibroids) – especially with torsion of a pedunculated fibroid or in pregnant patient (degeneration), PID, endometriosis
  - other: ectopic pregnancy (ruptured/expanding/leaking), spontaneous abortion (threatened or incomplete), dysmenorrhea and endometriosis
- non-gynecological
  - GI: appendicitis, constipation, bowel obstruction, gastroenteritis, diverticulitis, IBD, IBS
  - GU: cystitis, pyelonephritis, ureteric stone
  - other: porphyria, abdominal angina, aneurysm, hernia, zoster

Red Flags
- Unstable vital signs
- Fever
- Signs/symptoms of shock
- Rapid onset severe pain

Be vigilant in those at extremes of ages (very young, elderly) as they often present atypically!

Abdominal Assessment in all 4 Quadrants

If elevated AST and ALT: think hepatocellular injury
AST > ALT: alcohol – related
ALT > AST: viral, drug, toxin
If elevated ALP and GGT: “think biliary tree” stones

Old age, pregnancy (T3), and chronic corticosteroid use can blunt peritoneal findings, so have increased suspicion of intrabdominal process in these individuals!

Gynecological Causes of Pelvic Pain:
- Ovarian cyst
- Dysmenorrhea
- Mittelschmerz
- Endometriosis
- Ovarian torsion
- Uterine fibroids/neoplasm
- Adnexal neoplasm
- PID + cervicitis

Unstable patients should not be sent for imaging.

All women of childbearing age are assumed to be pregnant. Every pregnancy is potentially ectopic. A β-hCG must be obtained!
History and Physical Exam
- pain: OPQRST
- associated symptoms: vaginal bleeding, bowel or bladder symptoms, radiation
- vitals
- gynecological exam: assess for cervical motion tenderness = chandelier sign (suggests PID)
- abdominal exam

Investigations
- bloodwork
  - β-hCG for all women of childbearing age
  - CBC and differential, electrolytes, glucose, BUN/Cr, G&S, PTT/INR
- imaging
  - pelvic and abdominal U/S: evaluate adnexa, look for free fluid in the pelvis or masses, evaluate thickness of endometrium, confirm intrauterine pregnancy if β-hCG positive
  - doppler flow studies for ovarian torsion

Management
- general: analgesia, determine if admission and consults needed
  - gynecology consult if history and physical suggestive of serious cause
  - other consults as indicated
- specific:
  - ovarian cysts
    - unruptured or ruptured and hemodynamically stable: analgesia and follow-up
    - ruptured with significant hemoperitoneum: may require surgery
  - ovarian torsion: surgical detorsion or removal of ovary
  - uncomplicated leiomyomas, endometriosis and secondary dysmenorrhea can usually be treated on an outpatient basis, discharge with gynecology follow-up
  - PID: requires broad spectrum antibiotics

Disposition
- admission: patients requiring surgery, IV antibiotics/pain management
- discharge: negative workup and resolving symptoms; give clear instructions for appropriate follow-up

Altered Level of Consciousness (LOC)

Definitions
- altered mental status: collective, non-specific term referring to change in cognitive function, behaviour, or attentiveness, including:
  - delirium (see Psychiatry, PS19)
  - dementia (see Psychiatry, PS20)
  - lethargy: state of decreased awareness and alertness (patient may appear wakeful)
  - stupor: unresponsiveness but aroused
  - coma: a sleep-like state, not arousable to consciousness
- use the GCS to evaluate LOC (see Initial Patient Assessment/Management, ER2)

![Figure 10. Etiology of coma](Image)
MANAGEMENT OF ALTERED LOC

History
- obtain collateral from family, friends, police, paramedics, old chart, etc.
- onset and progression
  - abrupt onset suggests CNS hemorrhage/ischemia or cardiac cause
  - progression over hours to days suggests progressive CNS lesion or toxic/metabolic cause
- preceding events
  - it is essential to determine patient's baseline LOC preceding deterioration
  - antecedent trauma, seizure activity, fever
  - past medical history (e.g. similar episode, depression, overdose)

Physical Examination
- ABCs, vitals including temperature, cardiac, chest, respiratory, abdominal exam, and the "five Ns" (see sidebar)
- complete neuro exam, in particular examination of the eyes (pupil size and reactivity), look for MedicAlert® bracelet

Investigations
- bloodwork
  - rapid blood sugar, CBC, electrolytes, Cr, BUN, LFTs, glucose, serum osmolality, VBG, PT/PTT/INR, troponins
  - serum EtOH, acetaminophen and salicylate levels
- imaging
  - CT head
- other tests
  - ECG, U/A, UTox

Diagnosis
- administer appropriate universal antidotes
  - thiamine 100 mg IV if history of EtOH or patient looks malnourished
  - one ampule D50W IV if low blood sugar on finger-prick
  - naloxone 0.4-2 mg IV or IM if opiate overdose suspected
- distinguish between structural and toxic-metabolic coma
  - structural coma
    - pupils, extraocular movements and motor findings, if present, are usually asymmetric
    - look for focal or lateralizing abnormalities
  - toxic-metabolic coma
    - dysfunction at lower levels of the brainstem (e.g. caloric unresponsiveness)
    - respiratory depression in association with an intact upper brainstem (e.g. equal and reactive pupils; see exceptions in Table 12)
    - extraocular movements and motor findings are symmetric or absent
- essential to re-examine frequently – status can change rapidly
- diagnosis may become apparent only with the passage of time
  - delayed deficit after head trauma suggestive of epidural hematoma (characteristic "lucid interval")

Table 12. Toxic-Metabolic Causes of Fixed Pupils

<table>
<thead>
<tr>
<th>Dilated to Normal</th>
<th>Dilated</th>
<th>Constricted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axonina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticholinergic agents (e.g. atropine, TCAs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methanol (rare)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid withdrawal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothermia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbiturates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholinergic agents (e.g. organophosphates)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opiates (e.g. heroin), except meperidine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disposition
- admission: if ongoing decreased LOC; admit to service based on tentative diagnosis or transfer patient if appropriate level of care not available
- discharge: readily reversible alteration of LOC; ensure adequate follow-up care available

Chest Pain

Rule Out Life-Threatening Causes
- CVS: acute coronary syndrome, pericarditis, cardiac tamponade, aortic dissection
- respiratory: pulmonary embolism (PE), pneumothorax (tension or spontaneous)
- GI: esophageal rupture, pneumomediastinum
Additional Differential Diagnosis
- cardiac: stable angina
- respiratory: pneumonia
- GI: peptic ulcer disease (PUD), pancreatitis, cholecystitis, esophagitis, reflux, esophageal spasm
- MSK: rib fractures, costochondritis, zoster, etc.
- psychogenic/anxiety (diagnosis of exclusion)

Initial Resuscitation and Management
- O₂, IV, cardiac monitoring, CXR (portable if unstable), ECG

History
- must evaluate cardiac risk factors (see TIMI Score, Cardiology, C24)
- classic presentations (but presentation seldom classic)
  - aortic dissection: syncope with sudden severe tearing pain, often radiating to back, ± focal
    pain/neurologic loss in extremities secondary to major vessel ischemia
  - pulmonary embolism: pleuritic chest pain (75%), dyspnea, anxiety, tachycardia, PERC Score
  - pericarditis: anterior precordial pain, pleuritic, relieved by sitting up and leaning forward
  - acute coronary syndrome (ACS): retrosternal squeezing/pressure pain, radiation to arm/neck, dyspnea, nausea/vomiting, syncope
  - esophageal: frequent heartburn, acid reflux, dysphagia, relief with antacids
- ACS more likely to be atypical in females, diabetics, and >80 yr

Physical Examination
- vitals (BP in both arms, but unreliable indicator of dissection)
- palpate chest wall for tender points; present in 25% of acute MI, but may suggest MSK cause if
  symptoms fully reproduced and all serious etiologies have been ruled out
- cardiac exam, respiratory exam, peripheral vascular exam

Investigations
- bloodwork
  - CBC, electrolytes, BUN/Cr
  - CK-MB: if normal, does not rule out MI
  - troponin I: more sensitive (but positive later than CK-MB; can have false positives in renal
    failure, must follow for 8 h post onset of symptoms)
  - D-dimer: if negative, can rule out PE in low probability patients (see sidebar)
- ECG (see Table 13)
  - always compare with previous
- PE and acute MI may have normal ECG in up to 50% of cases
- consider 15-lead ECG if hypotensive or if ECG shows inferior MI or AV node involvement
- CXR
  - always compare with previous
- PE (see DVT, ER33)
  - 50% completely normal
  - atelectasis, elevated hemidiaphragm, pleural effusion
- aortic dissection (see sidebar ER12 for features)
  - change from previous CXR is the most accurate finding
  - widened mediastinum (most consistent finding)
  - CXR is normal in 20% of thoracic dissections
  - pneumothorax (PTX)
    - may need inspiration and expiration views
  - if large, may see tracheal shift (away from tension PTX, towards a non-tension PTX)
- V/Q scan or CT, venous leg Doppler, required to rule out PE in patients with intermediate or
  high probability (see sidebar for Wells’ Score, E34)

Disposition
- admission and monitoring: patients at risk of developing dysrhythmias
- consult: cardiology for patients with ACS; cardiothoracic surgery for patients with valvular
  lesions, esophageal rupture, or aortic dissection
- discharge: patients with a low probability of life-threatening illness due to resolving symptoms
  and negative workup; instruct the patient to return if they develop SOB or increased chest pain
**ACUTE MYOCARDIAL INFARCTION**

- see Cardiology, C24

**Management**

- immediate stabilization
  - oxygen 4 L/min
  - IV access
  - cardiac monitors
  - STAT ECG
  - cardiac enzymes (CK, troponins)
  - ASA 162-325 mg chewed
  - nitroglycerin 0.3 mg SL q5min x 3 (IV for CHF, HTN, unresolved pain)
  - morphine 2-3 mg IV q5-30min if unresponsive to nitroglycerin
  - low molecular weight heparin 1 mg/kg SC bid (30 mg IV STAT post TNK infusion)
  - thrombolytics (within 30 min) or primary percutaneous coronary intervention (PCI) (within 90 min)
  - agents include rt-PA, streptokinase, and TNK
  - evaluate indications and contraindications prior to use
  - other: antisydrhythms, cardioversion, defibrillation, transthoracic pacing, angioplasty
  - cardiology consult

**Epistaxis**

- see Otolaryngology, OT26
- 90% of nosebleeds stem from the anterior nasal septum (at Kesselbach's plexus located in Little's area)
- can be life-threatening

**Etiology**

- most commonly caused by trauma (digital, blunt, foreign bodies)
- other causes: barometric changes, nasal dryness, chemicals (cocaïne, Otrivin®), or systemic disease (coagulopathies, hypertension, etc.)

**Investigations**

- bloodwork: CBC, PT/PTT (as indicated)
- imaging: x-ray, CT as needed
**Treatment**
- aim is to localize bleeding and achieve hemostasis
- first-aid: ABCs, lean forward, pinch cartilaginous portion of nose for 20 min twice
- assess blood loss: vitals, IV normal saline, cross match 2 units packed RBC if significant
- determine site of bleeding: use topical anaesthetic/vasoconstrictor to facilitate; use nasal speculum and good lighting
- attempt to control the bleeding
  - first line: Otrivin® or cocaine
  - second line: cauterize with silver nitrate (one side of septum only because if both are cauterized this can lead to septal perforation!)
  - if these fail, or if bleeding is posterior → nasal packing (must monitor for complications)
  - if packing fails, consult ENT

**Disposition**
- discharge: discharged upon stabilization and appropriate follow-up; educate patients about prevention (e.g. humidifiers, saline spray, topical ointments, avoiding irritants, managing hypertension)
- admission: severe cases of refractory bleeding

### Headache

#### see also Neurology, N38

#### Etiology
- the common
  - common migraine (no aura)/classic migraine (involves aura)
    - gradual onset, unilateral/bilateral, throbbing
    - nausea/vomiting, photo/phonophobia
    - treatment: analgesics, neuroleptics, vasoactive meds
  - tension/muscular headache
    - never during sleep, gradual over 24 h
    - posterior/occipital
    - increased with stressors
    - treatment: modify stressor, local measures, NSAIDs, tricyclic antidepressants
- the deadly
  - subarachnoid hemorrhage (SAH) (see Neurosurgery, NS18)
    - sudden onset, increased with exertion
    - reaches maximum intensity within minutes, nausea and vomiting, meningeal signs
    - diagnosis: CT, LP (5-10% of patients with SAH have negative initial CT)
      - sensitivity of CT decreases with time and is much less sensitive by 48-72 h
    - management: urgent neurosurgery consult
  - increased ICP
    - worse in morning, when supine or bending down, with cough or Valsalva
    - physical exam: neurological deficits, cranial nerve palsies, papilledema
    - diagnosis: CT scan
    - management: consult neurosurgery
  - meningitis (see Infectious Diseases, ID19)
    - flu-like presentation initially (fever, nausea/vomiting, malaise), meningeal signs, purpuric rash
    - altered LOC and confusion
    - perform CT to rule out increased ICP then do LP for diagnosis
    - treatment: early empiric antibiotics (depending on age group), steroid therapy
  - temporal arteritis (causes great morbidity in terms of blindness) (see Ophthalmology, OP38)
    - unilateral scalp tenderness, jaw claudication, visual disturbances
    - labs: elevated ESR, CRP
    - temporal artery biopsy is gold standard for diagnosis
    - associated with polymyalgia rheumatica
    - treatment: high-dose steroids immediately if suspected

#### Disposition
- admission: if underlying diagnosis is critical or emergent, if there are abnormal neurological findings, if patient is elderly or immunocompromised (atypical presentation), or if pain is refractory to oral medications
- discharge: most patients can be discharged with appropriate analgesia and follow up with their family physician; instruct patients to return for fever, vomiting, neurologic changes, or increasing pain

---

**DDx Subarachnoid Hemorrhage**

**BATS**

- Berry aneurysm
- Arteriovenous malformation/Adult polycystic kidney disease
- Trauma
- Stroke

*Note: up to 5% of patients with subarachnoid hemorrhage have a normal CT scan; if suspect SAH with a negative CT, perform a LP.*

**Meningitis**

*Do not delay IV antibiotics for LP.*
Joint Pain

• see Rheumatology, RH3

Rule Out Life-Threatening Causes
• septic joint (see Orthopedics, OR10)

Differential Diagnosis
• articular pain
  ▪ monoarticular
    • infectious: bacterial, viral, fungal
    • hemarthrosis: trauma/fracture, anticoagulants, bleeding diatheses
    • crystal induced: gout, calcium pyrophosphate deposition, hydroxyapatite
    • inflammatory: seropositive, seronegative
    • neoplasm
    • degenerative: osteoarthritis
  ▪ polyarticular
    • infectious: Lyme disease, bacterial endocarditis, septicemia, gonococcus, viral
    • post-infectious: rheumatic fever, reactive arthritis, enteric infections
    • inflammatory: seropositive, seronegative
    • degenerative: osteoarthritis
• non-articular
  ▪ musculoskeletal
    • localized: tendonitis, bursitis, capsulitis, muscle sprain
    • generalized: fibromyalgia, polymyalgia rheumatica
• other
  ▪ neurologic: spinal stenosis/spondylolysis, degenerative disc disease, cauda equina syndrome, neoplasm, thoracic outlet syndrome, Charcot joint
  ▪ vascular: intermittent claudication

History and Physical Examination
• associated symptoms: fever, constitutional symptoms, skin lesions, conjunctivitis, urethritis
• patterns of joint involvement: polyarticular vs. monoarticular, symmetric vs. asymmetric
• inflammatory symptoms: prolonged morning stiffness, stiffness and pain ease through the day, midday fatigue, soft tissue swelling
• non-inflammatory symptoms: stiffness short lived after inactivity, short duration stiffness in the morning, pain increases with activity
• assess ROM, presence of joint effusion, warmth
• watch for: localized joint pain, erythema, warmth, swelling with pain on active ROM, inability to bear weight, fever as these may indicate presence of septic joint

Investigations
• bloodwork
  ▪ CBC, ESR, CRP, WBC, INR/PTT, blood cultures, urate
• imaging
  ▪ joint x-ray ± contralateral joint for comparison
• other investigations
  ▪ joint aspirate → send for: WBC, protein, glucose, Gram stain, crystals

Management
• septic joint: IV antibiotics ± joint decompression and drainage
• antibiotics can be started empirically if septic arthritis cannot be ruled out
• crystalline synovitis: NSAIDs at high dose, colchicine within first 24 h, corticosteroids
• do not use allopurinol, as it may worsen acute attack
• acute polyarthritis: NSAIDs, analgesics (acetaminophen ± opioids), local or systemic corticosteroids
• osteoarthritis: NSAIDs, acetaminophen
• soft tissue pain: allow healing with enforced rest ± immobilization
  ▪ nonpharmacologic treatment: local heat or cold, electrical stimulation, massage
  ▪ pharmacologic: oral analgesics, NSAIDs, muscle relaxants, corticosteroid injections, topical agents

Otalgia

Differential Diagnosis (see also Otolaryngology, OT6)
• local
  ▪ infections: acute otitis externa, acute otitis media, otitis media with effusion, mastoiditis, myringitis, malignant otitis in diabetics, herpes simplex/zoster, auricular cellulitis, external canal abscess
  ▪ others: trauma, neoplasm, foreign body, cerumen impactions, granulomatosis with polyangitis
**History**
- OPQRST
  - associated symptoms: aural fullness (feeling of pressure), otorrhea, hearing loss, tinnitus, vertigo, pruritis, fever
  - risk factors: Q-tip use, hearing aids, headphones

**Physical Exam**
- observe for otorrhea, palpation of outer ear/mastoid, otoscope to see bulging erythematous TM, perforation

**Investigations**
- consider audiogram if hearing loss
- CT head if suspicion of mastoiditis, malignant OM

**Management**
- debridement and antibiotics for cerumen and infection

---

### Seizures

- see Neurology, N14

**Definition**
- paroxysmal alteration of behaviour and/or EEG changes resulting from abnormal, excessive activity of neurons

**Categories**
- generalized seizure (consciousness always lost): tonic/clonic, absence, myoclonic, atonic
- partial seizure (focal): simple partial, complex partial
- causes: primary seizure disorder, structural (trauma, intracranial hemorrhage, infection, increased ICP), metabolic disturbance (hypo/hyperglycemia, hypo/hypernatremia, hypocalcemia, hypomagnesemia, toxins/drugs)
- differential diagnosis: syncope, pseudoseizures, migraines, movement disorder, narcolepsy/cataplexy, myoclonus

**History**
- from patient and bystander: flaccid and unconscious, often with deep rapid breathing
- preceding aura, rapid onset, loss of bladder/bowel control, tongue-biting (sides of the tongue)
- timing: length of seizure

**Physical Examination**
- injuries to head and spine and bony prominences (e.g. elbows), tongue laceration, aspiration, urinary incontinence

**Investigations**
- known seizure disorder: anticonvulsant levels
- Accu-Chek®
  - first time seizure: CBC, serum glucose, electrolytes, BUN/Cr, Ca^{2+}, Mg^{2+}; consider prolactin, β-hCG, toxicology screen
  - initial imaging: CT; x-ray if suspected extremity injuries. Definitive imaging: MRI, EEG

---

### Table 14. Management of Status Epilepticus

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Steps</th>
</tr>
</thead>
</table>
| 0-5        | Give oxygen; ensure adequate ventilation  
Monitor: vital signs, electrocardiography, oximetry  
Establish IV access; obtain blood samples for glucose level, CBC, electrolytes, toxins, and anticonvulsant levels |
| 6-9        | Give 50 mL 50% glucose (preceded by thiamine 100 mg IM in adults) |
| 10-20      | IV lorazepam 0.1 mg/kg at 2 mg/min or IV diazepam 0.2 mg/kg at 5 mg/min  
Diazepam can be repeated if seizures do not stop after 5 min; if diazepam is used to stop the status, then phenytoin should be administered promptly to prevent the recurrence of status |
| 21-60      | If status persists, administer 15-20 mg/kg of phenytoin intravenously no faster than 50 mg/min in adults and 1 mg/kg/min in children |
| >60        | If status does not stop after 20 mg/kg of phenytoin, give additional doses of 5 mg/kg to a maximal dose of 30 mg/kg  
If status persists, then give 20 mg/kg of phenobarbital IV at 100 mg/min. When phenobarbital is given after a benzodiazepine, ventilatory assistance is usually required  
If status persists, then give general anaesthesia (e.g. pentobarbital). Vaspressors or fluid volume are usually necessary. Electroencephalogram should be monitored. Neuromuscular blockade may be needed |

Adapted from: Cecil’s Essentials of Medicine, 7th edition, Table 125-7. Used with permission

---

Minimum Workup in an Adult with 1st Time Seizure
- CBC and differential  
- Electrolytes including Ca^{2+}, Mg^{2+}, P04^{3-}  
- Head CT

If administering phenytoin, patient must be on a cardiac monitor as dysrhythmias and/or hypotension may occur.
Disposition
- the decision to admit or discharge should be based on the underlying disease process identified
  - if a patient has returned to baseline function and is neurologically intact, then consider discharge with outpatient follow-up
  - first-time seizure patients being discharged should be referred to a neurologist for follow-up
  - admitted patients should generally have a neurology consult
  - patient should not drive until medically cleared (local regulations vary)
    - complete notification form to appropriate authority re: ability to drive
  - warn regarding other safety concerns (e.g. no swimming, bathing children alone, etc.)

Shortness of Breath
- see Respiratory, R3 and Cardiology, C5

Etiology
- categorized into one of two groups: respiratory or cardiovascular
  - respiratory system dyspnea: discomfort related to disorders of the central controller (brain), the ventilatory pump (ventilatory muscles, peripheral nerves), and the gas exchanger (alveoli and pulmonary capillaries)
  - cardiovascular system dyspnea: cardiac diseases (acute ischemia, heart failure, systolic dysfunction, valvular disorders, pericardial diseases, arrhythmias), anemia, and deconditioning

History/Physical
- acute SOB is often due to a relatively limited number of conditions. Associated symptoms and signs are key to the appropriate diagnosis
  - substernal chest pain with cardiac ischemia
  - fever, cough and sputum with respiratory infections
  - urticaria with anaphylaxis
  - wheezing with acute bronchospasm
  - dyspnea may be the sole complaint and the physical examination may reveal few abnormalities (e.g. pulmonary embolism, pneumothorax)
  - chest tightness may be indicative of bronchospasm
  - a sensation of rapid, shallow breathing may correspond to interstitial disease
  - a sense of heavy breathing is typical of deconditioning
  - vitals including pulse oximetry
    - wheeze (airway) vs. crackles (parenchymal), JVP, and murmurs

Investigations
- bloodwork
  - CBC and differential (hematocrit to exclude anemia), electrolytes, consider VBG
  - serial cardiac enzymes and ECG if considering cardiac source
- imaging
  - CXR (hyperinflation and bullous disease suggestive of obstructive lung disease, or changes in interstitial markings consistent with inflammation, infection or interstitial fluid)
  - CT chest usually is not indicated in the initial evaluation of patients with dyspnea, but can be valuable in patients with interstitial lung disease, occult emphysema, or chronic thromboembolic disease (PE)

Disposition
- the history and physical examination lead to accurate diagnoses in patients with dyspnea in approximately two-thirds of cases; the decision to admit or discharge should be based on the underlying disease process identified
  - consider intubation in CO₂ retainers (e.g. COPD)
  - if the decision to discharge is chosen, provide appropriate discharge instructions to return in case of returning/worsening SOB

Syncope

Definition
- sudden, transient loss of consciousness and postural tone with spontaneous recovery
- usually caused by generalized cerebral or reticular activating system hypoperfusion

Etiology
- cardiogenic: dysrhythmia, outflow obstruction (e.g. PE, tamponade, tension pneumothorax, pulmonary HTN), MI, valvular disease
- non-cardiogenic: peripheral vascular (hypovolemia), vasovagal, cerebrovascular disorders, CNS, metabolic disturbances (e.g. EtOH intoxication)
History
• gather details from witnesses, and clarify patient's experience (e.g. dizziness, ataxia, or true syncope)
• two key historical features 1. Prodrome 2. Situation
• distinguish between syncope and seizure (see Neurology, N15)
  ▪ some patients may have myoclonic jerks with syncope – NOT a seizure
  ▪ signs and symptoms during presyncope, syncope and postsyncope
  ▪ past medical history, drugs
  ▪ think anatomically in differential; pump (heart), blood, vessels, brain
• syncope is cardiogenic until proven otherwise if:
  ▪ there is sudden loss of consciousness with no warning or prodrome OR
  ▪ syncope is accompanied by chest pain

Physical Examination
• postural BP and HR
• cardiovascular, respiratory and neuro exam
• physical findings in the elderly patient who falls (I HATE FALLING):
  ▪ Inflammation of joints (or joint deformity)
  ▪ Hypotension (orthostatic blood pressure changes)
  ▪ Auditory and visual abnormalities
  ▪ Tremor (Parkinson's disease or other causes of tremor)
  ▪ Equilibrium (balance) problem
  ▪ Foot problems
  ▪ Arrhythmia (dysrhythmia), heart block or valvular disease
  ▪ Leg-length discrepancy
  ▪ Lack of conditioning (generalized weakness)
  ▪ Illness
  ▪ Nutrition (poor; weight loss)
  ▪ Gait disturbance

Investigations
• ECG (tachycardia, bradycardia, blocks, Wolff-Parkinson White, long QT interval), bedside glucose
• bloodwork: CBC, electrolytes, BUN, creatinine, ABGs, troponin, Ca²⁺, Mg²⁺, β-hCG
• consider toxicology screen

Management
• ABCs, IV, O₂, monitor
• examine for signs of trauma caused by syncopal episode
• cardiogenic syncope: admit to medicine/cardiology
• low risk syncope: discharge with follow-up as indicated by cause (non-cardiogenic syncope may still be admitted)

Disposition
• decision to admit is based on etiology
• most patients will be discharged
• on discharge, instruct patient to follow up with family physician
  ▪ educate re: avoiding orthostatic or situational syncope
  ▪ patients with recurrent syncope should avoid high-risk activities (e.g. driving)

Sexual Assault
• legally required to report sexual assault if victim is <16 yr of age to Children's Aid Society (CAS)

Epidemiology
• 1 in 4 women and 1 in 10 men will be sexually assaulted in their lifetime
• it is estimated that only 7% of rapes are reported

General Approach
• ABCs, treat acute, serious injuries
• ensure patient is not left alone and provide ongoing emotional support
• set aside adequate time for exam (usually 1.5 h)
• obtain consent for medical exam and treatment, collection of evidence, disclosure to police (notify police as soon as consent obtained)
• Sexual Assault Kit (document injuries, collect evidence) if <72 h since assault
• label samples immediately and pass directly to police
• offer community crisis resources (e.g. shelter, hotline)
• do not report unless victim requests (legally required if <16 yr old)
History

- Ensure privacy for the patient – others should be asked to leave
- Questions to ask: who? when? where did penetration occur? what happened? any weapons or physical assault?
- Post-assault activities (urination, defecation, change of clothes, shower, douche, etc.)
- Gynecologic history
  - Gravity, parity, last menstrual period
  - Contraception use
  - Last voluntary intercourse (sperm motile 6-12 h in vagina, 5 d in cervix)
- Medical history: acute injury/illness, chronic diseases, psychiatric history, medications, allergies, etc.

Physical Examination

- Evidence collection is always secondary to treatment of serious injuries
- Never re-traumatize a patient with the examination
- General examination
  - Mental status
  - Sexual maturity
  - Patient should remove clothes and place in paper bag
  - Document abrasions, bruises, lacerations, torn frenulum/broken teeth (indicates oral penetration)
- Pelvic exam and specimen collection
  - Ideally before urination or defecation
  - Examine for seminal stains, hymen, signs of trauma
  - Collect moistened swabs of dried seminal stains
  - Pubic hair combings and cuttings
  - Speculum exam
    - Lubricate with water only
    - Vaginal lacerations, foreign bodies
    - Pap smear
    - Oral/cervical/rectal culture for gonorrhea and chlamydia
    - Posterior fornix secretions if present or aspiration of saline irrigation
    - Immediate wet smear for motile sperm
    - Air-dried slides for immotile sperm, acid phosphatase, ABO group
  - Others
    - Fingernail scrapings
    - Saliva sample from victim

Investigations

- VDRL: repeat in 3 mo if negative
- Serum β-hCG
- Blood for ABO group, Rh type, baseline serology (e.g. hepatitis, HIV)

Management

- Involve local/regional sexual assault team
- Medical
  - Suture lacerations
  - Tetanus prophylaxis
  - Gynecology consult for foreign body, complex lacerations
  - Assumed positive for gonorrhea and chlamydia
    - Management: azithromycin 1 g PO x 1 dose (alt: doxycycline 100 mg PO bid x 7 d) and cefixime 800 mg PO x 1 dose
  - May start prophylaxis for hepatitis B and HIV
  - Pre and post counselling for HIV testing
  - Pregnancy prophylaxis offered
    - Levonorgestrel 0.75 mg PO STAT, repeat within 12 h (Plan B+)
  - Psychological
    - High incidence of psychological sequelae
    - Have victim change and shower after exam completed

Disposition

- Discharge if injuries/social situation permit
- Follow-up with MD in rape crisis centre within 24 h
- Best if patient does not leave ED alone

Domestic Violence

- Women are usually the victims, but male victimization also occurs
- Identify the problem (need high index of suspicion)
  - Suggestive injuries (bruises, sprains, abrasions, occasionally fractures, burns or other injuries; often do not match up with history provided)
  - Somatic symptoms (chronic and vague complaints)
  - Psychosocial symptoms
  - Clinician impression (your ‘gut feeling’, e.g. overbearing partner that won’t leave patient’s side)

Risk of Sexually Transmitted Disease After Sexual Assault

- Gonorrhea: 6-18%
- Chlamydia: 4-17%
- Syphilis: 0.5-3%
- HIV: <1%

How do you get a patient who is accompanied by her partner alone without arousing suspicion? Order an x-ray.
• if disclosed, be supportive and assess danger
• if necessary, order an x-ray to get patient alone to question
• patient must consent to follow-up investigation/reporting (unless for children)

Management
• treat injuries
• ask about sexual assault and children at home (encourage notification of police)
• document findings
• safety plan
• follow-up: family doctor/social worker

Medical Emergencies

Anaphylaxis and Allergic Reactions

Etiology
• anaphylaxis is an exaggerated immune mediated hypersensitivity reaction that leads to systemic histamine release, increased vascular permeability, and vasodilation. Regardless of the etiology, the presentation and the management of anaphylactic reactions are the same
  ▪ allergic (re-exposure to allergen)
  ▪ non-allergic (e.g. exercise induced)

Presentation
• classic presentation of anaphylaxis includes:
  1. rapid onset and progression of symptoms
  2. life threatening compromise of one or more of airway (breathing/swallowing difficulty, stridor, voice change), breathing (shortness of breath, hypoxemia, wheezing, respiratory arrest), and circulation (tachycardia, hypotension, confusion, decreased urine output, chest pain)
  3. involvement of skin (erythema, urticaria, warmness) and/or mucosa (angioedema, obstruction, GI symptoms). Not always present
• most common allergens causing anaphylaxis are food (nuts, seafood), stings, and drugs (antibiotics, anesthetics)
• the presentation of anaphylaxis is diverse and there is no one specific symptom or sign for it
  ▪ combinations of symptoms and signs will make anaphylaxis more likely
• life threatening differentials for anaphylaxis include asthma and septic shock

Management
1. immediate initial management (call for help and perform concurrently)
   ▪ give 0.5 mL of 1:1000 epinephrine IM to lateral thigh. (0.01 mL/kg up to 0.4 mL for children)
   ▪ remove causative agent if possible
   ▪ if severely compromised ABC or LOC, consult ICU immediately
   ▪ otherwise, provide 100% Oxygen through mask, give bolus 1000 mL (20 mL/kg for children)
   ▪ crystalloid IV then reassess. If IV access difficult give fluid through intraosseous route
   ▪ have continuous pulse oximetry and telemetry monitoring
   ▪ frequently monitor blood pressure
2. secondary treatment
   ▪ diphenhydramine (Benadryl®) 50 mg IM or IV q4-6h
   ▪ methylprednisolone 50-100 mg IV (dose depending on severity)
   ▪ salbutamol (Ventolin®) via nebulizer if bronchospasm

Disposition
• monitor for 4-6 h in ED (minimum) and arrange follow up with family physician in 24-48 h
• can have second phase (biphasic) reaction up to 48 h later, patient may need to be supervised (oral steroids on discharge may prevent this)
• educate patient on avoidance of allergens
• 3-day course of:
  ▪ H1 antagonist (cetirizine 10 mg PO OD or Benadryl® 50 mg PO q4-6h)
  ▪ H2 antagonist (ranitidine 150 mg PO OD)
  ▪ corticosteroid (prednisone 50 mg PO OD) generally given for 5 d

Asthma
• see Respirology, R6
• chronic inflammatory airway disease with episodes of bronchospasm and inflammation resulting in reversible airflow obstruction
Investigations
- O₂ saturation
- peak flow meter
- ± ABG if in severe respiratory distress
- CXR if diagnosis in doubt or concerns of pneumonia, pneumothorax, etc.

Table 15. Asthma Assessment and Management

<table>
<thead>
<tr>
<th>Classifications</th>
<th>History and Physical Examination</th>
<th>Management</th>
</tr>
</thead>
</table>
| Respiratory Arrest  | • Exhausted, confused, diaphoretic, cyanotic  
| Imminent            | • Silent chest, ineffective respiratory effort  
|                     | • Decreased HR, RR > 30, pCO₂ > 45 mmHg  
|                     | • O₂ sat < 90% despite supplemental O₂  
|                     | • 100% O₂, cardiac monitor, IV access  
|                     | • Intubate (consider induction with ketamine)  
|                     | • β-agonist: nebulizer 5 mg continually  
|                     | • Anticholinergics: nebulizer 0.5 mg x 3  
|                     | • IV steroids: methylprednisolone 125 mg  
| Severe Asthma       | • Agitated, diaphoretic, laboured respirations  
|                     | • Speaking in words  
|                     | • No relief from β-agonist  
|                     | • O₂ sat < 90%, FEV₁ < 50%  
|                     | • Anticipate need for intubation  
|                     | • Similar to above management  
|                     | • Magnesium sulphate 2 g IV  
|                     | • O₂ to achieve O₂-sat > 92%  
| Moderate Asthma     | • SOB at rest, cough, congestion, chest tightness  
|                     | • Speaking in phrases  
|                     | • Inadequate relief from β-agonist  
|                     | • FEV₁ 50-80%  
|                     | • β-agonist: MDI or nebs q5min  
|                     | • Steroids: prednisone 40-60 mg PO  
|                     | • Anticholinergics (Atrovent) MDI or nebs x3  
| Mild Asthma         | • Exertional SOB/cough with some nocturnal symptoms  
|                     | • Difficulty finishing sentences  
|                     | • FEV₁ > 80%  
|                     | • β-agonist  
|                     | • Monitor FEV₁  
|                     | • Consider steroids (MDI or PO)  

Disposition
- β-agonist MDI regular use (2-4 puffs q2-4h) until symptoms controlled then prn
- prednisone 30-60 mg/d for 7-14 d with no taper
- inhaled corticosteroids
- follow-up with primary care physician

Cardiac Dysrhythmias

Bradydysrhythmias and AV Conduction Blocks
- AV conduction blocks
  - 1st degree: prolonged PR interval (>200 msec), no treatment required
  - 2nd degree
    - Mobitz I: gradual prolongation of PR interval then dropped QRS complex, usually benign
    - Mobitz II: PR interval constant with dropped QRS complex, can progress to 3rd degree AV block
  - 3rd degree: P wave unrelated to QRS complex, PP and RR intervals constant
    - atropine and transcutaneous pacemaker (TCP) (atropine with caution)
    - if TCP fails consider dopamine, epinephrine IV
  - long term treatment for Mobitz II and 3rd degree block – internal pacemaker
- sinus bradycardia (rate < 60 bpm)
  - can be normal (especially in athletes)
  - can be caused by vagal stimulation, vomiting, myocardial infarction/ischemia, increased ICP, sick sinus node, hypothyroidism, drugs (e.g. β-blockers, CCBs)
  - treat if symptomatic (hypotension, chest pain)
    - acute: atropine ± transcutaneous pacing
    - sick sinus: transcutaneous pacing
    - drug induced: discontinue/reduce offending drug

Supraventricular Tachydysrhythmias (narrow QRS)
- sinus tachycardia (rate > 100 bpm)
  - causes: increased sympathetic tone, drugs, fever, hypotension, anemia, thyrotoxicosis, MI, PE, emotional, pain, etc.
  - search for and treat underlying cause, consider β-blocker if symptomatic
- regular rhythm
  - vagal maneuvers (carotid massage, Valsalva), adenosine 6 mg IV push, if no conversion give 12 mg, can repeat 12 mg dose once
  - rhythm converts: probable re-entry tachycardia (AVNRT more common than AVRT)
    - monitor for recurrence
    - treat recurrence with adenosine or longer acting medications

5 Essential Elements on History
- Cause of exacerbation
- Previous ER/ICU visits
- Previous intubations
- Timing of recent steroid use
- Frequency of asthma medication use

Treatment of Asthma
- ASTHMA
  - Adrenergics (β-agonists)
  - Steroids
  - Hydration
  - Mask (O₂)
- Antibiotics (if concurrent bacterial pneumonia)

Clinical Features of Instability
- Hypotension (sBP < 90)
- CHF or pulmonary edema
- Chest pain
- Altered LOC (may indicate shock)
Atrial Fibrillation (AFib)
- most common sustained dysrhythmia; no organized P waves (atrial rate >300/min), irregularly irregular heart rate, narrow QRS (typically)
- etiology: HTN, CAD, thyrotoxicosis, EtOH (holiday heart), valvular disease, pericarditis, cardiomyopathy, sick sinus syndrome
- treatment principles: stroke prevention, treat symptoms, identify/treat underlying cause
- decreases cardiac output by 20-30% (due to loss of organized atrial contractions)
- acute management
  - if unstable: immediate synchronized cardioversion
  - if onset of AFib is >48 h: rate control, anticoagulate 3 wk prior to and 4 wk after cardioversion or do transesophageal echo to rule out clot
  - if onset <48 h: may cardiovert
    - electrical cardioversion: synchronized direct current (DC) cardioversion
    - chemical cardioversion: procainamide, flecainide, propafenone
- long term management: rate or rhythm control, consider anticoagulation (CHADS2 score, see sidebar)

Ventricular Tachydysrhythmias (wide QRS)
- ventricular tachycardia (VT) (rate usually 140-200 bpm)
  - definition: 3 or more consecutive ventricular beats at >100 bpm
  - etiology: CAD with MI is most common cause
  - treatment: sustained VT (>30 s) is an emergency
    - hemodynamic compromise: synchronized DC cardioversion
    - no hemodynamic compromise: synchronized DC cardioversion, lidocaine, amiodarone, procainamide
- ventricular fibrillation: call a code blue, follow ACLS for pulseless arrest
- torsades de pointes
  - looks like VT but QRS 'rotates around baseline' with changing axis and amplitude (twisted ribbon)
  - etiology: prolonged QT due to drugs (e.g. quinidine, TCAs, erythromycin, quinolones), electrolyte imbalance (hypokalemia, hypomagnesemia), congenital
  - treatment:
    - IV MgSO4, temporary overdrive pacing, isoproterenol
    - correct cause of prolonged QT

Chronic Obstructive Pulmonary Disease (COPD)
- see Respirology, R8
- progressive development of irreversible airway obstruction, typically caused by smoking
- acute exacerbation: episode of increased dyspnea, coughing, increase in sputum volume or purulence

History and Physical Examination
- worsening dyspnea or tachypnea
- acute change in frequency, quantity and colour of sputum production
- triggers: pneumonia, urinary tract infection, PE, CHF, MI, drugs

Investigations
- CBC, electrolytes, ABG, CXR, ECG, PFTs

Management
- keep O2 sat 88-92% (beware of CO2 retainers, but do not withhold O2 if hypoxic)
- apply BiPAP if severe distress, arterial pH <7.35 or hypercapnic
- ipratropium is bronchodilator of choice, add salbutamol
- steroids: prednisone 40 mg PO (tapered over 3 wk)
- antibiotics: TMP-SMX, cephalosporins, respiratory quinolones (if signs of infection)
- ICU admission, if life-threatening, for ventilation (chance of ventilation dependency)
- lower threshold to admit if co-morbid illness

Disposition
- can use up to 4-6 puffs qid of ipratropium and salbutamol for exacerbations
- continue antibiotics if started and give tapering steroids
Congestive Heart Failure

• also see Cardiology, C30

Etiology
• decreased myocardial contractility: ischemia, infarction, cardiomyopathy, myocarditis
• pressure overload states: hypertension, valve abnormalities, congenital heart disease
• restricted cardiac output: myocardial infiltrative disease, cardiac tamponade
• volume overload

Causes of Exacerbation or Precipitants
• please refer to the FAILURE mnemonic on the side bar

Presentation
• left-sided heart failure
  ▪ dyspnea, decreased exercise tolerance, paroxysmal nocturnal dyspnea, orthopnea, nocturia, fatigue, possibly altered mental status, syncope, angina, systemic hypotension
  ▪ hypoxia, decreased air entry to lungs, rales, S3 or S4, pulmonary edema (on CXR), pleural effusion (usually right sided)
• right-sided heart failure
  ▪ dependent bilateral pitting edema, JVP elevation, hepatic enlargement, ascites
• patients often present with a combination of right-sided and left-sided symptoms

Investigations
• labs: CBC, electrolytes, AST, ALT, bilirubin, creatinine, BUN, cardiac enzymes, BNP (brain natriuretic peptide)
• chest x-ray (see sidebar)
• ECG: look for MI, ischemia (ST elevation/depression, T-wave inversion)
  ▪ in CHF: LVH, atrial enlargement, conduction abnormalities
• ABG: if severe or refractory to treatment
  ▪ hypoxemia, hypercapnia and acidosis are signs of severe CHF
• echocardiogram: not usually used in emergency evaluation, previous results may aid in diagnosis
• may be precipitated by dysrhythmia (e.g. sudden onset AFib) – correct if new
• rule out serious differentials such as PE, pneumothorax, pneumonia/empyema, COPD exacerbation

Management (acute)
• ABC, may require intubation if severe hypoxia
• sit upright, cardiac monitoring and continuous pulse oximetry
• saline lock IV, Foley catheter (to follow effectiveness of diuresis)
• 100% O₂ by mask
  ▪ if poor response may require BiPAP or intubation
• drugs
  ▪ nitroglycerin 0.3 mg SL q5min prn ± topical nitro patch (0.2-0.8 mg/h)
  ▪ if not responding or ischemia: 10-200 µg/min IV, titrate
  ▪ diuretic if volume overloaded (e.g. furosemide 40-80 mg IV), use caution if cause is valvulopathy
  ▪ morphine 1-2 mg IV prn
  ▪ if hypotensive: dobutamine (2.5 µg/kg/min IV) or dopamine (5-10 µg/kg/min IV), titrate up to sBP 90-100 mmHg
  ▪ ASA 160 mg chew and swallow
• treat precipitating factor (See side bars for common precipitants)
• cardiology or medicine consult

DVT and Pulmonary Embolism

• see also Respirology, R17

Risk Factors
• Virchow’s triad
  ▪ alterations in blood flow (venous stasis)
  ▪ injury to endothelium
  ▪ hypercoagulable state (including pregnancy, use of OCP, malignancy)
• clinical risk factors
Presentation

- DVT: calf pain, leg swelling/erythema/edema, palpable cord on exam; can be asymptomatic
- PE: dyspnea, pleuritic chest pain, hemoptyis, tachypnea, cyanosis, hypoxia, fever
- clinical signs/symptoms are unreliable for diagnosis and exclusion of DVT/PE; investigation often needed (see Figures 11 and 12)
- calculate the PERC (PE rule out criteria) score to assess the need for PE work-up before assessing the likelihood of a PE (Wells criteria)

Investigations (see Figures 11, 12 and 13)

- ECG and CXR are useful to look for other causes (e.g. ACS, pneumonia)
- D-dimer is only useful if it is negative in low risk patients (highly sensitive)
- ultrasound has high sensitivity and specificity for proximal clot but only 73% sensitivity for DVT below the knee (may need to repeat in 1 wk)
- CT angiography has high sensitivity and specificity for PE, may also suggest other etiology
- V/Q scan useful when CT angio not available, or patient unable to tolerate IV contrast (e.g. renal failure, allergy)

Management of DVT/PE

- LMWH unless patient also has renal failure
  - dalteparin 200 IU/kg SC q24h or enoxaparin 1.5 mg/kg SC q24h
  - warfarin started at same time as LMWH (5 mg PO OD initially)
- LMWH discontinued when INR has been therapeutic (2-3) for 2 consecutive days
  - early ambulation with analgesia is safe if appropriately anticoagulated
  - IVC filter or surgical thrombectomy considered if anticoagulation is contraindicated
  - consider thrombolyis if extensive DVT or PE causing hemodynamic compromise
  - often can be treated as outpatient, may require analgesia for chest pain (narcotic or NSAID)
  - admit if hemodynamically unstable, require supplemental O₂, major comorbidities, lack of sufficient social supports, unable to ambulate, need invasive therapy
  - consider referral to medicine for coagulopathy and malignancy work-up
  - long term anticoagulation
    - if reversible risk factor: 3-6 mo of warfarin
    - idiopathic VTE: may need longer term warfarin (5 yr or more)

Figure 11. Approach to Suspected DVT

Figure 12. Approach to suspected PE
Diabetic Emergencies

• see also Endocrinology, E11

**Diabetic Ketoacidosis (DKA)**
- severe insulin deficiency resulting in hyperglycemia (11–55 mmol/L), dehydration and electrolyte abnormalities
- history and physical examination – often young, type 1 DM, may be first presentation of undiagnosed DM (may occur in small percentage of type 2 patients)
  - early symptoms: polyuria, polydipsia, malaise, nocturia, weight loss
  - late signs and symptoms
    - anorexia, nausea, vomiting, dyspnea (often due to acidosis), fatigue
    - abdominal pain
    - drowsiness, stupor, coma
    - Kussmaul’s respiration
    - fruity acetone breath
- investigations
  - CBC, glucose, electrolytes, BUN/creatinine, Ca²⁺, Mg²⁺, phosphate, urine glucose and ketones
  - ABG
  - ECG (MI possible precipitant; electrolyte disturbances may predispose to dysrhythmia)
- management
  - rehydration
    - bolus of NS, then high rate NS infusion (beware of overhydration and cerebral edema, especially in pediatric patients)
    - beware of a pseudohypernatremia due to hyperglycemia (add 3 Na⁺ per 10 glucose over 5.5 mmol/L)
  - potassium
    - essential to avoid hypokalemia: replace KCl (20 mEq/L if adequate renal function and initial K⁺ <5.5 mmol/L)
    - use cardiac monitoring if potassium levels normal or low
  - insulin
    - critical, as this is the only way to turn off gluconeogenesis/ketosis
    - do not give insulin if K⁺ <3.3 mmol/L
    - initial bolus of 5-10 U short-acting/regular insulin (or 0.2 U/kg) IV in adults (controversial – may just start with infusion)
    - followed by continuous infusion at 5-10 U (or 0.1 U/kg) per hour
    - add D5W to IV fluids when blood glucose <15 mM to prevent hypoglycemia
    - bicarbonate is not given unless patient is at risk of death or shock (typically pH <7.0)

**Hyperosmolar Hyperglycemic State (HHS)**
- state of extreme hyperglycemia (44-133.2 mmol/L) due to relative insulin deficiency, increased counter-regulatory hormones, gluconeogenesis, and dehydration (due to osmotic diuresis) in type 2 DM, high mortality (5-20%)
- history and physical examination
  - mental disturbances, coma, delirium, seizures
  - polyuria
  - nausea, vomiting
- investigations
  - CBC, electrolytes, creatinine, BUN, glucose, Mg²⁺, phosphate, urine glucose and ketones
  - ABG
  - ECG
- management
  - rehydration with IV NS (total water deficit estimated at average 100 cc/kg body weight)
  - O₂ and cardiac monitoring, frequent electrolyte and glucose monitoring
  - insulin as required
  - identify and treat precipitant if present (the 5 Is)

**Clinical Criteria to Prevent Unnecessary Diagnostic Testing in Emergency Department Patients with Suspected Pulmonary Embolism**

*J Thromb Haemost 2004;2:1247-1255*

**Purpose:** To develop pulmonary embolism (PE) rule-out criteria (PERC) that can be used at the bedside, and prevents overtesting for PERC. Also, to prevent over-testing for PE, which includes the D-dimer test that frequently results in false positives.

**Study:** 21 variables were collected prospectively from 3148 ED patients evaluated for possible PE to develop rule-out criteria. The application of the developed rules was investigated in 1427 low-risk patients and 382 very low-risk patients.

**Results:** Eight variables were included in a block rule (age <50 yr, pulse <100 bpm, SaO₂ >94%, no unilateral leg swelling, no hemoptysis, no recent trauma or surgery, no prior PE or DVT, no hormone use) and a negative score was used to rule-out PE. In low-risk and very low-risk patients, the rule had a sensitivity of 86 and 100%, respectively and a specificity of 27 and 15%, respectively.

**Summary:** D-dimer testing for PE may not be favourable if all eight factors in the PERC are negative.
Hypoglycemia
• very common ED presentation
• management focus
  ■ treatment of hypoglycemia
  ■ investigation of cause (most often due to exogenous insulin, alcohol, sulfonylureas)
• history and physical examination
  ■ last meal, known diabetes, prior similar episodes, drug therapy and compliance
  ■ liver/renal/endocrine/neoplastic disease
  ■ depression, alcohol or drug use
• management
  ■ IV access and rapid blood glucose measurement
  ■ D50W 50 mL IV push, glucose PO if mental status permits
  • if IV access not possible, glucagon 1-2 mg IM, repeat x 1 in 10-20 min
  • O2, cardiac, frequent BG monitoring
  • thiamine 100 mg IM
  • full meal as soon as mental status permits
  • if episode due to long acting insulin, or sulfonylureas, watch for prolonged hypoglycemia due to long t1/2 (may require admission for monitoring)
  • search for cause

Electrolyte Disturbances

Table 16. Electrolyte Disturbances

<table>
<thead>
<tr>
<th>Electrolyte Disturbance</th>
<th>Common Causes</th>
<th>Symptoms</th>
<th>Treatment</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypernatremia</td>
<td>Inadequate H2O intake (elderly/disabled) or inappropriate excretion of H2O (diuretics, Li and DI)</td>
<td>Lethargy, weakness, irritability, and edema. Seizures and coma occur with severe elevations of Na+ levels (&gt;158 mmol/L)</td>
<td>Salt restrict and give free water</td>
<td>No more than 12 mmol/L in 24 h drop in Na+ (0.5 mmol/L/h) due to risk of cerebral edema, seizures, death</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Hypo-osmolar (dilutional e.g. CHF, cirrhosis, ascites) and hyper-osmolar (usually glucose)</td>
<td>Acute: Neurologic symptoms Z0 to cerebral edema, headache, decreased LOC, depressed reflexes</td>
<td>Water restrict</td>
<td>Limit total rise to 8 mmol/L in 24 h (0.5 mmol/L/h maximum) as patients are at risk of central pontine myelinolysis</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Rhabdomyolysis, insulin deficiency, metabolic acidosis</td>
<td>Nausea, palpitations, muscle stiffness, areflexia</td>
<td>Protect heart: Calcium gluconate Shift K+ into cells: Insulin, NaHCO3, salbutamol</td>
<td>ECG: Peaked/narrow T wave, decreased P wave, prolonged PR interval, widening of QRS, AV block, V fib</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Metabolic alkalosis, insulin, diuretics, anorexia, salbutamol</td>
<td>Nausea, vomiting, fatigue, muscle cramps, constipation</td>
<td>K-Dur®, K+ sparing diuretics, IV solutions with 20-40 mEq KCl per liter over 3-4 h</td>
<td>ECG: U waves most important, flattened/inverted T waves, prolonged QT, depressed ST May need to restore Mg2+</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Hyper-PTH and malignancy account for approx. 90% of cases</td>
<td>Multisystem including CVS, GI (grosans), renal (stones), hematological, MSK (bones), psychiatric (moans)</td>
<td>Isotonic saline + furosemide if hypercalcemic Bisphosphonates, dialysis, chelation (EDTA or oral phosphate)</td>
<td>Patients with more severe or symptomatic hypercalcemia are usually dehydrated and require saline hydration as initial therapy</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Iatrogenic, low Mg2+, liver dysfunction,1° hypo-PTH</td>
<td>Laryngospasm, hyperreflexia, parasthesia, tetany, Chvostek’s and Trouseau’s sign</td>
<td>Acute (ionized Ca2+ &lt;0.7 mM) requires immediate treatment: IV calcium gluconate 1-2 g in 10-20 min followed by slow infusion</td>
<td>Prolonged QT interval can arise leading to dysrhythmia as can upper airway obstruction</td>
</tr>
</tbody>
</table>

Hypertensive Emergencies

Hypertensive Emergency (Hypertensive Crisis)

Etiology
• essential hypertension, emotional exertion, pain, use of sympathomimetic drugs (cocaïne, amphetamine, etc.), MAOI use with ingestion of tyramine-containing food (cheese, red wine, etc.), pheochromocytoma, pregnancy

Presentation
• elevation of systolic and diastolic BP (irrespective of BP) with acute end-organ damage (CNS, renal, CVS, retinal)
Table 17. Signs and Symptoms of Hypertensive Emergencies

<table>
<thead>
<tr>
<th>Complication</th>
<th>Central Nervous System</th>
<th>Retinal</th>
<th>Renal</th>
<th>Cardiac</th>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/TIA, headache, altered mental status, seizures, hemorrhage</td>
<td>Vision change, hemorrhage, exudates, papilledema</td>
<td>Nocturia, elevated creatinine, proteinuria, hematuria, oliguria</td>
<td>Ischemia/angina, infarct, dissection (back pain), congestive heart failure</td>
<td>Nausea, vomiting, abdominal pain, elevated liver enzymes</td>
<td></td>
</tr>
</tbody>
</table>

Investigations
- CBC, electrolytes, BUN, creatinine, urinalysis
- peripheral blood smear: to detect microangiopathic hemolytic anemia
- CXR: if SOB or chest pain
- ECG, troponins, CK: if chest pain
- CT head: if neurological findings or severe headache
- toxicology screen if sympathomimetic overdose suspected

Management
- in general, the strategy for management is to gradually and progressively reduce blood pressure in 24-48 h. Refer to Table 18 for common agents
  - lower BP by 25% over the initial 60 min by initiating antihypertensive therapy (usually nitroprusside and labetolol) or adjusting antihypertensive
  - if preeclampsia, immediately consult OB/GYN (see Obstetrics, OB16)
  - transfer to ICU for further reduction in BP under monitored setting
- in case of ischemic stroke: do not rapidly reduce blood pressure, maintain BP above 150/100 for 5 d
- in case of aortic dissection: rapid reduction of sBP to 110-120 STAT (do not resuscitate with IV fluids)
- in case of excessive catecholamines: avoid β-blockers (except labetolol)
- in case of acute coronary syndrome: address ischemia initially, then BP

Hypertensive Urgency
- definition: severely elevated blood pressure (usually sBP >180, dBP >115) with no evidence of end-organ damage
- most commonly due to non-adherence with medications
- treatment: initiate/adjust antihypertensive therapy, monitor in ED (up to 6 h) and discharge with follow up for 48-72 h
- goal: differentiate hypertensive emergencies from hypertensive urgencies

Table 18. Most Commonly Used Agents for the Treatment of Hypertensive Crisis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Onset of Action</th>
<th>Duration of Action</th>
<th>Adverse Effects*</th>
<th>Special Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VASODILATORS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Nitroprusside (vascular smooth muscle dilator) 1st line</td>
<td>0.25-10 µg/kg/min</td>
<td>Immediate</td>
<td>3-5 min</td>
<td>N/V, muscle twitching, sweating, cyanide intoxication, coronary steal syndrome</td>
<td>Most hypertensive emergencies (especially CHF, aortic dissection) Use in combination with β-blockers (e.g. esmolol) in aortic dissection Caution with high ICP and azotemia</td>
</tr>
<tr>
<td>Nicardipine (CCB) 2 mg IV bolus, then 4 mg/kg/h IV</td>
<td>15-30 min</td>
<td>40 min</td>
<td>Tachycardia, headache, flushing, local phlebitis (e.g. encephalopathy, RF, eclampsia, sympathetic crisis)</td>
<td>Most hypertensive emergencies Caution with acute CHF</td>
<td></td>
</tr>
<tr>
<td>Fenoldopam Mesylate (dopamine receptor antagonist)</td>
<td>0.05-0.1 µg/kg/min IV</td>
<td>&lt;5 min</td>
<td>8-10 min</td>
<td>Tachycardia, headache, nausea, flushing (e.g. acute RF)</td>
<td>Most hypertensive emergencies Caution with glaucoma</td>
</tr>
<tr>
<td>Enalapril (ACEI)</td>
<td>0.625-1.25 mg IV q6h</td>
<td>15-30 min</td>
<td>12-24 h</td>
<td>Theoretical fall in pressure in high renin states not seen in studies</td>
<td>Acute LV failure Avoid in acute MI, pregnancy, acute RF</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>5-20 µg/min IV</td>
<td>1-2 min</td>
<td>3-5 min</td>
<td>Hypotension, bradycardia, headache, lightheadedness, dizziness</td>
<td>MI/pulmonary edema</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>5-10 mg IV/IM q20min (max 20 mg)</td>
<td>5-20 min</td>
<td>2-6 h</td>
<td>Dizziness, drowsiness, headache, tachycardia, Na+ retention</td>
<td>Eclampsia</td>
</tr>
</tbody>
</table>

With CNS manifestations of severe hypertension, it is often difficult to differentiate causal relationships (i.e. hypertension could be secondary to primary cerebral event (Cushing effect)).

**Drugs that Increase Adrenergic Stimulation**
- MAOIs
- TCAs
- Amphetamines
- Cocaine

Most commonly used agents for hypertensive crisis are labetalol and nitroprusside.
Table 18. Most Commonly Used Agents for the Treatment of Hypertensive Crisis (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Onset of Action</th>
<th>Duration of Action</th>
<th>Adverse Effects*</th>
<th>Special Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADRENERGIC INHIBITORS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labetalol</td>
<td>20 mg IV bolus q10min or 0.5-2 mg/min</td>
<td>5-10 min</td>
<td>3-6 h</td>
<td>Vomiting, scalp tingling, burning in throat, dizziness, nausea, heart block, orthostatic hypotension</td>
<td>Most hypertensive emergencies (esp. eclampsia) Avoid in acute CHF, heart block &gt; 1st degree</td>
</tr>
<tr>
<td>Esmolol</td>
<td>250-500 µg/kg/min 1 min, then 50 µg/kg/min for 4 min; repeat</td>
<td>1-2 min</td>
<td>10-20 min</td>
<td>Hypotension, nausea, bronchospasm</td>
<td>Aortic dissection, acute MI SVT dysrhythmias, perioperative HTN Avoid in acute CHF, heart block &gt; 1st degree</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>5-15 mg q5-15min</td>
<td>1-2 min</td>
<td>3-10 min</td>
<td>Tachycardia, headache, flushing</td>
<td>Catecholamine excess (e.g. pheochromocytoma)</td>
</tr>
</tbody>
</table>

*Hypotension may occur with all of these agents

Stroke

- see Neurology, N43
- can be ischemic (80% of all strokes) or hemorrhagic

Presentation
- sudden onset persisting neurological deficits

Table 19. Signs and Symptoms of Stroke

<table>
<thead>
<tr>
<th>Sign/symptoms</th>
<th>General</th>
<th>Language/throat</th>
<th>Vision</th>
<th>Coordination</th>
<th>Motor</th>
<th>Sensation</th>
<th>Reflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased LOC, changed mental status, confusion, neglect</td>
<td>Dyssarthria, aphasia, swallowing difficulty</td>
<td>Diplopia, eye deviation, asymmetric pupils, visual field defect</td>
<td>Ataxia, intention tremor, lack of coordination</td>
<td>Increased tone, loss of power, spasticity</td>
<td>Loss of sensation</td>
<td>Hyperreflexia, clonus</td>
<td></td>
</tr>
</tbody>
</table>

Note: headache is variable

- patients with hemorrhagic stroke can present with sudden onset thunderclap headache that is usually described as “worst headache in my life”
- constellation of neurological deficits can point to certain vascular territories (Table 20)
- stroke mimics: seizure, migraine, hypoglycemia, Todds paralysis, peripheral nerve injury, Bell’s palsy, tumour, syncope

Table 20. Stroke Syndromes

<table>
<thead>
<tr>
<th>Region of Stroke</th>
<th>Stroke Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior Cerebral Artery</td>
<td>Primarily frontal lobe function affected</td>
</tr>
<tr>
<td></td>
<td>Altered mental status, impaired judgment, contralateral lower extremity weakness and hypoesthesia, gait apraxia</td>
</tr>
<tr>
<td>Middle Cerebral Artery</td>
<td>Contralateral hemiparesis (arm and face weakness &gt; leg weakness) and hypoesthesia, ipsilateral hemianopia, gaze preference to side of lesion ± agnosia, receptive/expressive aphasia</td>
</tr>
<tr>
<td>Posterior Cerebral Artery</td>
<td>Affects vision and thought</td>
</tr>
<tr>
<td></td>
<td>Homonymous hemianopia, cortical blindness, visual agnosia, altered mental status, impaired memory</td>
</tr>
<tr>
<td>Vertebrobasilar Artery</td>
<td>Wide variety of CN, cerebellar and brainstem deficits: vertigo, nystagmus, diplopia, visual field deficits, dysphagia, dysarthria, facial hypoesthesia, syncope, ataxia</td>
</tr>
<tr>
<td></td>
<td>Loss of pain and temperature sensation ipsilateral face and contralateral body</td>
</tr>
</tbody>
</table>

Investigations
- CBC, electrolytes, blood glucose, coagulation studies, ± cardiac biomarkers, ± toxicology screen
- non-contrast CT head: look for hemorrhage, ischemia
- ECG ± echocardiogram: rule out atrial fibrillation, acute MI as source of emboli
  - other imaging: carotid dopplers, CTA, MRA as appropriate

Exclusion Criteria for tPA:
- Suspected subarachnoid hemorrhage
- Previous intracranial hemorrhage
- Cerebral infarct or severe head injury within the past 3 mo
- Recent pericarditis
- Major surgery within the past 14 d
- GI or urinary hemorrhage within the past 21 d
- Recent lumbar puncture or arterial puncture at noncompressible site
- Patient is pregnant
- BP >185 mmHg systolic, or >110 mmHg diastolic
- Bleeding diathesis
- Prolonged PTT (more than 40 s) or INR >1.4
- Platelet count <100,000
- Blood glucose <2.8 or >22 mmol/L
- Intracranial hemorrhage on CT or large volume infarct
- Seizure at onset causing deficit
- Previously ADL dependent (clinical judgment)
Management

- thrombolysis: immediate assessment for eligibility. Need acute onset, <4.5 h from drug administration time AND compatible physical findings AND normal CT with no bleed
- intubation with RSI if GCS ≤8, rapidly decreasing GCS, or inadequate airway protection reflexes
- elevating head of bed if risk of elevated ICP, aspiration, or worsening cardiopulmonary status
- NPO, IV ± cardiac monitoring
  - judge fluid rate carefully to avoid overhydration (cerebral edema) as well as underhydration (underperfusion of the ischemic penumbra)
- BP control: only treat severe hypertension (sBP >200, dBP >120, mean arterial BP >140) or hypertension associated with hemorrhagic stroke transformation, cardiac ischemia, aortic dissection, or renal damage; use IV nitroprusside or labetolol
- glycemic control: keep fasting glucose less than 6.5 in acute phase (5 d)
- acute ischemic stroke: thrombolytics (rt-PA, e.g. alteplase) if within 4.5 h of symptom onset with no evidence of hemorrhage on CT scan
- antiplatelet agents: prevent recurrent stroke or stroke after TIAs, e.g. Aspirin® (1st-line); clopidogrel, Aggrenox® (2nd-line)
- anticoagulation: DVT prophylaxis if immobile; treat atrial fibrillation if present

Medications

- acute ischemic stroke: thrombolytics (rt-PA, e.g. alteplase) if within 4.5 h of symptom onset with no evidence of hemorrhage on CT scan
- antiplatelet agents: prevent recurrent stroke or stroke after TIAs, e.g. Aspirin® (1st-line); clopidogrel, Aggrenox® (2nd-line)
- anticoagulation: DVT prophylaxis if immobile; treat atrial fibrillation if present

Gynecologic/Urologic Emergencies

Vaginal Bleed

- see Gynecology, GY6 and Obstetrics, OB22

Etiology

- pregnant patient
  - 1st/2nd trimester pregnancy: ectopic pregnancy, abortion (threatened, incomplete, complete, missed, inevitable, septic), molar pregnancy, implantation bleeding, friable cervix (most common cause)
  - 2nd/3rd trimester pregnancy: placenta previa, placental abruption, premature rupture of membranes, preterm labour
  - other: trauma, bleeding cervical polyp
- postpartum
  - postpartum hemorrhage, uterine inversion, retained placental tissue, endometritis
  - non-pregnant patients
  - dysfunctional uterine bleeding, uterine fibroids, pelvic tumours, trauma, endometriosis, PID, exogenous hormones

History

- characterize bleeding (frequency, duration, number of pads/tampons, cyclicity)
- pain (if present OPQRSTU)
- menstrual history, sexual history, STI history, syncope/pre-syncope
- details of pregnancy including gush of fluid and fetal movement (>20 wk)

Physical Examination

- ABC (especially noting postural BP/HR and mucous membrane)
- abdominal examination (peritoneal signs, tenderness, distention, mass)
- speculum examination (NOT IF 2nd/3rd trimester bleeding. Perform only when placenta previa is ruled out with ultrasound)
  - look for active bleeding, trauma/anomaly, and cervical dilatation
  - use sterile speculum if pregnant
  - bimanual examination (cervical tenderness, size of uterus, cervical length/dilatation)
  - sterile gloves if pregnant

Investigations

- β-hCG test for all patients with child-bearing potential
- CBC, blood and Rh type, quantitative β-hCG, PTT, INR
- type and cross if significant blood loss
- transvaginal ultrasound (rule out ectopic pregnancy and spontaneous abortion)
- abdominal ultrasound (rule out placenta previa and fetal demise)
- postpartum
  - U/S for retained products
  - β-hCG if concerned about retained tissue

7 Causes of Emboli from the Heart

- Atrial fibrillation
- MI
- Endocarditis
- Valvular disease
- Dilated cardiomyopathy
- Left heart myxoma
- Prosthetic valves

Causes of Acute Ataxia

UNABLE TO STAND

- Underlying weakness (mimic ataxia)
- Nutritional neuropathy (vitamin B12 deficiency)
- Arteritis/vasculitis
- Basilar migraine
- Labyrinthitis/vestibular neuritis
- Encephalitis/infection
- Trauma (post-concussive)
- Other (rare genetic or metabolic disease)
- Stroke (ischemia or hemorrhage)
- Toxins (drugs, toluene, mercury)
- Alcohol
- Neoplasm/paraneoplastic syndrome
- Demyelination (Miller Fisher, Guillain Barré, MS)

Causes of Emboli from the Heart

- Atrial fibrillation
- MI
- Endocarditis
- Valvular disease
- Dilated cardiomyopathy
- Left heart myxoma
- Prosthetic valves

An ectopic pregnancy can be ruled out by confirming an intrauterine pregnancy by bedside U/S unless the patient is using NF.
Management
- ABCs
- pulse oximeter and cardiac monitors if unstable
- Rh immune globulin (Rhogam®) for vaginal bleeding in pregnancy and Rh-negative mother
- 1st/2nd trimester pregnancy
  - ectopic pregnancy: definitive treatment with surgery or methotrexate
  - intrauterine pregnancy, no concerns of coexistent ectopic: discharge patient with obstetrics follow-up
  - U/S indeterminate or β-hCG >1000-2000 IU: further work-up and/or gynecology consult
  - abortions: if complete, discharge if stable; for all others, acquire gynecology consult
- 2nd/3rd trimester pregnancy
  - placenta previa or placental abruption: obstetrics consult for possible admission
- postpartum
  - manage ABCs: start 2 large bore IV rapid infusion, type and cross 4 units of blood, consult OB/GYN immediately
- non-pregnant
  - dysfunctional uterine bleeding (prolonged or heavy flow ± breakthrough bleeding and without ovulation, a diagnosis of exclusion)
    - <35–40 yr of age: Provera® 10 mg PO OD x 10 d, warn patient of a withdrawal bleed, discharge if stable
    - if unstable, admit for IV hormonal therapy, possible D&C.
    - >35–40 yr of age: uterine sampling necessary prior to initiation of hormonal treatment to rule out endometrial cancer, U/S for any masses felt on exam
    - tranexamic acid (Cyklokapron®) to stabilize clots
  - structural abnormalities: fibroids or uterine tumours may require excision for diagnosis/treatment, U/S for workup of other pelvic masses, Pap smear/biopsy for cervical lesions

Disposition
- the decision to admit or discharge should be based on the stability of the patient, as well as the nature of the underlying cause; consult gynecology for admitted patients
- if patient can be safely discharged, ensure follow up with family physician or gynecologist
  - instruct patient to return to emergency for increased bleeding, presyncope

Table 21. Complications of Pregnancy

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Fetal</th>
<th>Maternal</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Pregnancy failure</td>
<td>Eclectic pregnancy</td>
</tr>
<tr>
<td>1-12 wk</td>
<td>Spontaneous abortion</td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Fetal demise</td>
<td>Hyperemesis gravidarum</td>
</tr>
<tr>
<td></td>
<td>Gestational trophoblastic disease</td>
<td>UTI/pyelonephritis</td>
</tr>
<tr>
<td>Second</td>
<td>Disorders of fetal growth</td>
<td>Gestational diabetes mellitus</td>
</tr>
<tr>
<td>13-27 wk</td>
<td>IUGR</td>
<td>Rh incompatibility</td>
</tr>
<tr>
<td></td>
<td>Oligo/polyhydramnios</td>
<td>UTI/pyelonephritis</td>
</tr>
<tr>
<td>Third</td>
<td>Vasa previa</td>
<td>Preecampsia/ eclampsia</td>
</tr>
<tr>
<td>28-41 wk</td>
<td></td>
<td>Placenta previa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Preterm labour/PPROM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placental abruption</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uterine rupture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DVT</td>
</tr>
</tbody>
</table>

Nephrolithiasis (Renal Colic)
- see Urology, U16

Epidemiology and Risk Factors
- 10% of population (twice as common in males)
- recurrence 50% at 5 yr
- peak incidence 30-50 yr of age
- 75% of stones <5 mm pass spontaneously within 2 wk, larger stones may require consultation

Clinical Features
- urinary obstruction → upstream distention of ureter or collecting system → severe colicky pain
- may complain of pain at flank, groin, testes, or tip of penis
- writhing, never comfortable, nausea, vomiting, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
- occasionally symptoms of trigonal irritation (frequency, urgency)
- fever, chills, rigors in secondary pyelonephritis
- peritoneal findings/anterior abdominal tenderness usually absent
Differential Diagnosis of Renal Colic
- acute ureteric obstruction
- acute abdomen: biliary, bowel, pancreas, AAA
- gynecological: ectopic pregnancy, torsion/rupture of ovarian cyst
- pyelonephritis (fever, chills, pyuria, vomiting)
- radiculitis (L1): herpes zoster, nerve root compression

Investigations
- screening
  - CBC → elevated WBC in presence of fever suggests infection
  - electrolytes, Cr, BUN → to assess renal function
  - urinalysis: R&Ms (WBCs, RBCs, crystals), C&S
- imaging
  - non-contrast spiral CT is the study of choice
  - abdominal ultrasound may demonstrate stone or hydronephrosis (consider in females of child bearing age)
  - abdominal x-ray will identify large radiopaque stones (calcium, struvite, and cystine stones) but may miss smaller stones, uric acid stones or stones overlying bony structures. Consider as an initial investigation in patients who have a history of radiopaque stones and similar episodes of acute flank pain (CT necessary if film is negative)
- strain all urine → stone analysis

Management
- analgesics: NSAIDs [usually ketorolac (Toradol®) preferable over opioids], antiemetics, IV fluids
- urology consult may be indicated, especially if stone >5 mm, or if patient has signs of obstruction or infection
- α-blocker (e.g. tamsulosin) helpful to increase stone passage in select cases

Disposition
- most patients can be discharged
- ensure patient is stable, has adequate analgesia, and is able to tolerate oral medications
- may advise hydration, and limitation of protein, sodium, oxalate and alcohol intake

Ophthalmologic Emergencies
- see also Ophthalmology, OP17

History/Physical
- patient may complain of pain, tearing, itching, redness, photophobia, foreign body sensation, trauma
- mechanism of foreign body insertion – if high velocity injury suspected (welding, metal grinding, metal striking metal), must obtain orbital x-rays, ultrasound, or CT scan to exclude presence of intraocular metallic foreign body
- see Table 22 for important considerations of red eye in the emergency department
- visual acuity in both eyes, pupils, extraocular structures, fundoscopy, tonometry, slit lamp exam

Management of Ophthalmologic Foreign Body
- copious irrigation with saline for any foreign body
- remove foreign body under slit lamp exam with cotton swab or sterile needle
- antibiotic drops qid until healed
- patching may not improve healing or comfort – do not patch contact lens wearers
- limit use of topical anesthetic to examination only
- consider tetanus prophylaxis
- ophthalmology consult if globe penetration suspected

Table 22. Differential Diagnosis of Red Eye in the Emergency Department

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Possible Serious Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light sensitivity</td>
<td>Iritis, keratitis, abrasion, ulcer</td>
</tr>
<tr>
<td>Unilateral</td>
<td>Above + herpes simplex, acute angle closure glaucoma</td>
</tr>
<tr>
<td>Significant pain</td>
<td>Above + scleritis</td>
</tr>
<tr>
<td>White spot on cornea</td>
<td>Corneal ulcer</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>All of the above</td>
</tr>
<tr>
<td>Non-reactive pupil</td>
<td>Acute glaucoma, iritis</td>
</tr>
<tr>
<td>Copious discharge</td>
<td>Gonococcal conjunctivitis</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>All of the above</td>
</tr>
</tbody>
</table>

Indications for Admission to Hospital
- Intractable pain
- Fever (suggests infection) or other evidence of pyelonephritis
- Single kidney with ureteral obstruction
- Bilateral obstructing stones
- Intractable vomiting
- Compromised renal function

Always assess visual acuity in both eyes when a patient presents to the ER with an ophthalmologic complaint.

Any etiology of red eyes may also present with blurred vision.

Other Ophthalmologic Emergencies
(See also Ophthalmology, OP5)

Infectious: Red eye (Table 22), endophthalmitis, hypopyon.
Trauma: Globe rupture, orbital blow-out fractures, corneal injuries, eyelid laceration, hyphaema, lens dislocation, retrobulbar hemorrhage.
Painful vision loss: Acute iritis, corneal abrasion, globe rupture, lens dislocation, retrobulbar hemorrhage, optic neuritis, temporal arteritis, endophthalmitis, keratitis.
Painless vision loss: Central retinal vein occlusion, amaurosis fugax, occipital stroke.

Contraindications to Pupil Dilation
- Shallow anterior chamber
- Iris-supported lens implant
- Potential neurological abnormality requiring pupillary evaluation
- Caution with CV disease – mydriatics can cause tachycardia
### Table 23. Select Ophthalmologic Emergencies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Signs and Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute angle closure glaucoma</strong></td>
<td>Unilateral red, painful eye</td>
<td>Ophthalmology consult for laser iridotony</td>
</tr>
<tr>
<td></td>
<td>Decreased visual acuity, halos around lights</td>
<td>Topical (β)-blockers, adrenergics and cholinergics</td>
</tr>
<tr>
<td></td>
<td>Fixed, mid-dilated pupil</td>
<td>Systemic carbonic anhydrase inhibitors and hyperosmotic agents</td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marked increase in IOP (&gt;40 mmHg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shallow anterior chamber ± cells</td>
<td></td>
</tr>
<tr>
<td><strong>Chemical burn</strong></td>
<td>Known exposure to acids or alkali (worse)</td>
<td>IRRIGATE AT SITE OF ACCIDENT</td>
</tr>
<tr>
<td></td>
<td>Pain, decreased visual acuity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vascularization or defects of cornea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Iris and lens damage</td>
<td></td>
</tr>
<tr>
<td><strong>Orbital cellulitis</strong></td>
<td>Red, painful eye, decreased visual acuity</td>
<td>ADMISSION, OPHTHALMOLOGY CONSULT</td>
</tr>
<tr>
<td></td>
<td>Headache, fever</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lid erythema, edema and difficulty opening eye</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Conjunctival injection and chemosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proptosis, ophthalmoplegia ± RAPD</td>
<td></td>
</tr>
<tr>
<td><strong>Retinal artery occlusion</strong></td>
<td>Sudden, painless, monocular vision loss RAPD</td>
<td>RESTORE BLOOD FLOW &lt;2 h</td>
</tr>
<tr>
<td></td>
<td>Cherry red spot and retinal pallor on funduscopy</td>
<td>MASSAGE GLOBE</td>
</tr>
<tr>
<td><strong>Retinal artery detachment</strong></td>
<td>Flashes of light, floaters, curtains of blackness/</td>
<td>OPHTHALMOLOGY CONSULT FOR SCERAL BUCKLE/</td>
</tr>
<tr>
<td></td>
<td>peripheral vision loss</td>
<td>PNEUMATIC RETINOPLEX</td>
</tr>
<tr>
<td></td>
<td>Painless</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loss of red reflex, decreased IOP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Detached areas are grey ± RAPD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Dermatologic Emergencies

### Life Threatening Dermatoses

**Rash Characteristics**

**A. Diffuse Rashes**

- staphylococcal scalded skin syndrome (SSSS)
  - caused by an exotoxin from infecting strain of coagulase-positive S. aureus
  - mostly occurs in children
  - prodrome: fever, irritability, malaise and skin tenderness
  - sudden onset of diffuse erythema: skin is red, warm, and very tender
  - flaccid bullae that are difficult to see, then desquamate in large sheets
  - Nikolsky’s sign: gentle lateral stroking of skin causes epidermis to separate
- toxic epidermal necrolysis (TEN) [>30% of Body SA]
  - see also **Dermatology, D22**
  - caused by drugs (e.g. phenytoin, sulfas, penicillins and NSAIDs), bone marrow transplantation, blood product transfusions
  - usually occurs in adults
  - diffuse erythema followed by necrosis
  - severe mucous membrane blistering
  - entire epidermis desquamation
  - high mortality (>50%)
- toxic shock syndrome (TSS)
  - see also **Infectious Diseases, ID26**
  - caused by superantigen from S. aureus or GAS activating T-cell and cytokines
  - patient often presents with onset of shock and multi-organ failure, fever
  - diffuse erythematous macular rash
  - at least 3 organ systems involved: CNS, respiratory, GI, muscular, mucous membranes, renal, liver, hematologic, skin (necrotizing fasciitis, gangrene)
- vesicobullous lesions
- erythema multiforme (EM)
  - see **Dermatology, D22**
  - immunologic reaction to herpes simplex
  - viral prodrome 1-14 d before rash
  - “target lesion”: central grey bulla or wheal surrounded by concentric rings of erythema and normal skin
Stevens-Johnson syndrome (SJS) [<10% of Body SA]
- related to drugs such as antiepileptics and biologic agents, e.g. infliximab
- EM with constitutional symptoms and mucous membrane involvement (milder mucous membrane involvement than TEN)

B. Discrete Lesions
- pyoderma gangrenosum
  - often associated with immunocompromised patients (HIV, leukemia or lymphoma) with Gram-negative sepsis
  - often occurs in arms, hands, feet, or perineal region
  - usually begins as painless macule/vesicle → pustule/bulla on red/blue base → sloughing, leaving a gangrenous ulcer
- disseminated gonococcal infection (DGI)
  - see also Dermatology, D32
  - fever, skin lesions (pustules/vesicles on erythematous base ~5 mm in diameter), arthritis (joint swelling and tenderness), septic arthritis (in larger joints, e.g. knees, ankles and elbows)
  - most commonly in gonococcus positive women during menstruation or pregnancy
  - skin lesions usually appear in extremities and resolve quickly (<7 d)
- meningococcemia
  - flu-like symptoms of headache, myalgia, nausea and vomiting
  - petechial, macular or maculopapular lesions with grey vesicular centres
  - usually a few millimeters in size but may become confluent and hemorrhagic
  - usually appear in extremities but may appear anywhere
  - look for signs of meningeal irritation: Brudzinski, Kernig, nuchal rigidity, jolt accentuation

History and Physical Examination
- determine onset, course, location of skin lesions
- fever, joint pain
- associated symptoms: CNS, resp, GU, GI, renal, liver, mucous membranes
- medication history
- vitals

Investigations
- immediate consultation if patient unstable
- CBC, electrolytes, creatinine, AST, ALT, ALP, blood culture, skin biopsy, serum immunoglobulin levels (serum IgE)

Management
- general: judicious IV fluids and electrolyte control, consider vasopressors if hypotensive, prevention of infection
- determine if admission and consult needed: dermatology or infectious diseases
- specific management is determined by etiology
  - SSSS, TSS, DGI and meningococcemia
    - IV antibiotics
    - EM, SJS, and TEN
    - stop precipitating medication
    - fluids
    - symptomatic treatment: antihistamines, antacids, topical corticosteroids, systemic corticosteroids (controversial), prophylactic oral acyclovir, consider IVIG
    - TEN: debride necrotic tissue

Disposition
- most cases will require urgent care and hospitalization
- TEN: early transfer to burn centre improves outcome

Environmental Injuries

Heat Exhaustion and Heat Stroke
- predisposing factors: young persons who overexert themselves, older adults who cannot dissipate heat at rest (e.g. using anticholinergic drugs such as antihistamines or TCAs), and patients with schizophrenia who are using anticholinergic or neuroleptic medications

Heat Exhaustion (HE)
- clinical features relate to loss of circulating volume caused by exposure to heat stress
  - “water depletion”: HE occurs if lost fluid not adequately replaced
  - “salt depletion”: HE occurs when losses replaced with hypotonic fluid
Heat Stroke
• life-threatening emergency resulting from failure of normal compensatory heat-shedding mechanisms
• divided into classical and exertional subtypes (see Table 24)
• if patient does not respond relatively quickly to cooling treatments, consider other possible etiologies of hyperpyrexia (e.g. meningitis, thyroid storm, anticholinergic poisoning, delirium tremens, other infections)

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Heat Exhaustion</th>
<th>Classical Heat Stroke</th>
<th>Exertional Heat Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Non-specific malaise, headache, fatigue</td>
<td>• Occurs in setting of high ambient temperatures (e.g. heat wave, poor ventilation)</td>
<td>• Occurs with high endogenous heat production (e.g. exercise) and overwhelmed homeostatic mechanisms</td>
<td></td>
</tr>
<tr>
<td>• Body temp &lt;40.5°C (usually normal)</td>
<td>• Often patients are older, poor, and sedentary or immobile</td>
<td>• Patients often younger, more active</td>
<td></td>
</tr>
<tr>
<td>• No coma or seizures</td>
<td>• Temp usually &gt;40.5°C</td>
<td>• Skin often diaphoretic</td>
<td></td>
</tr>
<tr>
<td>• Dehydration (T HR, orthostatic hypotension)</td>
<td>• Altered mental status, seizures, delirium, coma</td>
<td>• Other features as for classical HS, but may also have DIC, acute renal failure, rhabdomyolysis, marked lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>• May have elevated AST, ALT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 25. Classification of Hypothermia

<table>
<thead>
<tr>
<th>Class</th>
<th>Temp</th>
<th>Symptoms/Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>32-34.9°C</td>
<td>Tachypnea, tachycardia, ataxia, dysarthria, shivering</td>
</tr>
<tr>
<td>Moderate</td>
<td>28-31.9°C</td>
<td>Loss of shivering, dysrhythmias, Osborne (J) waves on ECG, decreased LOC, combative behaviour, muscle rigidity, dilated pupils</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;28°C</td>
<td>Coma, hypotension, acidemia, ventricular fibrillation, asystole, flaccidity, apnea</td>
</tr>
</tbody>
</table>

R-e-warming Options
• gentle fluid and electrolyte replacement in all (due to cold diuresis)
• Passive External Re-warming (PER)
  • suitable for most stable patients with core temperature >32.2°C
  • involves covering patient with insulating blanket; body generates heat and re-warms through metabolic process, shivering
• Active External Re-warming (AER)
  • involves use of warming blankets
  • beware of “afterdrop” phenomenon
  • safer when done in conjunction with active core re-warming
• Active Core Re-warming (ACR)
  • generally for patients with core temperature <32.2°C, and/or with cardiovascular instability
  • avoids “afterdrop” seen with AER alone
  • re-warm core by using
    • warmed humidified oxygen, IV fluids
    • peritoneal dialysis with warm fluids
    • gastric/colonic/pleural irrigation with warm fluids
    • external circulation (cardiopulmonary bypass machine) is most effective, fastest
Approach to Cardiac Arrest in the Hypothermic Patient
• do all procedures gently or may precipitate VFib
• check pulse and rhythm for at least 1 min; may have profound bradycardia
• if any pulse at all (even very slow) do NOT do CPR
• if in VFib try to defibrillate up to maximum 3 shocks if core temperature <30°C
• intubate if required, ventilate with warmed, humidified O₂
• medications (vasopressors, antidysrhythmics) may not be effective at low temperatures
  ▪ controversial; may try one dose
• focus of treatment is re-warming

FROSTBITE
Classification
• ice crystals form between cells
• classified according to depth – similar to burns (1st to 3rd degree)
  • 1st degree
    ▪ symptoms: initial paresthesia, pruritus
    ▪ signs: erythema, edema, hyperemia, no blisters
  • 2nd degree
    ▪ symptoms: numbness
    ▪ signs: blistering (clear), erythema, edema
  • 3rd degree
    ▪ symptoms: pain, burning, throbbing (on thawing); may be painless if severe
    ▪ signs: hemorrhagic blisters, skin necrosis, edema, no movement

Management
• treat for hypothermia: O₂, IV fluids, maintenance of body warmth
• remove wet and constrictive clothing
• immerse in 40–42°C agitated water for 10–30 min (very painful; administer adequate analgesia)
• clean injured area, leave injured region open to air
• consider aspiration/debridement of blisters (controversial)
• debride skin
• tetanus prophylaxis
• consider penicillin G as frost bite injury at high risk of infection
• surgical intervention may be required to release restrictive eschars
• never allow a thawed area to re-chill/freeze

Burns
• see Plastic Surgery, PL16

Physical Examination
• burn size
  ▪ rule of nines (see Figure 14); does not include 1st degree burns
• burn depth
  ▪ superficial: epidermis only (e.g. sunburn)
  ▪ partial thickness: into superficial dermis deep or hair follicles, sweat glands
  ▪ full thickness: all layers of the skin
  ▪ deep: involvement of fat, muscle, even bone

Management
• remove noxious agent/stop burning process
• establish airway if needed (indicated with burns >40% BSA or smoke inhalation injury)
• resuscitation for 2nd and 3rd degree burns (after initiation of 2 large bore IVs)
• fluid boluses if unstable
  ▪ Parkland Formula: Ringer’s lactate 4 cc/kg/%BSA burned; give half in first 8 h, half in next 16 h; maintenance fluids are also required if patient cannot tolerate PO hydration
  ▪ urine output is best measure of resuscitation, should be 40–50 cc/h or 0.5 cc/kg/h; avoid diuretics
• pain relief: continuous morphine infusion with breakthrough bolus
• investigations: CBC, electrolytes, urinalysis, CXR, ECG, ABG, carboxyhemoglobin
• burn wound care: prevent infection, clean/debride with mild soap and water, sterile dressings
• escharotomy or fasciotomy for circumferential burns (chest, extremities)
• topical antibiotics, systemic antibiotics infrequently indicated
• tetanus prophylaxis if burn is deeper than superficial dermis

Disposition
• admit
  ▪ 2nd degree burns >10% BSA; any significant 3rd degree burns
  ▪ 2nd degree on face, hands, feet, perineum or across major joints
  ▪ electrical, chemical burns and inhalation injury
  ▪ burn victims with underlying medical problems or immunosuppressed patients
Inhalation Injury

Etiology
- carbon monoxide (CO), cyanide (CN) poisoning
- direct thermal injury: limited to upper airway
- smoke causes bronchospasm and edema from particulate matter and toxic inhalants (tissue asphyxiates, pulmonary irritants, systemic toxins)

History and Physical
- risk factors: closed space fires, period of unconsciousness, noxious chemicals involved
- cherry red skin (unreliable, usually post-mortem finding)
- singed nasal hairs, soot on oral/nasal membranes, sooty sputum
- hoarseness, stridor, dyspnea
- decreased LOC, confusion
- PO_{2} normal but O_{2} saturation low suggests CO poisoning

Investigations
- measure carboxyhemoglobin levels, co-oximetry
- ABG
- CXR ± bronchoscopy

Management
- CO poisoning: 100% O_{2} ± hyperbaric O_{2} (controversial)
- direct thermal injury: humidified oxygen, early intubation, pulmonary toilet, bronchodilators

Bites

MAMMALIAN BITES
- see Plastic Surgery, PL10

History
- time and circumstances of bite, symptoms, allergies, tetanus immunization status, comorbid conditions, rabies risks, HIV/hepatitis risk (human bite)
- high morbidity associated with clenched fist injuries, “fight bites”

Physical Examination
- assess type of wound: abrasion, laceration, puncture, crush injury
- assess for direct tissue damage: skin, bone, tendon, neurovascular status

Investigations
- if bony injury or infection suspected check for fracture and gas in tissue with x-rays
- get skull films in children with scalp bite wounds, ± CT to rule out cranial perforation

Initial Management
- wound cleansing and copious irrigation as soon as possible
- irrigate/debride puncture wounds if feasible, but not if sealed or very small openings; avoid hydrodissection along tissue planes
- debridement is important in crush injuries to reduce infection and optimize cosmetic and functional repair
- culture wound if signs of infection (erythema, necrosis or pus); obtain anaerobic cultures if wound foul smelling, necrotizing, or abscess; notify lab that sample is from bite wound

Prophylactic Antibiotics
- types of infections resulting from bites: cellulitis, lymphangitis, abscesses, tenosynovitis, osteomyelitis, septic arthritis, sepsis, endocarditis, meningitis
- a 3-5 d course of antibiotics is recommended for all bite wounds to the hand and should be considered in other bites if any high-risk factors present (efficacy not proven)
- dog and cat bites (pathogens: Pasteurella multocida, S. aureus, S. viridans)
  - 80% of cat bites, 5% of dog bites become infected
  - 1st line: amoxicillin + clavulanic acid
- human bites (pathogens: Eikenella corrodens, S. aureus, S. viridans, oral anaerobes)
  - 1st line: amoxicillin + clavulanic acid
- rabies (see Infectious Diseases, ID21)
  - reservoirs: warm-blooded animals except rodents, lagomorphs (e.g. rabbits)
  - post-exposure vaccine is effective; treatment depends on local prevalence
- suturing
  - vascular structures (i.e. face and scalp) are less likely to become infected, therefore consider suturing
  - allow avascular structures (i.e. pretibial regions, hands and feet) to heal by secondary intention
  - tetanus immunization if >10 yr or incomplete primary series
SNake bites
- History, physical exam, investigations and initial management similar to mammalian bites
- Additional management issues
  - Snake bites are rarely fatal but proper precautions must be taken
  - Supportive management, observe for compartment syndrome, analgesia, tetanus prophylaxis
  - Contact Provincial Poison Information Centre for consultation
  - For the Massasauga Rattle Snake ONLY: if no signs of local tissue damage and an INR is normal at 6 h after the bite, the patient may be discharged
  - There is NO evidence that constriction bands are helpful and can be harmful
  - If envenomation present, administer antivenom as directed by local Poison Information Centre

Insect bites
- Bee stings
  - 5 types of reactions to stings (local, large local, systemic, toxic, unusual)
  - History and physical exam key to diagnosis; no lab test will confirm
  - Investigations: CBC, electrolytes, BUN, creatinine, glucose, ABGs, ECG
  - ABC management, epinephrine 0.1 mg IV over 5 min if shock, antihistamines, cimetidine 300 mg IV/IM/PO, steroids, β-agonists for SOB/wheezing 3 mg in 5 mL NS via nebulizer, local site management
  - West Nile virus (see Infectious Diseases, ID27)

Near Drowning
- Most common in children <4 yr and teenagers
- Causes lung damage, hypoxemia and may lead to hypoxic encephalopathy
- Must also assess for shock, C-spine injuries, hypothermia, scuba-related injuries (barotrauma, air emboli, lung re-expansion injury)
- Complications: volume shifts, electrolyte abnormalities, hemolysis, rhabdomyolysis, renal, DIC

Physical Examination
- ABCs, vitals: watch closely for hypotension
- Lungs: rales (ARDS, pulmonary edema), decreased breath sounds (pneumothorax)
- CVS: murmurs, dysrhythmias, JVP (CHF, pneumothorax)
- H&N: assess for C-spine injuries
- Neuro: GCS or AVPU, pupils, focal deficits

Investigations
- Labs: CBC, electrolytes, ABGs, Cr, BUN, urinalysis
- Imaging: CXR (pulmonary edema, pneumothorax)
- ECG

Management
- ABCs, treat for trauma, shock, hypothermia
- Cardiac and O₂ saturation monitors, IV access
- Intensive respiratory care
  - Ventilator assistance if decreased respirations, pCO₂ >50 mmHg, or pO₂ <60 mmHg on maximum O₂
  - May require intubation for airway protection, ventilation, pulmonary toilet
  - High flow O₂/CPAP/BiPAP may be adequate but some may need mechanical ventilation with PEEP
- Dysrhythmias: usually respond to corrections of hypoxemia, hypothermia, acidosis
- Vomiting: very common, NG suction to avoid aspiration
- Convulsions: usually respond to O₂; if not, diazepam 5-10 mg IV slowly
- Bronchospasm: bronchodilators
- Bacterial pneumonia: not necessary to prophylax with antibiotics unless contaminated water or hot-tub (Pseudomonas)
- Must observe for at least 24 h as non-cardiogenic pulmonary edema may develop late

Disposition
- Non-significant submersion: discharge after short observation
- Significant submersion (even if asymptomatic): long period of observation (24 h) as pulmonary edema may appear late
- CNS symptoms or hypoxemia: admit
- Severe hypoxemia, decreased LOC: ICU
Toxicology

Alcohol Related Emergencies

- see also Psychiatry, PS22

Acute Intoxication

- slurred speech, CNS depression, disinhibition, lack of coordination
- nystagmus, diplopia, dysarthria, ataxia → may progress to coma
- hypotension (peripheral vasodilation)
- if obtunded rule out
  - head trauma/intracranial hemorrhage
  - associated depressants/street drugs, toxic alcohols
  - may also contribute to respiratory/cardiac depression
  - hypoglycemia (screen with bedside glucometer)
  - hepatic encephalopathy: confusion, altered LOC, coma
    - precipitating factors: GI bleed, infection, sedation, electrolyte abnormalities, protein meal
    - Wernicke's encephalopathy (ataxia, ophthalmoplegia, delirium)
    - post-ictal state, basilar stroke

Withdrawal

- beware of withdrawal signs (see Table 26)
- treatment:
  - diazepam 10-20 mg IV/PO or lorazepam 2-4 mg IV/PO q1hr until calm
    - frequency of dosing may have to be increased depending on clinical response
  - may use CIWA protocol and give benzodiazepines as above until CIWA <10
  - thiamine 100 mg IM/IV then 50-100 mg/d
  - magnesium sulfate 4 g IV over 1-2 h (if hypomagnesemic)
  - admit patients with delirium tremens (DT), or multiple seizures

<table>
<thead>
<tr>
<th>Time Since Last Drink</th>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-8 h</td>
<td>Mild withdrawal</td>
<td>Generalized tremor, anxiety, agitation, but no delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autonomic hyperactivity (sinus tachycardia), insomnia, nausea, vomiting</td>
</tr>
<tr>
<td>1-2 d</td>
<td>Alcoholic hallucinations</td>
<td>Visual (most common), auditory and tactile hallucinations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitals often normal</td>
</tr>
<tr>
<td>8 h-2 d</td>
<td>Withdrawal seizures</td>
<td>Typically brief generalized tonic-clonic seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May have several within a few hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT head if focal seizures have occurred</td>
</tr>
<tr>
<td>3-5 d</td>
<td>Delirium tremens (DT)</td>
<td>5% of untreated withdrawal patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severely confused state, fluctuating levels of consciousness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agitation, insomnia, hallucinations/delusions, tremor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachycardia, hyperpyrexia, diaphoresis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High mortality rate</td>
</tr>
</tbody>
</table>

Cardiovascular Complications

- HTN
- cardiomyopathy: SOB, edema
- dysrhythmias (“holiday heart”)
  - atrial fibrillation (most common), atrial flutter, SVT, VT (especially Torsades if hypomagnesemic/hypokalemic)

Metabolic Abnormalities

- alcoholic ketoacidosis
  - anion gap (AG) metabolic acidosis, urine ketones, low glucose and normal osmolality
  - history of chronic alcohol intake with abrupt decrease/cessation
  - malnourished, abdominal pain with nausea and vomiting
  - treatment: dextrose, thiamine (100 mg IM/IV prior to dextrose), volume repletion (with NS)
  - generally resolves in 12-24 h
- other alcohols
  - ethylene glycol → CNS, CVS, renal findings
  - methanol
    - early: lethargy, confusion
  - late: headache, visual changes, N/V, abdominal pain, tachypnea
- both produce severe metabolic acidosis with anion gap (as the alcohol is metabolized) and osmolar gap (initially after ingestion but before metabolism)

Alcohol levels correlate poorly with intoxication.

Alcohol intoxication may invalidate informed consent.

CIWA Withdrawal Symptoms

- Nausea and vomiting
- Tremor
- Paroxysmal sweats
- Anxiety
- Agitation
- Visual disturbances
- Tactile disturbances
- Auditory disturbances
- Headache
- Disorientation

10 symptoms each scored out of 7 except orientation is out of 4.

Common Deficiencies

- Thiamine
- Niacin
- Folate
- Glycogen
- Magnesium
- Potassium

Alcohol levels correlate poorly with intoxication.
• EtOH co-ingestion is protective
• treatment
  • urgent hemodialysis required
  • fomepizole 15 mg/kg IV bolus OR EtOH 10% IV bolus and infusion to achieve blood level of 22 mmol/L (EtOH loading may be done PO)
  • consider folic acid for methanol and pyridoxine and thiamine for ethylene glycol – both help reduce conversion to active metabolites
• other abnormalities associated with alcohol: hypomagnesemia, hypophosphatemia, hypocalcemia, hypoglycemia, hypokalemia

**Gastrointestinal Abnormalities**
• gastritis
  • common cause of abdominal pain and GI bleed in chronic alcohol users
• pancreatitis
  • serum amylase very unreliable in patients with chronic pancreatitis, may need serum lipase
  • hemorrhagic form (15%) associated with increased mortality
  • fluid resuscitation very important
• hepatitis
  • AST/ALT ratio >2 suggests alcohol as the cause as well as elevated GGT with acute ingestion
• peritonitis/spontaneous bacterial peritonitis
  • leukocytosis, fever, generalized abdominal pain/tenderness
  • occasionally accompanies cirrhosis
  • paracentesis for diagnosis (common pathogens: *E. coli*, *Klebsiella*, *Streptococcus*
• GI bleeds
  • most commonly gastritis or ulcers, even if patient known to have varices
  • consider Mallory-Weiss tear secondary to retching
  • often complicated by underlying coagulopathies
  • minor: treat with antacids
  • severe or recurrent: endoscopy

**Disposition**
• before patient leaves ED ensure:
  • stable vital signs, can walk unassisted, fully oriented
• offer social services to find shelter or detox program
• ensure patient can obtain any medications prescribed and can complete any necessary follow-up

---

### Approach to the Overdose Patient

#### History
• age, weight, underlying medical problems, medications
• substance and how much
• time since exposure determines prognosis and need for decontamination, symptoms since
• route
• intention, suicidality

#### Physical Examination
• focus on: ABCs, LOC/GCS, vitals, pupils

#### ABCs of Toxicology
• basic axiom of care is symptomatic and supportive treatment
• address underlying problem only once patient is stable

**A**irway (consider stabilizing the C-spine)

**B**reathing

**C**irculation

**D**rugs
  • ACLS as necessary to resuscitate the patient
  • universal antidotes

**D**raw bloods

**D**ecommodation (decrease absorption)

**E**xpose (look for specific toxidromes)/Examine the patient

**F**ull vitals, ECG monitor, Foley, x-rays

**G**ive specific antidotes and treatments

Go back and reassess

Call poison information centre

Obtain corroborative history from family, bystanders

---

### Principles of Toxicology

4 principles to consider with all ingestions:

- Resuscitation (ABCs)
- Screening (toxidrome? clinical clues?)
- Decrease absorption of drug
- Increase elimination of drug

### Suspect Overdose when:

- Altered level of consciousness/coma
- Young patient with life-threatening dysrhythmia
- Trauma patient
- Bizarre or puzzling clinical presentation
D1 – Universal Antidotes

- treatments that will not harm patients and may be essential

Dextrose (glucose)
- give to any patient presenting with altered LOC
- measure blood glucose prior to glucose administration if possible
- adults: 0.5-1.0 g/kg (1-2 mL/kg) IV of D50W
- children: 0.25 g/kg (2-4 mL/kg) IV of D25W

Oxygen
- do not deprive a hypoxic patient of oxygen no matter what the antecedent medical history (i.e. even COPD with CO2 retention)
- if depression of hypoxic drive, intubate and ventilate
- exception: paraquat or diquat (herbicides) inhalation or ingestion (oxygen radicals increase morbidity)

Naloxone (central µ-receptor competitive antagonist, shorter t½ than naltrexone)
- antidote for opioids: administration is both diagnostic and therapeutic (1 min onset of action)
- used for the undifferentiated comatose patient
- loading dose
  - adults
    - 2 mg initial bolus IV/IM/SL/SC or via ETT (ETT dose = 2-2.5x IV dose)
    - if no response after 2-3 min, increase dose by 2 mg increments until a response or to max 10 mg
    - known chronic user, suspicious history, or evidence of track marks, give 0.01 mg/kg
  - child
    - 0.01 mg/kg initial bolus IV/IO/ETT
    - 0.1 mg/kg if no response and opioid still suspected to max of 10 mg
- maintenance dose
  - may be required because half-life of naloxone (30-80 min) is much shorter than many opioids
  - hourly infusion rate at 2/3 of initial dose that produced patient arousal

Thiamine (Vitamin B1)
- 100 mg IV/IM with IV/PO glucose to all patients
- given to prevent/treat Wernicke's encephalopathy
- a necessary cofactor for glucose metabolism (may worsen Wernicke's encephalopathy if glucose given before thiamine), but do not delay glucose if thiamine unavailable
- must assume all undifferentiated comatose patients are at risk

D2 – Draw Bloods

- essential tests (see Table 28)
  - CBC, electrolytes, BUN/creatinine, glucose, INR/PTT, osmolality
  - ABGs, measure O2 sat
  - acetylsalicylic acid (ASA), acetaminophen, EtOH levels
- potentially useful tests
  - drug levels – this is NOT a serum drug screen
  - Ca2+, Mg2+, PO43–
  - protein, albumin, lactate, ketones, liver enzymes, CK – depending on drug and clinical presentation

Serum Drug Levels
- treat the patient, not the drug level
- negative toxicology screen does not rule out a toxic ingestion – signifies only that the specific drugs tested were not detectable in the specimen
- specific drugs available on general screen vary by institution; check before ordering
- urine screens also available (qualitative only)
Table 27. Toxic Gaps (see also Nephrology, NP14)

**METABOLIC ACIDOSIS**
- Increased AG: “MUDPILES CAT” (* = toxic)
- Methanol*
- Uremia
- Diabetic ketoacidosis/Starvation ketoacidosis
- Phenformin*/Paraldehyde*
- Isoniazid, Iron, Ibuprofen
- Lactate (anything that causes seizures or shock)
- Ethyleneglycol*
- Salicylates*
- Cyanide, carbon monoxide*
- Alcoholic Ketoacidosis

- Increased POG: “MAE DIE” (if it ends in “-ol”, it will likely increase the POG)
- Methanol
- Acetone
- Ethanol
- Diuretics (glycerol, mannitol, sorbitol)
- Isopropanol
- Ethylene glycol

**Decreased AG**
- Electrolyte imbalance (increased Na+/K+/Mg²⁺)
- Hypoalbuminemia (50% fall in albumin ~5.5 mmol/L decrease in the AG)
- Lithium, bromine elevation
- Paraproteins (multiple myeloma)

**Normal AG**
- High K⁺: pyelonephritis, obstructive nephropathy, renal tubular acidosis (RTA), IV, TPN
- Low K⁺: small bowel losses, acetazolamide, Renal Tubular Acidosis I, II

**Table 28. Use of the Clinical Laboratory in the Initial Diagnosis of Poisoning**

<table>
<thead>
<tr>
<th>Test</th>
<th>Finding</th>
<th>Selected Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABG</td>
<td>Hypoventilation (↑ pCO₂)</td>
<td>CNS depressants (opioids, sedative-hypnotic agents, phenothiazines, EtOH)</td>
</tr>
<tr>
<td></td>
<td>Hyperventilation (↓ pCO₂)</td>
<td>Salicylates, CO, other asphyxiants</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>↑ AGMA</td>
<td>“MUDPILES CAT”: see “Metabolic Acidosis”, ER50</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia</td>
<td>Digitalis glycosides, fluoride, potassium</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>Theophylline, caffeine, β-adrenergic agents, soluble barium salts, diuretics, insulin</td>
</tr>
<tr>
<td>Glucose</td>
<td>Hypoglycemia</td>
<td>Oral hypoglycemia agents, insulin, EtOH, ASA</td>
</tr>
<tr>
<td>Osmolality and Osmolar Gap</td>
<td>Elevated osmolar gap</td>
<td>“MAE DIE”: see “Toxic Gaps”, above</td>
</tr>
<tr>
<td>ECG</td>
<td>Wide QRS complex</td>
<td>TCAs, quinidine, other class 1A and 1C antidysrhythmic agents</td>
</tr>
<tr>
<td></td>
<td>Prolonged QT interval</td>
<td>Quinidine and related antidysrhythmics, terfenadine, astemizole, antipsychotics</td>
</tr>
<tr>
<td></td>
<td>Atrioventricular block</td>
<td>Ca²⁺ antagonists, digitalis glycosides, phenytoin/phenobarbital</td>
</tr>
<tr>
<td>Abdominal X-Ray</td>
<td>Radiopaque pills or objects</td>
<td>“CHIPES”: Calcium, Chloral hydrate, CuCl₂, Heavy metals, Iron, Potassium, Enteric coated Salicylates, and some foreign bodies</td>
</tr>
<tr>
<td>Serum Acetaminophen</td>
<td>Elevated level (&gt;140 mg/L or 1000 µmol/L, 4 h after ingestion)</td>
<td>May be only sign of acetaminophen poisoning</td>
</tr>
</tbody>
</table>

**D3 – Decontamination and Enhanced Elimination**

**Ocular Decontamination**
- saline irrigation to neutralize pH; alkali exposure requires ophthalmology consult

**Dermal Decontamination (wear protective gear)**
- remove clothing, brush off toxic agents, irrigate all external surfaces

**Gastrointestinal Decontamination**
- single dose activated charcoal (SDAC) (see Table 31 for drug toxidromes that are treated with charcoal)
  - adsorption of drug/toxin to AC prevents availability
  - contraindications: caustics, SBO, perforation
  - dose: 10 g/kg drug ingested or 1g/kg body weight
  - odourless, tasteless, prepared as slurry with H₂O
  - whole bowel irrigation
    - 500 mL/h (child) to 2000 mL/h (adult) of polyethylene glycol solution by mouth until clear effluent per rectum
    - start slow (500 mL in an adult) and aim to increase rate hourly as tolerated

**Substances NOT Adsorbed by Activated Charcoal**
- Lithium
- Iron
- Alcohols
- Lead
- Caustics

**Plasma Osmolar Gap (POG)**
= (2 Na⁺ + glucose + urea) – plasma osmolarity
“2 salts and a sugar BUN” – plasma osmolarity
Normal POG <10 mOsm/kg

**Anion Gap (AG)**
= Na⁺ – Cl⁻ – HCO₃⁻
Normal AG ≤12 mM/L
• indications
  • awake, alert, can be nursed upright OR intubated and airway protected
  • delayed release product
  • drug/toxin not bound to charcoal
  • drug packages (if any evidence of breakage → emergency surgery)
  • recent toxin ingestion
  • contraindications
    • evidence of ileus, perforation, or obstruction
  • surgical removal in extreme cases
    • indicated for drugs that are toxic, form concretions, or cannot be removed by conventional means
  • no evidence for the routine use of cathartics (i.e. ipecac)

Urine Alkalinization
• may be used for: ASA, methotrexate, phenobarbital, chlorpropamide
• weakly acidic substances can be trapped in alkali urine (pH >7.5) to increase elimination

Multidose Activated Charcoal (MDAC)
• may be used for: carbamazepine, phenobarbital, quinine, theophylline
• for toxins which undergo enterohepatic recirculation
• removes drug that has already been absorbed by drawing it back into GI tract
• various regimens: 12.5 g (1/4 bottle) PO q1h or 25 g (1/2 bottle) PO q2h until non-toxic

Hemodialysis
• indications/criteria for hemodialysis
  • toxins that have high water solubility, low protein binding, low molecular weight, adequate concentration gradient, small volume of distribution (Vd) or rapid plasma equilibration
  • removal of toxin will cause clinical improvement
  • advantage is shown over other modes of therapy
  • predicted that drug or metabolite will have toxic effects
  • impairment of normal routes of elimination (cardiac, renal, or hepatic)
  • clinical deterioration despite maximal medical support
• useful for the following toxins:
  • methanol
  • ethylene glycol
  • salicylates
  • lithium
  • phenobarbital
  • chloral hydrate (→ trichloroethanol)
• others include theophylline, carbamazepine, valproate, methotrexate

Position Paper Update: Ipecac Syrup for Gastrointestinal Decontamination
Clin Toxicol 2013;51:134-139
Study: Systematic review of 12 new studies (2003-2011) and summary of older studies (animal studies, volunteer studies, marker studies, case reports).
Conclusions: There is debate in the literature as to whether or not the use of ipecac should be completely abandoned, or whether it may remain useful in certain special circumstances. Concerns regarding the use of ipecac include the variability of its effects depending on elapsed time of administration and its interference with other treatments such as activated charcoal. Furthermore, ipecac has a number of side effects such as diarrhea, drowsiness and prolonged vomiting, as well as some rare side effects which may contribute to death. Despite these, ipecac has a high margin of safety. While routine administration of ipecac is not appropriate, it may be beneficial in certain circumstances. For example, its use may be considered when there is a substantial risk of serious toxicity, there are no contraindications (such as high risk of aspiration), no alternative treatment option exists or when the administration of ipecac will have no effect on the alternative treatment option and there can be timely delivery of ipecac (<90 min).

E – Expose and Examine the Patient
• vital signs (including temperature), skin (needle tracks, colour), mucous membranes, pupils, odours and CNS
• head-to-toe survey including
  • C-spine
  • signs of trauma, seizures (incontinence, “tongue biting”; etc.), infection (meningismus), chronic alcohol/drug abuse (track marks, nasal septum erosion)
• mental status

Table 29. Specific Toxidromes

<table>
<thead>
<tr>
<th>Toxidrome</th>
<th>Overdose Signs and Symptoms</th>
<th>Examples of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics</td>
<td>Hyperthermia</td>
<td>“Hot as a hare”</td>
</tr>
<tr>
<td></td>
<td>Dilated pupils</td>
<td>“Blind as a bat”</td>
</tr>
<tr>
<td></td>
<td>Dry skin</td>
<td>“Dry as a bone”</td>
</tr>
<tr>
<td></td>
<td>Vasostriction</td>
<td>“Red as a beet”</td>
</tr>
<tr>
<td></td>
<td>Agitation/hallucinations</td>
<td>“Mad as a hatter”</td>
</tr>
<tr>
<td></td>
<td>Ileus</td>
<td>“The bowel and bladder”</td>
</tr>
<tr>
<td></td>
<td>Urinary retention</td>
<td>lose their tone and the heart goes on alone*</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td>Belladonna alkaloids (e.g. atropine)</td>
</tr>
<tr>
<td>Cholinergics</td>
<td>“DUMBELS”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diaphoresis, Diarrhea, Decreased blood pressure, Urination, Miosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bronchospasm, Bronchorrhea, Bradycardia, Emesis, Excitation of skeletal muscle, Lacrimation, Salivation, Seizures</td>
<td>Anticholinesterases: physostigmine,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insecticides (organophosphates, carbamates)</td>
</tr>
</tbody>
</table>
Table 29. Specific Toxidromes (continued)

<table>
<thead>
<tr>
<th>Toxidrome</th>
<th>Overdose Signs and Symptoms</th>
<th>Examples of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapyramidal</td>
<td>Dysphonia, dysphagia, rigidity and tremor, motor restlessness, crawling sensation (akathisia), constant movements (dyskinesia), dystonia (muscle spasms, laryngospasm, trismus, oculogyric crisis, torticollis)</td>
<td>Major tranquilizers, antipsychotics</td>
</tr>
<tr>
<td>Hemoglobin Derangements</td>
<td>Increased respiratory rate, decreased level of consciousness, cyanosis unresponsive to O2, lactic acidosis</td>
<td>Carbon monoxide poisoning (carbon monoxide hemoglobin), drug ingestion (methemoglobin, sulfmethemoglobin)</td>
</tr>
<tr>
<td>Narcotic Opioids, Sedative/Hypnotics, EtOH</td>
<td>Hypothermia, hypotension, respiratory depression, dilated or constricted pupils (pinpoint in opioid OD), CNS depression</td>
<td>EtOH, benzodiazepines, opioids (morphine, heroin, fentanyl, etc.), barbiturates, gamma hydroxybutyrate</td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td>Increased temperature, CNS excitation (including seizures), tachycardia, hypertension, nausea and vomiting, diaphoresis, dilated pupils</td>
<td>Amphetamines, caffeine, cocaine, LSD, phenylcyclidine, ephedrine and other decongestants, thyroid hormone, sedative or EtOH withdrawal</td>
</tr>
<tr>
<td>Serotonin Syndrome</td>
<td>Mental status changes, autonomic hyperactivity, neuromuscular abnormalities, hyperthermia, diarrhea, HTN</td>
<td>MAOI, TCA, SSRI, opioid analgesics, cough medicine, weight reduction medications</td>
</tr>
</tbody>
</table>

Note: ASA poisoning and hypoglycemia mimic sympathomimetic toxidrome

F – Full Vitals, ECG Monitor, Foley, X-rays

G – Give Specific Antidotes and Treatments

Urine Alkalization Treatment for ASA Overdose
- urine pH >7.5
- fluid resuscitate first, then 3 amps NaHCO3/litre of D5W @ 1.5 x maintenance
- add 20-40 mEq KCl/litre if patient is able to urinate

Table 30. Protocol for Warfarin Overdose

<table>
<thead>
<tr>
<th>INR</th>
<th>Management: Consider Prothrombin Complex Concentrate (PCC) (Octaplex®, Beriplex®) for any elevated INR, AND either life-threatening bleeding or a plan for the patient to undergo a surgical procedure within the next 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5.0</td>
<td>Cessation of warfarin administration, observation, serial INR/PT</td>
</tr>
<tr>
<td>5.1–9.0</td>
<td>If no risk factors for bleeding, hold warfarin x 1-2 d and reduce maintenance dose OR Vitamin K 1-2 mg PO if patient at increased risk of bleeding</td>
</tr>
<tr>
<td>9.1–20.0</td>
<td>Hold warfarin, vitamin K 2-4 mg PO, serial INR/PT, additional vitamin K if necessary</td>
</tr>
<tr>
<td>&gt;20.0</td>
<td>Hold warfarin, vitamin K 10 mg IV over 10 min, increase vitamin K dosing (q4h) if needed</td>
</tr>
</tbody>
</table>

Table 31. Specific Antidotes and Treatments for Common Toxins – call local poison information centre for specific doses and treatment recommendations

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Treatment</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Decontaminate (SDAC) N-acetylcysteine</td>
<td>Often clinically silent; evidence of liver/renal damage delayed &gt;24 h Toxic dose &gt;200 mg/kg (&gt;7.5 g adult) Monitor drug level 4 h post-ingestion; also liver enzymes, INR, PT, BUN, Cr Hypoglycemia, metabolic acidosis, encephalopathy → poor prognosis</td>
</tr>
<tr>
<td>Acute Dystonic Reaction</td>
<td>Benztropine: 1-2 mg IM/IV then 2 mg PO x 3 d OR Diphenhydramine 1-2 mg/kg IV then 25 mg PO qid x 3 d</td>
<td>Benztropine (Cogentin®) has euphoric effect and potential for abuse</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Decontaminate (SDAC) Supportive care</td>
<td>Special antidotes available. Consult Poison Information Centre (PIC)</td>
</tr>
</tbody>
</table>
Table 31. Specific Antidotes and Treatments for Common Toxins – (continued)
call local poison information centre for specific doses and treatment recommendations

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Treatment</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>Decontaminate (SDAC)</td>
<td>Monitor serum pH and drug levels closely</td>
</tr>
<tr>
<td></td>
<td>Alkalize urine; want urine pH &gt; 7.5</td>
<td>Monitor K⁺ level; may require supplement for urine alkalination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemodialysis may be needed if intractable metabolic acidosis, very high levels, or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>end-organ damage (i.e. unable to diurese)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Decontaminate (SDAC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flumazenil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Supportive care</td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>Decontaminate (SDAC)</td>
<td>Consult PIC</td>
</tr>
<tr>
<td></td>
<td>Consider high dose insulin euglycemia therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(HDE) Some dialyzable, some use intralipids</td>
<td></td>
</tr>
<tr>
<td>Calcium Channel</td>
<td>Decontaminate (SDAC)</td>
<td>Order ECG, electrolytes (especially Ca²⁺, Mg²⁺, Na⁺, K⁺)</td>
</tr>
<tr>
<td>Blockers</td>
<td>CaCl₂ 1-4 g of 10% sol'n IV if hypotensive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other: HDE inotropes or intralipids</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>Decontaminate (SDAC) if oral</td>
<td>β-blockers are contraindicated in acute cocaine toxicity</td>
</tr>
<tr>
<td></td>
<td>Aggressive supportive care</td>
<td>Intrapid for life-threatening symptoms</td>
</tr>
<tr>
<td>CO Poisoning</td>
<td>See ER46</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Supportive care</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100% O₂</td>
<td></td>
</tr>
<tr>
<td>Cyanide</td>
<td>Hydroxocobalamin</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>Decontaminate (SDAC)</td>
<td>Use for life-threatening dysrhythmias unresponsive to conventional therapy</td>
</tr>
<tr>
<td></td>
<td>Digoxin-specific Ab fragments</td>
<td>6 h serum digoxin &gt; 12 nmol/L, initial K⁺ &gt; 5 mM, ingestion</td>
</tr>
<tr>
<td></td>
<td>10-20 vials IV if acute; 3-6 if chronic</td>
<td>&gt;10 mg (adult) / &gt;4 mg (child)</td>
</tr>
<tr>
<td></td>
<td>1 vial (40 mg) neutralizes 0.5 mg of toxin</td>
<td>Common dysrhythmias include VFib, VTach, and conduction blocks</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Thiamine 100 mg IM/IV</td>
<td>Hypoglycemia very common in children</td>
</tr>
<tr>
<td></td>
<td>Manage airway and circulatory support</td>
<td>Mouthwash = 70% EtOH; perfumes and colognes = 40-60% EtOH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider hemodialysis</td>
</tr>
<tr>
<td>Ethylene Glycol/</td>
<td>Fomepizole (4-methylpyrazole)</td>
<td>CBC, electrolytes, glucose, ethanol level</td>
</tr>
<tr>
<td>Methanol</td>
<td>15 mg/kg IV load over 30 min, then 10 mg/kg q12h OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethanol (10%) 10 mL/kg over 30 min, then 1.5 mL/h</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>Protamine sulfate 25-50 mg IV</td>
<td>For unfractionated heparin overdose only</td>
</tr>
<tr>
<td>Insulin IM/SG/</td>
<td>Glucose IV/PO/NG tube</td>
<td>Glyburide carries highest risk of hypoglycemia among oral agents</td>
</tr>
<tr>
<td>Oral Hypoglycemic</td>
<td>Glucagon: 1-2 mg IM (if no access to glucose)</td>
<td>Consider octreotide for oral hypoglycemics (50-100 μg SC q6h) in these cases; consult local PIC</td>
</tr>
<tr>
<td>MDMA</td>
<td>Decontaminate (SDAC), supportive care</td>
<td>Monitor CK; treat rhabdomyolysis with high flow fluids: aggressive external cooling for hyperthermia</td>
</tr>
<tr>
<td>Opioids</td>
<td>See Universal antidotes</td>
<td></td>
</tr>
<tr>
<td>TCAs</td>
<td>Decontaminate (SDAC)</td>
<td>Rumazenil antidote contraindicated in combined TCA and benzodiazepine overdose</td>
</tr>
<tr>
<td></td>
<td>Aggressive supportive care</td>
<td>Also consider cardiac and hypotension support, seizure control</td>
</tr>
<tr>
<td></td>
<td>NaHCO₃ bolus for wide QRS/seizures</td>
<td>Intralipid therapy (consult local PIC)</td>
</tr>
</tbody>
</table>

Disposition from the Emergency Department

- methanol, ethylene glycol
  - delayed onset, admit and watch clinical and biochemical markers
- TCAs
  - prolonged/delayed cardiotoxicity warrants admission to monitored (ICU) bed
  - if asymptomatic and no clinical signs of intoxication: 6 h ED observation adequate with proper decontamination and no ECG abnormalities
  - sinus tachycardia alone (most common finding) with history of OD warrants observation in ED
- hydrocarbons/smoke inhalation
  - pneumonitis may lag 6-8 h
  - consider observation for repeated clinical and radiographic examination
- ASA, acetaminophen
  - if borderline level, get second level 2-4 h after first
  - for ASA must have at least 2 levels going down before discharge (3 levels minimum)
- oral hypoglycemics
  - admit all patients for minimum 24 h if hypoglycemic and 12 h after last octreotide dose
  - observe asymptomatic patient for at least 8 h

Psychiatric Consultation

- once patient medically cleared, arrange psychiatric intervention if required
- beware – suicidal ideation may not be expressed
Psychiatric Emergencies

Approach to Common Psychiatric Presentations

- see also Psychiatry, PS2
- before seeing patient, ensure your own safety; have security/police available if necessary

**History**

- safety
  - assess suicidality: suicidal ideation (SI), intent, plan, lethal means, past attempts
  - assess homicidality: homicidal ideation (HI), access to weapons, intended victim, history of violence
  - driving and children
  - command hallucinations
- identify current stressors and coping strategies
- mood symptoms: manic, depressive
- anxiety: panic attacks, generalized anxiety, phobias, OCD, PTSD
- psychotic symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behaviour, negative symptoms (affective flattening, alogia, avolition)
- substance use history: most recent use, amount, previous withdrawal reactions
- past psychiatric history, medications, adherence with medications
- medical history: obtain collateral if available

**Physical**

- complete physical exam focusing on: vitals, neurological exam, signs of head trauma, signs of drug toxicity, signs of metabolic disorder
- mental status exam: general appearance, behavior, cooperation, speech, mood and affect, thought content and form, perceptual disturbances, cognition (including MMSE if indicated), judgment, insight, reliability

**Investigations**

- investigations vary with: age, established psychiatric diagnosis vs. first presentation, history and physical suggestive of organic cause
- as indicated: blood glucose, urine and serum toxicology screen, pregnancy test, electrolytes, TSH, AST/ALT, bilirubin, serum creatinine, BUN, osmolality
- blood levels of psychiatric medications
- CT head if suspect neurological etiology
- LP if indicated

**Acute Psychosis**

**Differential Diagnosis**

- primary psychotic disorder (e.g. schizophrenia)
- secondary to medical condition (e.g. delirium)
- drugs: substance intoxication or withdrawal, medications (e.g. steroids, anticholinergics)
- infectious (CNS)
- metabolic (hypoglycemic, hepatic, renal, thyroid)
- structural (hemorrhage, neoplasm)

**Management**

- violence prevention
  - remain calm, empathic and reassuring
  - ensure safety of staff and patients, have extra staff and/or security on hand
  - patients demonstrating escalating agitation or overt violent behavior may require physical restraint and/or chemical tranquilization (see Violent Patient, ER56)
- treat agitation: whenever possible, offer medication to patients as opposed to administering with force (helps calm and engage patient)
  - benzodiazepines: lorazepam 2 mg PO, IM or SL
  - antipsychotics: olanzapine 5 mg PO, haloperidol 5 mg PO/IM
- treat underlying medical condition
- psychiatry or Crisis Intervention Team consult
**Suicidal Patient**

**Epidemiology**
- attempted suicide F>M, completed suicide M>F
- second leading cause of death in people <24 yr

**Management**
- ensure patient safety: close observation, remove potentially dangerous objects from person and room
- assess thoughts (ideation), means, action (preparatory, practice attempts), previous attempts
- admit if there is evidence of intent and organized plan, access to lethal means, psychiatric disorder, intoxication (suicidal ideation may resolve with few days of abstinence)
- patient may require certification if unwilling to stay voluntarily
- do not start long-term medications in the emergency department
- psychiatry or crisis team consult

**Violent Patient**

**Differential Diagnosis**
- rule out lethal organic cause (e.g. EtOH, drugs, and head injuries)

**Prevention**
- be aware and look for prodromal signs of violence: anxiety, restlessness, defensiveness, verbal attacks
- try to de-escalate the situation: address the patient’s anger, empathize

**Restraints**
- pharmacological
  - often necessary – may mask clinical findings and impair exam
  - haloperidol 5-10 mg IM (be prepared for dystonic reactions, especially with multiple doses of neuroleptics over a short period) + lorazepam 2 mg IM/IV
  - look for signs of anticholinergic overdose first (see Table 29)
  - benzodiazepines best option if suspected substance-induced violence
- physical
  - present option to patient in firm but non-hostile manner
  - sufficient people to carry it out safely
  - restrain supine or on side; preferably 4-point restraints, never less than 2-points (opposite arm and leg)
  - suction and airway support available in case of vomiting
  - once restrained, search person/clothing for drugs and weapons

**Modified Pediatric ER Presentations**

**Table 32. Modified GCS**

<table>
<thead>
<tr>
<th>Modified GCS for Infants</th>
<th>Modified GCS for Children &lt;4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye Opening</strong></td>
<td><strong>Verbal Response</strong></td>
</tr>
<tr>
<td>4 – spontaneously</td>
<td>5 – coos, babbles</td>
</tr>
<tr>
<td>3 – to speech</td>
<td>4 – inratable cry</td>
</tr>
<tr>
<td>2 – to pain</td>
<td>3 – cries to pain</td>
</tr>
<tr>
<td>1 – no response</td>
<td>2 – moans to pain</td>
</tr>
<tr>
<td></td>
<td>1 – no response</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Modified GCS for Infants**

<table>
<thead>
<tr>
<th>Modified GCS for Children &lt;4 years</th>
<th><strong>Verbal Response</strong></th>
<th><strong>Motor Response</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye Opening</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 – spontaneously</td>
<td>5 – oriented, social, speaks, interacts</td>
<td>6 – normal, spontaneous movement</td>
</tr>
<tr>
<td>3 – to speech</td>
<td>4 – confused speech, disoriented, consolable</td>
<td>5 – localizes paim</td>
</tr>
<tr>
<td>2 – to pain</td>
<td>3 – inappropriate words, not consolable/aware</td>
<td>4 – withdraws to pain</td>
</tr>
<tr>
<td>1 – no response</td>
<td>2 – incomprehensible, agitated, restless, not aware</td>
<td>3 – decorticate flexion</td>
</tr>
<tr>
<td></td>
<td>1 – no response</td>
<td>2 – decerebrate flexion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 – no response</td>
</tr>
</tbody>
</table>
Respiratory Distress

- see also Pediatrics, P92

History and Physical Examination
- infants not able to feed, older children not able to speak in full sentences
- anxious, irritable, lethargic – may indicate hypoxia
- tachypnea >60 (>40 if preschool age, >30 if school age), retractions, tracheal tug
  - see Pediatrics Table 1, P3 for age specific vital signs
- pulsus paradoxus
- wheezing, grunting, vomiting

<table>
<thead>
<tr>
<th>Table 33. Stridorous Upper Airway Diseases: Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature</td>
</tr>
<tr>
<td>Age Range (yr)</td>
</tr>
<tr>
<td>Prodrome</td>
</tr>
<tr>
<td>Temperature</td>
</tr>
<tr>
<td>Radiography</td>
</tr>
<tr>
<td>Etiology</td>
</tr>
<tr>
<td>Barky Cough</td>
</tr>
<tr>
<td>Drooling</td>
</tr>
<tr>
<td>Appear Toxic</td>
</tr>
<tr>
<td>Intubation/ICU</td>
</tr>
<tr>
<td>Antibiotics</td>
</tr>
<tr>
<td>NOTE: Oral exam</td>
</tr>
</tbody>
</table>

¹Now rare with Hib vaccine in common use

Management
- croup (usually laryngotracheitis caused by parainfluenza viruses)
  - humidified O₂ should not be given (no evidence for efficacy)
  - racemic epinephrine q1h x 3 doses, observe for ‘rebound effects’ nebulized 1:1000 epi (racemic has limited availability)
  - dexamethasone x 1 dose
  - consider bacterial tracheitis/epiglottitis if unresponsive to croup therapy
- bacterial tracheitis
  - start croup therapy, but may have poor response
  - usually require intubation, ENT consult, ICU
  - start antibiotics (e.g. cloxacillin), pending C&S
- epiglottitis
  - 4 Ds: drooling, dyspnea, dysphagia, dysphonia + tripod sitting
  - do not examine oropharynx or agitate patient
  - immediate anesthesia, ENT call – intubate
  - then IV fluids, antibiotics, blood cultures
- asthma
  - supplemental O₂ if saturation <90% or PaO₂ <60%
  - bronchodilator therapy: salbutamol (Ventolin®) 0.15 mg/kg by masks q20min x 3
  - add 250-500 µg ipratropium (Atrovent®) to first 3 doses salbutamol
  - give corticosteroid therapy as soon as possible after arrival (prednisolone 2 mg/kg, dexamethasone 0.3 mg/kg)
  - if critically ill, not responding to inhaled bronchodilators or steroids: give IV bolus, then infusion of MgSO₄
  - IV β₂-agonists if critically ill and not responding to above

Admission Criteria for Croup
- Stridor at rest or significant respiratory distress
- Relapse after 2 doses of epinephrine or incomplete response
- Co-morbid respiratory or underlying condition

Admission Criteria for Asthma
- Respiratory distress 6 h after steroids
- Ventolin required >q3h
- Need for supplemental oxygen
- Consider if previous ICU admission
- Significant fatigue or lethargy
Febrile Infant and Febrile Seizures

**FEBRILE INFANT**
- see also Pediatrics, P54
- for fever >38°C without obvious focus
  - <28 d
    - admit
    - full septic work up (CBC and differential, blood C&S, urine C&S, LP ± stool C&S, CXR if indicated)
    - treat empirically with broad spectrum IV antibiotics
  - 28-90 d
    - as above unless infant meets Rochester criteria (see sidebar), investigate as indicated by history and physical
  - >90 d
    - toxic: admit, treat, full septic workup
    - non-toxic and no focus: investigate as indicated by history and physical

**FEBRILE SEIZURES**
- see also Pediatrics, P87

**Etiology**
- children aged 6 mo to 6 yr with fever or history of recent fever
- simple vs. complex febrile seizures
- normal neurological exam afterward
- no evidence of intracranial infection or history of previous non-febrile seizures
- often positive family history of febrile seizures
- relatively well looking after seizure

**Investigations and Management**
- if it is a febrile seizure: treat fever and look for source of fever
- if not a febrile seizure: treat seizure and look for source of seizure
- ± EEG (especially if first seizure), head U/S (if fontanelle open)

Table 34. Simple vs. Complex Febrile Seizures

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Simple</th>
<th>Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>&lt;15 min</td>
<td>&gt;15 min</td>
</tr>
<tr>
<td>Type of Seizure</td>
<td>Generalized</td>
<td>Focal features</td>
</tr>
<tr>
<td>Frequency</td>
<td>1 in 24 h</td>
<td>&gt;1 in 24 h</td>
</tr>
</tbody>
</table>

Abdominal Pain

- see also Pediatrics, P38

**History**
- nature of pain, associated fever
- associated GI, GU symptoms
- anorexia, decreased fluid intake

**Physical Examination**
- HEENT, respiratory, abdominal exam including DRE, testicular/genital exam

Table 35. Differential Diagnosis of Abdominal Pain in Infants/Children/Adolescents

<table>
<thead>
<tr>
<th>Medical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colic</td>
<td>Malrotation with volvulus</td>
</tr>
<tr>
<td>UTI</td>
<td>Hirschsprung’s disease</td>
</tr>
<tr>
<td>Constipation</td>
<td>Necrotizing enterocolitis</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>Incarcerated hernia</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Intussusception</td>
</tr>
<tr>
<td>HSP (Henoch Schonlein purpura)</td>
<td>Duodenal atresia</td>
</tr>
<tr>
<td>Inflammatory Bowel Disease</td>
<td>Appendicitis</td>
</tr>
<tr>
<td>HUS (Hemolytic Uremic Syndrome)</td>
<td>Cholecystitis</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Strep Throat</td>
<td>Testicular torsion</td>
</tr>
<tr>
<td>SCID crisis</td>
<td>Ectopic pregnancy</td>
</tr>
<tr>
<td>DKA</td>
<td>Trauma</td>
</tr>
<tr>
<td>Functional</td>
<td>Pyloric stenosis</td>
</tr>
</tbody>
</table>

*Remember to keep an index of suspicion for child abuse

<table>
<thead>
<tr>
<th>Red Flags for Abdominal Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Significant weight loss or growth retardation (need growth chart)</em></td>
</tr>
<tr>
<td><em>Fever</em></td>
</tr>
<tr>
<td><em>Joint pain with objective physical findings</em></td>
</tr>
<tr>
<td><em>Rash</em></td>
</tr>
<tr>
<td><em>Rectal bleeding</em></td>
</tr>
<tr>
<td><em>Rebound tenderness and radiation of pain to back, shoulders or legs</em></td>
</tr>
<tr>
<td><em>Pain wakes from sleep</em></td>
</tr>
<tr>
<td><em>Severe diarrhea and encopresis</em></td>
</tr>
</tbody>
</table>
**Common Infections**

- see also *Pediatrics*, P58

Table 36. Antibiotic Treatment of Pediatric Bacterial Infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Pathogens</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MENINGITIS SEPSIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal</td>
<td>GBS, E.coli, Listeria, Gram-negative bacilli</td>
<td>ampicillin + cefotaxime</td>
</tr>
<tr>
<td>1-3 mo</td>
<td>Same pathogens as above and below</td>
<td>ampicillin + cefotaxime + vancomycin</td>
</tr>
<tr>
<td>&gt;3 mo</td>
<td>S. pneumonia, H. influenzae type b (&gt;5 yr), meningococcus</td>
<td>ceftriaxone + vancomycin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>OTITIS MEDIA</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line</td>
<td>S. pneumoniae, H. influenzae type b, M. Catarrhalis</td>
<td>amoxicillin 80-90 mg/kg per day</td>
</tr>
<tr>
<td>2nd line</td>
<td>clarithromycin 15 mg/kg/d bid (for penicillin allergy)</td>
<td></td>
</tr>
<tr>
<td>Treatment failure</td>
<td>90 mg/kg/d amoxicillin and 6.4 mg/kg/d clavulanate divided into bid dosage</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>STREP PHARYNGITIS</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A β-hemolytic Streptococcus</td>
<td>penicillin/amoxicillin or erythromycin (penicillin allergy)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>UTI</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli, Proteus, H. influenzae, Pseudomonas, S. saprophyticus, Enterococcus, GBS</td>
<td>Oral: cephalexin (older children) IV: ampicillin and aminoglycoside</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PNEUMONIA</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 mo</td>
<td>Viral, S. pneumoniae, C. trachomatis, B. pertussis, S. aureus, H. influenzae</td>
<td>cefuroxime ± macrolide (erythromycin) OR ampicillin ± macrolide</td>
</tr>
<tr>
<td>3 mo-5 yr</td>
<td>Viral, S. pneumoniae, S. aureus, H. influenzae, Mycoplasma pneumoniae</td>
<td>amoxicillin/amoxicillin or cefuroxime</td>
</tr>
<tr>
<td>&gt;5 yr</td>
<td>As above</td>
<td>amoxicillin/amoxicillin + macrolide or cefuroxime + macrolide</td>
</tr>
</tbody>
</table>

**Child Abuse and Neglect**

- see also *Pediatrics*, P14
- obligation to report any suspected/known case of child abuse or neglect to CAS yourself (do not delegate)
- document injuries
- consider skeletal survey x-rays (especially in non-ambulatory child), ophthalmology consult, CT head
- injury patterns associated with child abuse
  - head injuries: torn frenulum, dental injuries, bilateral black eyes, traumatic hair loss, diffuse severe CNS injury, retinal hemorrhage
  - Shaken Baby Syndrome: diffuse brain injury, subdural/subarachnoid hemorrhage, retinal hemorrhage, minimal/no evidence of external trauma, associated bony fractures
  - skin injuries: bites, bruises/burns in shape of an object, glove/stocking distribution of burns, bruises of various ages, bruises in protected areas
  - bone injuries: rib fractures without major trauma, femur fractures age <1 yr of age, spiral fractures of long bones in non-ambulatory children, metaphyseal fractures in infants, multiple fractures of various ages, complex/multiple skull fractures
  - genitourinary/gastrointestinal injuries: chronic abdominal/perineal pain, injury to genitals/rectum, STI/pregnancy, recurrent vomiting or diarrhea

**Presentation of Neglect**

- Failure to thrive, developmental delay
- Inadequate or dirty clothing, poor hygiene
- Child exhibits poor attachment to parents
**Procedural Sedation**

- Procedural sedation: the technique of sedative or dissociative agent administration with or without analgesics to induce a state that allows a patient to tolerate an unpleasant or painful procedure while maintaining all protective cardiorespiratory functions (i.e. a depressed level of consciousness without loss of a patient’s protective airway reflexes).
  - must weigh degree of pain and expected relief versus risk/complications of sedation and procedure

**Requirements for Safe Procedural Sedation in the Emergency Department**

- Airway suitable for safe intubation and ventilation
- Appropriate equipment/personnel available
- Intact and functioning cardiorespiratory and neurological system
- Ideally, NPO for minimum 4-6 h
- Anesthetic history and drug allergies, including manifestations
- Appropriate IV access, monitoring (oxygen saturation, BP, HR, etc.)
- Informed consent obtained

**Common Procedural Sedation Medications (titrate to effect)**

- See Common Medications, below

**Common Medications**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>325-650 mg PO q4-6h prn</td>
<td>Pain control</td>
<td>Max 4 g daily</td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>30-100 g PO in 250 mL H2O</td>
<td>Poisoning/overdose</td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>325-650 mg PO q4h max 4g/d stroke/MI risk: 81-325 mg PO OD 160 mg chewed</td>
<td>Pain control</td>
<td>Cardiac prevention</td>
</tr>
<tr>
<td>β-blockers (metoprolol)</td>
<td>5 mg slow IV q5min x 3 if no contraindications</td>
<td>Acute MI</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>anxiety: 2-10 mg PO tid/qid alcohol withdrawal: 10-20 mg PO/IV q1h titrated to signs/symptoms</td>
<td>Anxiety</td>
<td>Alcohol withdrawal</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1 mg/kg SC bid</td>
<td>Acute MI</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>anaphylaxis: 0.1-0.5 mg IM; can repeat q10-15min</td>
<td>Anaphylaxis</td>
<td>Max 1 mg/dose</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.5-1.0 µg/kg IV</td>
<td>Procedural sedation</td>
<td>Very short acting narcotic (complication = apnea)</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>0.3 mg IV bolus q5min x 3doses</td>
<td>Reversal of procedural sedation</td>
<td>Benzodiazepine antagonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NB don’t use in chronic benzodiazepine user</td>
</tr>
<tr>
<td>Furosemide (Lasix®)</td>
<td>CHF: 40-80 mg IV HTN: 10-40 mg PO bid</td>
<td>Monitor for electrolyte imbalances</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>0.5-1.0 g/kg (1-2 mL/kg) IV of D50W</td>
<td>Hypoglycemia/DKA</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2.5-5.0 mg PO/IM initial effective dose 6-20 mg/d</td>
<td>Psychosis</td>
<td>Monitor with Parkinson’s; results in CNS depression</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>200-800 mg PO tid pm max 1200 mg/d</td>
<td>Mild to moderate acute pain Analgesia and anti-inflammatory properties</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>bolus 5-10 U (0.2 U/kg) then 5-10 U (0.1 U/kg) per hour</td>
<td>Hyperglycemia</td>
<td>Monitor blood glucose levels Consider K+ replacement, also measure blood glucose levels before administration</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>2-3 puffs inhaled tid-qid, max 12 puffs/d</td>
<td>Asthma</td>
<td>Contraindicated with peanut/soy allergy Caution with narrow-angle glaucoma</td>
</tr>
<tr>
<td>Lidocaine with epi</td>
<td>max 7 mg/kg SC</td>
<td>Local anesthetic</td>
<td>Not to be used in fingers, nose, toes, penis, ears</td>
</tr>
<tr>
<td>Lidocaine w/o epi</td>
<td>max 5 mg/kg SC</td>
<td>Local anesthetic</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>anxiety: 0.5-2 mg PO/IM/IV q6-8h status epilepticus; 4 mg IV repeat up to q6min</td>
<td>Anxiety</td>
<td>Status epilepticus</td>
</tr>
<tr>
<td>Midazolam</td>
<td>50 µg/kg IV</td>
<td>Procedural sedation</td>
<td>Short acting benzodiazepine (complication = apnea when used with narcotic) Fentanyl and midazolam often used together for procedural sedation</td>
</tr>
</tbody>
</table>

**Examples that may Require Sedation**

- Setting fractures
- Reducing dislocations
- Draining abscesses
- Exploring wounds/ulcers/superficial infections
- Endoscopic examination
- May also be required to reduce patient agitation if imaging is acutely required
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>15-30 mg PO q8-12h&lt;br&gt;0.1-0.2 mg/kg max 15 mg IV q4h</td>
<td>Mild to moderate acute/chronic pain&lt;br&gt;Prescribed in combination with NSAIDs or acetaminophen</td>
<td>GI and constipation side effects&lt;br&gt;DO NOT CRUSH, CUT or CHEW</td>
</tr>
<tr>
<td>Naloxone</td>
<td>0.5-2 mg or 0.01-0.02 mg/kg initial bolus IV/IM/SL/SC or via ETT (2-2.5x IV dose), increase dose by 2 mg until response/max 10 mg</td>
<td>Comatose patient&lt;br&gt;Opioid overdose&lt;br&gt;Reversal in procedural sedation</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>acute angina: 0.3-0.6 mg SL q5min, OR 5 µg/min IV increasing by 5-20 µg/min q3-5min</td>
<td>Angina&lt;br&gt;Acute MI</td>
<td>Not to be used with other anti-hypertensives&lt;br&gt;Not in RV MI</td>
</tr>
<tr>
<td>Percocet 10/325™</td>
<td>1-2 tabs PO q6h pm</td>
<td>Moderate pain control&lt;br&gt;Oxycodone + acetaminophen</td>
<td>Max 4 g acetaminophen daily</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Status epilepticus: see Table 14</td>
<td>Status epilepticus</td>
<td>Begin maintenance dose 12 h after loading dose&lt;br&gt;Continuous ECG, BP monitoring mandatory</td>
</tr>
<tr>
<td>Polysporin®</td>
<td>Apply to affected area bid-tid</td>
<td>Superficial infections</td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>0.25-1 mg/kg IV</td>
<td>Procedural sedation</td>
<td>Short acting&lt;br&gt;Anesthetic/sedative (complication = apnea, decreased BP)</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>2 puffs inhaled q4-6h (4 yr) max 12 puffs/d</td>
<td>Asthma</td>
<td>Caution with cardiac abnormalities</td>
</tr>
<tr>
<td>Thiamine</td>
<td>Wernicke’s encephalopathy: 100 mg IV/IM initially then 50-100 mg IM/IV OD PO x 3d</td>
<td>To treat/prevent Wernicke’s encephalopathy</td>
<td>Caution use in pregnancy</td>
</tr>
<tr>
<td>Tylenol #3®</td>
<td>1-2 tabs PO q4-6h pm</td>
<td>Pain control</td>
<td>Max 4 g acetaminophen daily</td>
</tr>
</tbody>
</table>

**References**

**Books**

**Journal Articles**
# Acronyms

- ACTH: Adrenocorticotropic Hormone
- ADH: Antidiuretic Hormone
- DM: Diabetes Mellitus
- CAD: Coronary Artery Disease
- DM: Graves' Disease
- FSH: Follicle Stimulating Hormone
- GH: Growth Hormone
- PRL: Prolactin
- TSH: Thyroid Stimulating Hormone
- ADHD: Attention Deficit Hyperactivity Disorder

## Basic Anatomy Review

- Major Endocrine Organs

## Dyslipidemias

- Overview of Lipid Transport
- Hypercholesterolemia
- Hypertriglyceridemia (Elevated TG)
- Combined Hyperlipidemia
- Dyslipidemia and the Risk for CAD
- Treatment of Dyslipidemias

## Disorders of Glucose Metabolism

- Overview of Glucose Regulation
- Pre-Diabetes
- Diabetes Mellitus (DM)
- Treatment of Diabetes
- Acute Complications
- Macrovascular Complications
- Microvascular Complications
- Other Complications
- Hypoglycemia
- Metabolic Syndrome

## Pituitary Gland

- Pituitary Hormones
- Growth Hormone (GH)
- Prolactin (PRL)
- Thyroid Stimulating Hormone (TSH)
- Adrenocorticotropic Hormone (ACTH)
- Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH)
- Antidiuretic Hormone (ADH)
- Pituitary Pathology

## Thyroid

- Thyroid Hormones
- Tests of Thyroid Function and Structure
- Thyrotoxicosis
- Graves’ Disease
- Subacute Thyroiditis
- Toxic Adenoma/Toxic Multinodular Goitre
- Thyrotoxic Crisis/Thyroid Storm
- Hypothyroidism
- Hashimoto’s Thyroiditis
- Myxedema Coma
- Sick Euthyroid Syndrome (SES)
- Non-Toxic Goitre
- Thyroid Nodules
- Thyroid Malignancies

## Adrenal Cortex

- Adrenocorticotropic Hormone (ACTH)
- Adrenocortical Hormones
- Adrenocortical Functional Work-Up
- Mineralocorticoid Excess Syndromes
- Cushing’s Syndrome
- Congenital Adrenal Hyperplasia
- Hyperandrogenism
- Adrenocortical Insufficiency

## Adrenal Medulla

- Catecholamine Metabolism
- Pheochromocytoma

## Disorders of Multiple Endocrine Glands

- Multiple Endocrine Neoplasm (MEN)

## Calcium Homeostasis

- Hypercalcemia
- Hypocalcemia
- Hyperphosphatemia
- Hypophosphotemia
- Hypermagnesemia
- Hypomagnesemia

## Metabolic Bone Disease

- Osteoporosis
- Osteomalacia and Rickets
- Renal Osteodystrophy
- Paget’s Disease of Bone

## Male Reproductive Endocrinology

- Androgen Regulation
- Tests of Testicular Function
- Hypogonadism and Infertility
- Erectile Dysfunction
- Gynecomastia

## Female Reproductive Endocrinology

## Paraneoplastic Syndrome

## Common Medications

- Diabetes Medications
- Dyslipidemia Medications
- Thyroid Medications
- Metabolic Bone Disease Medications
- Adrenal Medications

## Landmark Endocrinology Trials

## References
**Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA</td>
<td>dihydroepiandrosterone</td>
</tr>
<tr>
<td>HDL</td>
<td>high density lipoprotein</td>
</tr>
<tr>
<td>HHS</td>
<td>hyperosmolar hyperglycemic state</td>
</tr>
<tr>
<td>PGS</td>
<td>polycystic ovarian syndrome</td>
</tr>
<tr>
<td>POAG</td>
<td>primary open-angle glaucoma</td>
</tr>
<tr>
<td>PRL</td>
<td>prolactin</td>
</tr>
<tr>
<td>PTH</td>
<td>parathyroid hormone</td>
</tr>
<tr>
<td>PTU</td>
<td>propylthiouracil</td>
</tr>
<tr>
<td>DIY</td>
<td>peripheral arterial disease</td>
</tr>
<tr>
<td>RAAS</td>
<td>renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>Hb</td>
<td>hemoglobin</td>
</tr>
<tr>
<td>GRH</td>
<td>growth hormone releasing hormone</td>
</tr>
<tr>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
</tr>
<tr>
<td>CRH</td>
<td>corticotropin releasing hormone</td>
</tr>
<tr>
<td>POMC</td>
<td>pro-opiomelanocortin</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
</tr>
<tr>
<td>CRH</td>
<td>corticotropin releasing hormone</td>
</tr>
<tr>
<td>PRL</td>
<td>prolactin</td>
</tr>
<tr>
<td>T4</td>
<td>thyroxine</td>
</tr>
<tr>
<td>CRH</td>
<td>corticotropin releasing hormone</td>
</tr>
<tr>
<td>POMC</td>
<td>pro-opiomelanocortin</td>
</tr>
</tbody>
</table>

**Major Endocrine Organs**

**HYPOTHALAMUS**
- Corticotropin-RH (CRH)
- Gonadotropin-RH (GnRH)
- Thyrotropin-RH (TRH)
- Growth hormone-RH (GHRH)
- Antidiuretic hormone (ADH)*
- Oxytocin*

**THYROID GLAND**
- Triiodothyronine (T3)
- Thyroxine (T4)

**ADRENAL GLAND**
- Cortex
- Aldosterone
- Cortisol
- Androgens
- Medulla
- Catecholamines

**PARATHYROID GLANDS**
- Parathyroid hormone (PTH)

**PITUITARY GLAND**
- Anterior pituitary
  - Growth hormone (GH)
  - Prolactin (PRL)
  - Thyroid-stimulating hormone (TSH)
  - Luteinizing hormone (LH)
  - Follicle-stimulating hormone (FSH)
  - Adrenocorticotropic hormone (ACTH)
- Posterior pituitary
  - Antidiuretic hormone (ADH)*
  - Oxytocin*

**TESTES**
- Testosterone

**OVARIES**
- Estrogen
- Progesterone

**PANCREAS**
- Insulin
- Glucagon

**GENERAL FUNCTION OF ORGANS**

The Hypothalamic-Pituitary Axis

Information about cortical inputs, automatic function, environmental cues (light, temp) and peripheral hormonal feedback is synthesized at the coordinating center of the endocrine system, the hypothalamus. The hypothalamus then sends signals to the pituitary to release hormones that affect the thyroid, adrenals, gonads, growth, milk production and water balance.

**Anatomy**

- **Function**
  - Hypothalamic hormones: small peptides, non-binding protein → rapid degradation
  - High [ ] in pituitary-portal blood system
  - Low [ ] in peripheral circulation
  - Proximity of axis preserves the pulsatile output signals from the hypothalamic neurons.

**Thyroid**

- Thyroid hormone is critical to 1) brain and somatic development in fetus and infants, 2) metabolic activity in adults, and 3) function of virtually every organ system.

**Adrenal**

- Each gland, 6-8 g, has 1) a cortex with 3 layers that act like independent organs ( zona glomerulosa → aldosterone, fasciculata → cortisol, reticularis → androgen and estrogen precursors), and 2) a medulla that acts like a sympathetic ganglion to store/synthesize adrenaline and noradrenaline.

**Gonads**

- Bilfunctional: sex steroid synthesis and gamete production.

**Overview of Lipid Transport**

- Lipoproteins are spherical complexes that consist of a lipid core surrounded by a shell of water-soluble cholesterol, apoproteins and phospholipids.
- Lipoproteins transport lipids within the body.
- Apolipoproteins serve as enzyme co-factors, promote clearance of the particle by interacting with cellular receptors and stabilize the lipoprotein micelle.

**Dyslipidemias**

Definition
- Metabolic disorders characterized by elevations of fasting plasma LDL-cholesterol, and/or triglycerides (TG), and/or low HDL-cholesterol.

Figure 1. Endocrine system

[Image of endocrine system with cellular receptors and stabilized lipoprotein micelle]
Table 1. Lipoproteins

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Apolipoproteins</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exogenous pathway</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chylomicron</td>
<td>B-48, C, E, A-I, A-II, A-IV</td>
<td>• Transports dietary TG from gut to adipose tissue and muscle</td>
</tr>
<tr>
<td><strong>Endogenous Pathway</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL</td>
<td>B-100, C, E</td>
<td>• Transports hepatic synthesized TG from liver to adipose tissue and muscle</td>
</tr>
<tr>
<td>IDL</td>
<td>B-100, E</td>
<td>• Product of hydrolysis of TG in VLDL by lipoprotein lipase resulting in depletion of TG core • Enriched in cholesterol esters</td>
</tr>
<tr>
<td>LDL</td>
<td>B-100</td>
<td>• Formed by further removal of residual TG from IDL core by hepatic lipase resulting in greater enriched particles with cholesterol esters • Transports cholesterol from liver to peripheral tissues (gonads, adrenals)</td>
</tr>
<tr>
<td>HDL</td>
<td>A-I, A-II, C, E</td>
<td>• Transports cholesterol from peripheral tissues to liver • Acts as a reservoir for apolipoproteins</td>
</tr>
</tbody>
</table>

**Figure 2. Exogenous and endogenous biosynthetic lipid pathways**

**Table 2. Primary Hypercholesterolemia**

<table>
<thead>
<tr>
<th>Hypercholesterolemia</th>
<th>Etiology/Pathophysiology</th>
<th>Labs</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Hypercholesterolemia</td>
<td>• 1/500 in U.S. population • Autosomal codominant with high penetrance • More prevalent in French Canadian population • Defect in the normal LDL receptor on cell membranes</td>
<td>↑ LDL ↑ TC</td>
<td>• Tendinous xanthomatosis (achilles, patellar, and extensor tendons of hand) • Arcus cornealis • Xanthelasmata • Heterozygotes: premature CAD, 50% risk of MI in men by age 30 • Homozygotes: manifest CAD and other vascular disease early in childhood and can be fatal (&lt;20 y) if untreated</td>
<td>• Heterozygotes: improvement of LDL with HMG CoA reductase inhibitors, often in combination with niacin or bile acid sequestrants • Homozygotes: partial control with portacaval shunt or LDL apheresis in conjunction with niacin; large dose atorvastatin is modestly effective</td>
</tr>
<tr>
<td>Polygenic Hypercholesterolemia</td>
<td>• Most common • Few mild inherited defects in cholesterol metabolism</td>
<td>↑ TC ↑ LDL</td>
<td>• Asymptomatic until vascular disease develops • No xanthomata</td>
<td>• HMG CoA reductase inhibitors, ezetimibe, niacin, bile acid sequestrant</td>
</tr>
</tbody>
</table>
SECONDARY HYPERCHOLESTEROLEMIA

Etiology
• endocrine: hypothyroidism
• renal: nephrotic syndrome
• immunologic: monoclonal gammopathy
• hepatic: cholestatic liver disease (e.g. primary biliary cirrhosis)
• nutritional: diet, anorexia nervosa
• drugs: cyclosporin, anabolic steroids, carbamazepine

Hypertriglyceridemia (Elevated TG)

PRIMARY HYPERTRIGLYCERIDEMIA

Table 3. Primary Hypertriglyceridemias

<table>
<thead>
<tr>
<th>Hypertriglyceridemia</th>
<th>Etiology/Pathophysiology</th>
<th>Labs</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Lipoprotein Lipase Deficiency</td>
<td>Autosomal recessive defect of lipoprotein lipase or its cofactor</td>
<td>↑ TG</td>
<td>Hepatosplenomegaly</td>
<td>Decrease dietary fat intake to &lt;10% of total calories</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Chylomicrons</td>
<td>Splenic infarct</td>
<td>Decrease dietary simple carbohydrates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate ↑ in</td>
<td>Anemia, granulocytopenia, thrombocytopenia</td>
<td>Cook with medium chain fatty acids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VLDL</td>
<td>2o to hypersplenism</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lipemia retinalis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Eruptive xanthomata</td>
<td></td>
</tr>
<tr>
<td>Familial Hypertriglyceridemia</td>
<td>Several genetic defects resulting in ↑ hepatic VLDL synthesis or ↓ removal of VLDL</td>
<td>↑ TG</td>
<td>Possible premature CAD</td>
<td>Decrease dietary simple carbohydrates and fat intake</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ VLDL</td>
<td>Develop syndrome of obesity, hypertyglyceridemia, hyperinsulinemia and hyperuricemia in early adulthood</td>
<td>Abstain from EtOH</td>
</tr>
</tbody>
</table>

SECONDARY HYPERTRIGLYCERIDEMIA

Etiology
• endocrine: obesity/metabolic syndrome, hypothyroidism (more for high LDL, not TG), acromegaly, Cushing’s syndrome, diabetes mellitus
• renal: chronic renal failure, polyclonal and monoclonal hypergammaglobulinemia
• hepatic: chronic liver disease, hepatitis, glycogen storage disease
• drugs: alcohol, corticosteroids, estrogen, hydrochlorothiazide, retinoic acid, β-blockers without intrinsic sympathomimetic action (ISA), anti-retroviral drugs, atypical antipsychotics, oral contraceptive pills
• other: pregnancy

Combined Hyperlipidemia

Table 4. Primary Combined Hyperlipidemias

<table>
<thead>
<tr>
<th>Hyperlipidemia</th>
<th>Etiology/Pathophysiology</th>
<th>Labs</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Combined Hyperlipidemia</td>
<td>Over-population of VLDL and associated ↑ LDL 2o to excess hepatic synthesis of apolipoprotein B</td>
<td>↑ TC + ↑ TG</td>
<td>Xanthelasma</td>
<td>Weight reduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ VLDL ↑ LDL</td>
<td>CAD and other vascular disease</td>
<td>Decrease simple carbohydrates, fat, cholesterol, and EtOH in diet</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HMG CoA reductase inhibitors (statins)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Niacin, fibrates, ezetimibe</td>
</tr>
<tr>
<td>Dysbetalipoproteinemia</td>
<td>Abnormal apolipoprotein E</td>
<td>↑ TC + ↑ TG</td>
<td>Tuberous, eruptive, palmar xanthomata</td>
<td>Weight reduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ VLDL ↑ IDL</td>
<td>Impaired glucose tolerance</td>
<td>Decrease fat, cholesterol, and EtOH in diet</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CAD and PAD</td>
<td>HMG CoA reductase inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Niacin, fibrates</td>
</tr>
</tbody>
</table>

Dyslipidemia and the Risk for CAD

• increased LDL is a major risk factor for atherosclerosis and CAD as LDL is the major atherogenic lipid particle
• increased HDL is associated with decreased cardiovascular disease and mortality
• moderate hypertriglyceridemia (triglyceride level 2.3-9 mmol/L) is an independent risk factor for CAD, especially in people with diabetes mellitus and in post-menopausal women
• treatment of hypertriglyceridemia has not been shown to reduce CAD risk
Screening
- screen men over age 40, women over age 50 or post-menopausal
- if following risk factors present, screen at any age:
  - diabetes
  - cigarette smoking
  - hypertension (sBP >140, dBP >90)
  - obesity
  - family history of premature coronary artery disease
  - clinical signs of hyperlipidemia (xanthelasma, xanthoma, arcus cornealis)
  - evidence of atherosclerosis
  - rheumatoid arthritis, SLE, psoriasis
  - HIV infection on highly active antiretroviral therapy (HAART)
  - chronic kidney disease (estimated GFR <60 mL/min/1.73 m²)
  - erectile dysfunction
- screen children with a family history of hypercholesterolemia or chylomicronemia

Factors Affecting Risk Assessment
- metabolic syndrome
- apolipoprotein B (apo B):
  - each atherogenic particle (VLDL, LDL, LDL and lipoprotein A) contains one molecule of apo B
  - serum [apo B] reflects the total number of particles and may be useful in assessing cardiovascular risk and adequacy of treatment in high risk patients and those with metabolic syndrome
- C-reactive protein (hs-CRP) levels:
  - highly sensitive acute phase reactant
  - may be clinically useful in identifying those at a higher risk of cardiovascular disease than predicted by the global risk assessment

Treatment of Dyslipidemias

Approach to Treatment
For clinical guidelines see Can J Cardiol 2012;29:151-167
- estimate 10-yr risk of CAD using Framingham model
- establish treatment targets according to level of risk (see Table 5)

Table 6. Treatment of Hypercholesterolemia and Hypertriglyceridemia

### Treatment of Hypercholesterolemia
- **Conservative:** 4-6 mo trial unless high risk group, in which case medical treatment should start immediately
  - **Diet:**
    - Decrease fat: <30% calories
    - Decrease saturated fat: <10% calories
    - Decrease cholesterol: <200 mg/d
    - Increase fibre: >30 g/d
    - Decrease alcohol intake to ≤1-2 drinks/d
    - Smoking cessation
    - Aerobic exercise: ≥150 min/wk in bouts of ≥10 min
    - Weight loss: target body mass index (BMI) <25
  - **Medical**
    - HMG-CoA reductase inhibitors, ezetimibe, bile acid sequestrants, niacin (see Common Medications, E52)

- **Intensive Lipid Lowering in CAD: TNT**
  - **Study:** Multicentre, randomized, double-blinded trial with median follow-up of 4.9 yr
  - **Patients:** 10,001 patients with CAD and LDL-C <3.4 mmol/L
  - **Intervention:** 80 mg versus 10 mg atorvastatin daily.
  - **Main outcomes:** Death from CAD, MI, cardiac arrest, or stroke.
  - **Results:** A primary event occurred in 8.7% of the patients receiving intensive therapy, compared to 10.0% of patients receiving standard therapy (RR 0.8, p<0.001). There was no change in overall mortality. Incidence of persistent transaminase elevations was higher in the intensive therapy group (1.2% versus 0.3%, p<0.001).
  - **Conclusion:** Intensive statin therapy is associated with lower rates of CAD events than standard therapy, but also a higher rate of transaminase elevation.

- **Intensive Lipid Lowering in CAD: TNT**
  - **Study:** Randomized, double-blind, placebo-controlled trial (median follow-up 5.0 yr).
  - **Patients:** 20,536 patients with coronary disease, other occlusive arterial disease or diabetes (aged 40-80 yr) who had a total cholesterol level of ≥3.5 mmol/L.
  - **Intervention:** Simvastatin 40 mg/d or placebo.
  - **Main outcomes:** Mortality, fatal or non-fatal vascular events.
  - **Results:** The use of simvastatin significantly decreased total mortality (12.9 vs. 14.7, p=0.0003) and the first event rate of any cardiovascular event by 25% (p<0.001).
  - **Conclusion:** Treatment with simvastatin improved survival and cardiovascular outcomes in high-risk CAD patients.

### Treatment of Hypertriglyceridemia
- **Conservative:** 4-6 mo trial
  - **Diet:**
    - Decrease fat and simple carbohydrates
    - Increase omega-3 polyunsaturated fatty acid
    - Control blood sugars
    - Decrease alcohol intake to ≤1-2 drinks/d
    - Smoking cessation
    - Aerobic exercise: ≥150 min/wk in bouts of ≥10 min
    - Weight loss: target body mass index (BMI) <25
  - **Medical:** fibrates, niacin (see Common Medications, E52)
    - **Indications:**
      - Failed conservative measures
      - TG > 10 mmol/L (885 mg/dL) to prevent pancreatitis
      - Combined hyperlipidemia

Table 5. Target Lipids by Risk Group

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Definition (10-yr Risk of CAD)</th>
<th>Initiate Treatment if:</th>
<th>Primary Target LDL-C</th>
<th>Alternate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>Risk ≥20%, or Clinical atherosclerosis, Abdominal aortic aneurysm, Diabetes &gt;15 yr duration and age older than 30 yr, Diabetes with age older than 40 yr, Microvascular disease, High risk kidney disease, High risk hypertension</td>
<td>Consider treatment in all patients</td>
<td>≤2 mmol/L (78 mg/dL) or ≥50% ↓ in LDL</td>
<td>apo B ≤0.80 g/L or non-HDL-C ≤2.6 mmol/L</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Risk 10-19%</td>
<td>LDL &gt; 3.5 mmol/L (136.5 mg/dL). For LDL-C &lt;3.5 consider if: apo B ≥1.2 g/L or non-HDL-C ≥4.3 mmol/L</td>
<td>≤2 mmol/L (78 mg/dL) or ≥50% ↓ in LDL</td>
<td>apo B &lt;0.80 g/L or non-HDL-C ≤2.6 mmol/L</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>Risk &lt; 10%</td>
<td>LDL ≥5.0 mmol/L (195 mg/dL). Familial hypercholesterolemia</td>
<td>≥50% ↓ in LDL</td>
<td></td>
</tr>
</tbody>
</table>
**Overview of Glucose Regulation**

**Pre-Diabetes (Impaired Glucose Tolerance/Impaired Fasting Glucose)**
- 1-5% per yr go on to develop diabetes mellitus
- 50-80% revert to normal glucose tolerance
- weight loss may improve glucose tolerance
- increased risk of developing macrovascular complications
- lifestyle modifications decrease progression to DM by 58%

**Diagnostic Criteria**
- impaired fasting glucose (IFG): fasting blood glucose (FBG) 6.1-6.9 mmol/L (110-125 mg/dL)
- impaired glucose tolerance (IGT): 2h 75 g oral glucose tolerance test (OGTT) 7.8-11.0 mmol/L (140-200 mg/dL)

**Diabetes Mellitus (DM)**

**Definition**
- syndrome of disordered metabolism and inappropriate hyperglycemia secondary to an absolute/relative deficiency of insulin, or a reduction in biological effectiveness of insulin, or both

**Diagnostic Criteria**
- any one of the following is diagnostic:
  - presence of classic symptoms of DM (polyuria, polydipsia, polyphagia, weight loss, blurry vision, nocturia, ketonuria) PLUS random blood glucose (BG) ≥11.1 mmol/L (200 mg/dL)
  - on at least two separate occasions:
    - FPG ≥7.0 mmol/L (126 mg/dL) (fasting = no caloric intake for at least 8 h) OR
    - 2h 75 g OGTT ≥11.1 mmol/L (200 mg/dL) OR
    - random PG ≥11.1 mmol/L (200 mg/dL) OR
    - HbA1c ≥6.5%

*In the absence of symptomatic hyperglycemia, if a single laboratory test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, A1c, 2hPG in a 75 g OGTT) must be done on another day.*
Etiology and Pathophysiology

Table 7. Etiologic Classification of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Category</th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>• Usually &lt;30 yr of age</td>
<td>• Usually &gt;40 yr of age</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>• More common in Caucasians</td>
<td>• More common in Blacks, Hispanics, Aboriginals, and Blacks</td>
</tr>
<tr>
<td>Genetics</td>
<td>• Monozygotic twin concordance is 30-40%</td>
<td>• Greater heritability than Type 1 DM</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>• Synergistic effects of genetic, immune, and environmental factors that cause β-cell destruction resulting in impaired insulin secretion</td>
<td>• Impaired insulin secretion, peripheral insulin resistance (likely due to receptor and post receptor abnormality), and excess hepatic glucose production</td>
</tr>
<tr>
<td>Natural history</td>
<td>• After initial presentation, honeymoon period often occurs where glycemic control can be achieved with little or no insulin treatment as residual cells are still able to produce insulin</td>
<td>• Early on, glucose tolerance remains normal despite insulin resistance as β cells compensate with increased insulin production</td>
</tr>
<tr>
<td>Circulating autoantibodies</td>
<td>• Islet cell Ab present in up to 60-85%</td>
<td>• &lt;10%</td>
</tr>
</tbody>
</table>

Table 8. Comparison of Type 1 and Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Onset</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually &lt;30 yr of age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increasing incidence in pediatric population 2nd to obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usually &gt;40 yr of age</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Infections:
- Autoimmune
- Monogenic insulin resistance
- Genetic susceptibility
- Complex and multifactorial

Drug-induced:
- β-cell death
- GAD (glutamic acid decarboxylase)
- Islet cell Ab present in up to 60-85%
- 80% of β cells lost before features of diabetes present

Synergistic effects of genetic, immune, and environmental factors that cause β-cell destruction resulting in impaired insulin secretion.

Autoimmune process is believed to be triggered by environmental factors (e.g., viruses, bovine milk protein, urea compounds).

Beta cells are infiltrated with lymphocytes resulting in islet cell destruction.

80% of β cells mass destroyed before features of diabetes present.

Intensive blood glucose control in Type 2 DM – UKPDS 33

Lancet 1998;352:837-853

Randomized controlled trial (mean follow-up 10 yr).

Patients: 3867 patients with newly diagnosed Type 2 DM (mean age 53 yr, 67% men, 87% white, mean fasting plasma glucose (FPG) 6.1-10.0 mmol/L). Exclusions included severe cardiovascular disease, renal disease, retinopathy, and others.

Intervention: Intensive treatment with a sulfonylurea or insulin (target FPG <6 mmol/L) vs. conventional treatment with diet alone (target FPG <7.5 mmol/L) without hyperglycemic symptoms).

Main outcomes: Diabetes-related endpoints (MI, angina, heart failure, stroke, renal failure, amputation, retinopathy, blindness, death from hyperglycemia or hypoglycemia), diabetes-related death, and all-cause mortality.

Results: Patients allocated to intensive treatment had lower median HbA1c levels (p<0.001).

Outcome | RRR % (p value) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes-related endpoint</td>
<td>12 (0.029)</td>
</tr>
<tr>
<td>Diabetes-related death</td>
<td>10 (0.34)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6 (0.44)</td>
</tr>
</tbody>
</table>

Patients allocated to intensive therapy had more hypoglycemic episodes and greater weight gain.

Conclusion: Intensive blood glucose control reduces microvascular, but not macrovascular complications in Type 2 DM.
Table 8. Comparison of Type 1 and Type 2 Diabetes Mellitus (continued)

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal history of other autoimmune diseases</td>
<td>Age &gt; 40 yr</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>including Graves’, myasthenia gravis, autoimmune thyroid disease, celiac disease</td>
<td>Abdominal obesity/overweight</td>
<td>Fatty liver</td>
</tr>
<tr>
<td>and pernicious anemia</td>
<td>First-degree relative with DM</td>
<td>Hyperuricemia</td>
</tr>
<tr>
<td></td>
<td>Race/ethnicity (Black, Aboriginal, Hispanic, Asian-American, Pacific Islander)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HTN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyslipidemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PCOS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hx of gestational DM or macrosomic baby</td>
<td></td>
</tr>
<tr>
<td>Body Habitus</td>
<td>Normal to thin</td>
<td>Typical overweight with increased central obesity</td>
</tr>
<tr>
<td>Treatment</td>
<td>Insulin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lifestyle modification</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral antihyperglycemic agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Incretin therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin therapy</td>
<td></td>
</tr>
<tr>
<td>Acute Complication</td>
<td>Diabetic ketoacidosis (DKA) ) in severe cases</td>
<td>Hyperosmolar hyperglycemic state (HHS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DKA in severe cases</td>
</tr>
<tr>
<td>Screening</td>
<td>Subclinical prodrome can be detected in first and second-degree relatives of those with Type 1 DM by the presence of pancreatic islet autoantibodies</td>
<td>Screen individuals with risk factors</td>
</tr>
</tbody>
</table>

**Treatment of Diabetes**

**Glycemic Targets**
- HbA1c reflects glycemic control over 3 mo and is a measure of patient’s long-term diabetes control
- therapy in most individuals with type 1 or type 2 diabetes should be targeted to achieve a HbA1c ≤7.0% in order to reduce the risk of microvascular and if implemented early in the course of disease, macrovascular complications
- more intensive glucose control, HbA1c <6.5%, may be targeted in patients with a shorter duration of diabetes with no evidence of significant CVD and longer life expectancy, to further reduce risk of nephropathy and retinopathy; provided this does not result in a significant increase in hypoglycemia
- a HbA1c target <8.5% may be more appropriate in type 1 and type 2 patients with limited life expectancy, higher level of functional dependency, a history of recurrent severe hypoglycemia, multiple co-morbidities, extensive CAD, and a failure to attain established glucose targets despite treatment intensification
- there may be harm associated with strategy to target HbA1c <6.0% in certain patients with Type 2 DM (see ACCORD trial, E9)

**Diet**
- daily carbohydrate intake 45-60% of energy, protein 15-20% of energy and fat <35% of energy
- intake of saturated fats <7% and polyunsaturated fats <10% of total calories each
- limit sodium, alcohol and caffeine intake
- Type 1: carbohydrate counting is used to titrate insulin regimen
- Type 2: weight reduction

**Lifestyle**
- regular physical exercise to improve insulin sensitivity, lower lipid concentrations and control blood pressure
- smoking cessation

**Medical Treatment: Oral Antihyperglycemic Agents and/or Incretin Therapy (Type 2 DM)**
- initiate oral antihyperglycemic therapy and/or incretin therapy within 2-3 mo if lifestyle management does not result in glycemic control
- if HbA1c >9.0%, initiate pharmacologic therapy immediately and consider combination oral therapy or insulin immediately
- see Common Medications, E52 for details on antihyperglycemic agents

**Medical Treatment: Insulin (Figure 5)**
- used for Type 1 DM at onset, may be used in Type 2 DM at any point in treatment
- routes of administration: subcutaneous injections, continuous subcutaneous insulin infusion pump, IV infusion (regular insulin only)
- bolus insulins: short-acting (Insulin regular), rapid-acting analogue (Insulin aspart, Insulin lispro, Insulin glulisine)
- basal insulins: intermediate-acting (Insulin NPH), long-acting analogue (Insulin detemir, Insulin glargine)
- premixed insulins (% Humulin R and % NPH) 30/70; premixed insulin analogues (Biphasic Insulin aspart, Insulin lispro/lispro protamine)
- estimated total daily insulin requirement: 0.5-0.7 units/kg (often start with 0.3-0.5 units/kg/day)

Table 9. Available Insulin Formulations

<table>
<thead>
<tr>
<th>Insulin Type (trade name)</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting insulin analogues</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin aspart (NovoRapid&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>10-15 min</td>
<td>1-1.5 h</td>
<td>3-5 h</td>
</tr>
<tr>
<td>Insulin lispro (Humalog&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>10-15 min</td>
<td>1-2 h</td>
<td>3.5-4.75 h</td>
</tr>
<tr>
<td>Insulin glulisine (Apidra&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>10-15 min</td>
<td>1-1.5 h</td>
<td>3-5 h</td>
</tr>
<tr>
<td><strong>Short-acting insulins</strong></td>
<td>30 min</td>
<td>2-3 h</td>
<td>6.5 h</td>
</tr>
<tr>
<td>Humulin R&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novolin Toronto&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Intermediate-acting</strong></th>
<th>1-3 h</th>
<th>5-8 h</th>
<th>Up to 18 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humulin N&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novolin NPH&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Long-acting basal insulin analogues</strong></th>
<th>90 min</th>
<th>Not applicable</th>
<th>Up to 24 h (glargine 24 h, detemir 18-24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin detemir (Levemir&lt;sup&gt;®&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine (Lantus&lt;sup&gt;®&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Pre-Mixed Insulins</strong></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Premixed regular insulin – NPH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin 30/70&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novolin 30/70&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premixed insulin analogues</td>
<td>A single vial or cartridge contains a fixed ratio of insulin (% of rapid acting or short-acting insulin to % of intermediate-acting insulin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biphasic insulin aspart (NovoMix 30&lt;sup&gt;®&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro/lispro protamine (Humalog Mix25&lt;sup&gt;®&lt;/sup&gt; and Mix50&lt;sup&gt;®&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4. Approach to treatment of hyperglycemia in type 2 DM

Adapted from: Can J Diabetes 2008;32(suppl1):S56

Table 10. Approach to treatment of hyperglycemia in type 2 DM

<table>
<thead>
<tr>
<th>Hba1c Level</th>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9.0%</td>
<td>No symptoms</td>
<td>Add another agent from the list below:</td>
</tr>
<tr>
<td>≥ 9.0%</td>
<td>Symptomatic</td>
<td>Initiate insulin ± metformin</td>
</tr>
</tbody>
</table>

Timely adjustments to and/or addition of antihyperglycemic agents should be made to attain target Hba1c within 6 to 12 months

Effects of Intensive Glucose Lowering in Type 2 DM: The ACCORD Trial
NEJM 2010;362:1563-1574

Study: Multicentre RCT.
Population: 10,251 patients (mean age 62.2) with Type 2 DM, and cardiovascular risk factors.

Intervention: Intensive therapy targeting a Hba1c level of <6.0% or standard therapy targeting 7.0 to 7.6%.

Outcomes: First occurrence of nonfatal MI, nonfatal stroke, or death from CV causes.

Results: The intensive therapy arm was stopped early (3.5 yr vs. 5.6 yr planned) due to evidence of increased mortality. There was no difference in primary outcome for either study arm. There was a significant increase in all-cause mortality, CV-cause mortality, nonfatal MI, and all congestive heart failure in the intensive therapy group. There were increased rates of all hypoglycemic events, any hypoglycemic serious adverse events, fluid retention, and weight gain >10 kg, but lower systolic and diastolic blood pressure in the intensive treatment group. There was an increased incidence of elevated ALT (>3 times upper limit) and ACE drug use in the standard therapy group.

Conclusions: Intensive glucose lowering therapy in Type 2 DM does not improve clinical outcomes and actually increases the risk of mortality with more adverse events compared to standard therapy. Additional research is required to discern the cause.

Effects of Intensive Blood Pressure Control in Type 2 DM: The ACCORD Trial
NEJM 2010;362:1575-1585

Study: RCT, unblinded with 4.7 yr of mean follow-up.

Population: 7,733 patients with type 2 DM, risk factors for cardiovascular (CV) disease, systolic blood pressure (sBP) between 130-180 mmHg.

Intervention: sBP control less than 120 mmHg (intensive) or 140 mmHg (standard).

Primary Outcomes: Major CV event (composite nonfatal MI, nonfatal stroke, or CV-related death).

Results: Mean number of medications at 1 yr for intensive therapy was 3.4 (95% CI, 3.4-3.5) versus 2.1 (95%, 2.1-2.2) for standard therapy. There was a significant increase in all serious adverse events in the intensive treatment arm (3.3% vs. 1.2%, p < 0.001), especially bradycardia or arrhythmia (0.3% vs. 0.1%, p = 0.03) and hyperkalemia (0.4% vs. 0.0%, p < 0.01). There was no significant difference in primary outcomes in the two study arms, or all-cause mortality. There was a significant reduction in any stroke (0.32% vs. 0.57% p = 0.01) and nonfatal stroke incidences (0.30% vs. 0.47% p = 0.03) in the intensive therapy arm.

Conclusions: Intensive BP lowering to less than 120 mmHg versus 140 mmHg in patients with Type 2 DM and CV risk factors does not reduce major CV event risk reduction except for stroke events.

Effects of Combination Lipid Therapy in Type 2 DM: The ACCORD Trial
NEJM 2010;362:1583-1594

Study: RCT, double-blinded trial with 4.7 yr of mean follow-up.

Population: 5,518 patients with type 2 DM.

Intervention: Statin therapy in patients with Type 2 DM does not improve clinic outcomes and actually increases the risk of mortality with more adverse events compared to standard therapy. Additional research is required to discern the cause.
**Insulin Regimens**

**Table 10. Insulin Regimens for T2DM and T1DM**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Administration</th>
</tr>
</thead>
</table>
| T2DM Oral hypoglycemic agent + basal insulin | • Start with 10 units at bedtime of basal insulin  
• Titrate up by 1 unit until FBG <7.0 mmol/L (126 mg/dL) |
| T1DM Multiple daily injections (MDI) | • Estimated total insulin requirement is 0.5-0.7 U/kg  
• 40% is given as basal insulin at bedtime  
• 20% is given as bolus insulin before breakfast, lunch and dinner  
• Continue metformin but discontinue secretagogue |
| Split-mixed           | • Estimated total insulin requirement is 0.5-0.7 U/kg  
• 2/3 dose is given as pre-mixed insulin before breakfast  
• 1/3 dose is given as pre-mixed insulin before dinner  
• Continue metformin but discontinue secretagogue |

*Bolus insulin: Aspart, Glulisine, Lispro  
*Basal insulin: Gargine, Detemir, NPH  
*Pre-mixed insulin: Humulin 30/70, Novolin 30/70, Novomix 30, Humalog Mix25, Humalog Mix50

**Table 11. Titrating Insulin Doses**

<table>
<thead>
<tr>
<th>Hyperglycemic Reading</th>
<th>Insulin Correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>High AM sugar</td>
<td>Increase bedtime basal insulin</td>
</tr>
<tr>
<td>High lunch sugar</td>
<td>Increase AM rapid/regular insulin</td>
</tr>
<tr>
<td>High supper sugar</td>
<td>Increase lunch rapid/regular insulin, or Increase AM basal insulin</td>
</tr>
<tr>
<td>High bedtime sugar</td>
<td>Increase supper rapid/regular insulin</td>
</tr>
</tbody>
</table>

**Variable Insulin Dose Schedule (“Sliding/Supplemental/Correction Scale”)**
- for patients on Basal-Bolus MDI regimen: patient takes usual doses of basal insulin but varies doses of bolus insulin based on BG reading at time of dose
- use baseline bolus insulin dose when within BG target range; add or subtract units when above or below target
- when used in hospital (including perioperative management of diabetes) patient should also receive basal insulin to prevent fluctuations in blood sugar levels or long periods of hyperglycemia without intervention
- construction of a supplemental sliding scale for a patient on anti-hyperglycemics:
  - Correction Factor (CF) = 100/Total Daily Dose of insulin (TDD)
  - BG <4: call MD and give 15 g carbohydrates
  - BG between 4 to 8: no additional insulin
  - BG between 8 to (8 + CF): give one additional unit
  - BG between (8 + CF) to (8 + 2CF): give two additional units
  - BG between (8 + 2CF) to (8 + 3CF): give three additional units

**Insulin Pump Therapy [continuous subcutaneous insulin infusion (CSII)]**
- external battery-operated device provides continuous basal dose of rapid-acting insulin analogue (aspart, glulisine or lispro) through small subcutaneous catheter
- at meals, patient programs pump to deliver insulin bolus
- provides improved quality of life and flexibility
- risk of DKA if pump is inadvertently disconnected

**Conversion Chart for percentage HbA1c to average blood sugar control**

<table>
<thead>
<tr>
<th>Average blood sugar level (mmol/L)</th>
<th>Hemoglobin A1c (% HbA1c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>12%</td>
</tr>
<tr>
<td>16</td>
<td>11%</td>
</tr>
<tr>
<td>14</td>
<td>10%</td>
</tr>
<tr>
<td>12</td>
<td>9%</td>
</tr>
<tr>
<td>10</td>
<td>8%</td>
</tr>
<tr>
<td>8</td>
<td>7%</td>
</tr>
<tr>
<td>6</td>
<td>6%</td>
</tr>
</tbody>
</table>

Conversion chart adapted from Nathan DM et al.  
The clinical information value of a glycosylated hemoglobin assay. AJEM 1986;310:341-346

**DPP-IV Inhibitors**
- Newer antihyperglycemic agents (e.g. sitagliptin, saxagliptin) that inhibit the degradation of endogenous incretin hormones like GLP-1
- Stimulate insulin secretion, inhibit glucagon release from the pancreas

**GLP-1 Analogues (Incretins)**
- Human glucagon-like peptide-1 analogues: exenatide, liraglutide
- Increase insulin secretion, decreases inappropriate glucagon secretion, increases B-cell growth/replation, slows gastric emptying and decreases food intake
- Associated with weight loss
- Subcutaneous formulation

**Treatment of DKA/HHS**
- Fluids
- Insulin
- Potassium
- Search for and treat precipitant

**The 8 Is Precipitating DKA:**
- Infection
- Ischemia or Infarction
- Intravenous (glucocorticoids)
- Intoxication
- Insulin missed
- Initial presentation
- Intra-abdominal process (e.g. pancreatitis, cholecystitis)
- Intrasp/periop stress
### Acute Complications

#### Table 12. Acute Complications of Diabetes Mellitus: Hyperglycemic Comatose States

<table>
<thead>
<tr>
<th></th>
<th>Diabetic Ketoacidosis (DKA)</th>
<th>Hyperosmolar Hyperglycemic State (HHS)</th>
</tr>
</thead>
</table>

#### Pathophysiology
- Usually occurs in Type 1 DM
- Insulin deficiency with counterregulatory hormones (glucagon, cortisol, catecholamines, GH)
- Can occur with lack of insulin (non-adherence, inadequate dosage, 1st presentation) or increased stress (surgery, infection, exercise)
- Unrestricted hepatic glucose production → hyperglycemia → osmotic diuresis → dehydration and electrolyte disturbance → ↓ Na⁺ (veter shift to ECF)
- Fat mobilization → ↑ FFA → ketoacids → metabolic acidosis
- Severe hyperglycemia exceeds the renal threshold for glucose and ketone reabsorption → glucosuria and ketonuria
- Total body K⁺ depletion but serum K⁺ may be normal or elevated
- 2° to shift from ICF to ECF due to lack of insulin, ↑ plasma osmolality
- Total body PO₄³⁻ depletion

#### Clinical Features
- Polyuria, polydipsia, polyphagia with marked fatigue, nausea, vomiting
- Dehydration (orthostatic changes)
- LDC may be ↓ with ketoacidosis or with high serum osmolality
- Abdominal pain
- Fruity smelling breath
- Kussmaul’s respiration

#### Serum
- ↑ BG (typically 11.5-55 mmol/L, 198-990 mg/dL), ↓ Na⁺ (2° to hyperglycemia → for every ↑ in BG by 10 mmol/L (180 mg/dL) there is a ↓ in Na⁺ by 3 mmol/L)
- Normal or ↑ K⁺, ↓ HCO₃⁻; ↑ BUN, ↑ Cr, ketonemia, ↓ PO₄³⁻
- ↑ osmolality

#### ABG
- Metabolic acidosis with ↑ AG, possible 2° respiratory alkalosis
- If severe vomiting/dehydration there may be a metabolic alkalosis
- Metabolic acidosis absent unless underlying precipitant leads to acidosis (e.g. lactic acidosis in MI)
- History of ingesting large amounts of glucose containing fluids
- History of decreased fluid intake
- History of ingesting large amounts of glucose containing fluids
- Dehydration (orthostatic changes)
- ↓ LDC → lathyrophy, confusion, coma due to high serum osmolality
- Kussmaul’s respiration is absent unless the underlying precipitant has also caused a metabolic acidosis

#### Urine
- + ve for glucose and ketones
- – ve for ketones unless there is starvation ketosis
- Glycosuria

#### Treatment
- Immediate resuscitation and emergency measures if patient is stuporous or comatose
- Monitor degree of ketoacidosis with AG, not BG or serum ketone level
- Rehydration:
  - 1 L/ h NS in first 2 h
  - after 1st 2 L, 300-400 mL/h 0.45% NaCl (continue NS if corrected sodium is falling faster than 3 mosm/kg water/h)
  - once BG reaches 13.9 mmol/L (250 mg/dL) then switch to D5W to maintain BG in the range of 13.9–16.6 mmol/L (250-300 mg/dL)
- Insulin therapy:
  - critical to resolve acidosis, not hyperglycemia
  - do not use with hypokalemia (see below), until serum K⁺ is corrected to >3.3 mmol/L
  - use only regular insulin (R)
  - maintain on 0.1 U/kg/h insulin R infusion
  - check serum glucose hourly
- K⁺ replacement:
  - with insulin administration, hypokalemia may develop
  - if serum K⁺ <3.3 mmol/L, hold insulin and give 40 mEq/L K⁺ replacement
  - when K⁺ 3.5-5.0 mmol/L add KC1 20-40 mEq/L IV fluid to keep K⁺ in the range of 3.5-5.5 mEq/L
- HCO₃⁻;
  - if pH < 7.0 or if hypotension, arrhythmia or coma is present with a pH of <7.1 give HCO₃⁻ in 0.45% NaCl
  - do not give if pH >7.1 (risk of metabolic alkalosis)
  - can give in case of life-threatening hyperkalemia

#### Prognosis
- 2-5% mortality in developed countries
- Serious morbidity from sepsis, hypokalemia, respiratory complications, thromboembolic complications, and cerebral edema
- Overall mortality approaches 50% primarily because of the older patient population and underlying etiology/precipitant
Macrovacular Complications

- increased risk of coronary artery disease (CAD), ischemic stroke, and peripheral arterial disease secondary to accelerated atherosclerosis
- coronary artery disease (see Cardiology, C22)
  - risk of MI is 3-5x higher in those with diabetes compared to age-matched controls
  - CAD is the leading cause of death in Type 2 DM
  - most patients with DM are considered "high risk" under the risk stratification for CAD (see Dyslipidemias, E2)
- ischemic stroke (see Neurology, N43)
  - risk of stroke is approximately 2.5x higher in those with diabetes
  - level of glycemia is both a risk factor for stroke and a predictor of a poorer outcome in patients who suffer a stroke
  - HbA1c level is a significant and independent predictor of the risk of stroke
- peripheral arterial disease (see Cardiology, C44)
  - manifested by intermittent claudication in lower extremities, intestinal angina, foot ulceration
  - risk of foot gangrene is 30x higher in those with diabetes compared to age-matched controls
  - risk of lower extremity amputation is 15x higher in those with diabetes
- treatment
  - tight blood pressure control (<130/80 mmHg); especially for stroke prevention
  - tight glycemic control in early DM without established CVD (refer to ACCORD, VADT, ADVANCE, DCCT, EDIC, UKPDS extension studies)
  - tight low density lipoprotein (LDL) cholesterol control [LDL <2.0 mmol/L (77 mg/dL)]
  - ACE inhibitor or angiotensin receptor blocker in high-risk patients
  - smoking cessation

Microvascular Complications

DIABETIC RETINOPATHY (see Ophthalmology, OP35)

Epidemiology
- Type 1 DM: 25% affected at 5 yr, 100% at 20 yr
- Type 2 DM: 25% affected at diagnosis, 60% at 20 yr
- leading cause of blindness in North America between the ages of 20-74
- most important factor is disease duration

Clinical Features
- nonproliferative
  - asymptomatic but if macular involvement occurs vision may be impaired
  - microaneurysms, hard exudates, dot-blot and flame hemorrhages
- preproliferative
  - macular edema, cotton wool spots, venous shunts and beading, intra-retinal microvascular abnormalities (IRMA)
- proliferative
  - with neovascularization and fibrous scarring; great risk for loss of vision secondary to vitreous hemorrhage (floaters) and/or retinal detachment

Treatment and Prevention
- tight glycemic control (delays onset, decreases progression), tight lipid control, manage hypertension, smoking cessation
- pan-retinal laser photocoagulation for treatment of neovascularization
- vitrectomy
- annual follow-up visits with an optometrist or ophthalmologist examination through dilated pupils whether symptomatic or not (immediate referral after diagnosis of Type 2 DM; 5 yr after diagnosis of Type 1 DM)
- interval for follow-up should be tailored to severity of retinopathy

Laboratory Testing: Ketones

The nitroprusside test for ketones identifies acetone and acetoacetate but does NOT detect β-hydroxybutyrate (BHB), the ketone most frequently in excess. This has two clinical consequences:
- Be wary of a patient with a clinical picture of DKA but negative serum or urinary ketones. These could be false negatives because of the presence of BHB.
- As DKA is treated, BHB is converted to acetone and acetoacetate. Serum or urinary ketones may therefore rise, falsely suggesting that the patient is worsening when in fact they are improving.

Laboratory Testing: Microalbuminuria

The primary end point was the time to death from any cause. Other endpoints examined were death from CV causes and various CV events along with diabietic neuropathy, nephropathy, and retinopathy.

Results:
- Twenty-four patients in the intensive-therapy group died, as compared with 40 in the conventional-therapy group (hazard ratio, 0.54; 95% confidence interval [CI], 0.32 to 0.88; p=0.02).
- Intensive therapy was associated with a lower risk of death from CV causes (hazard ratio, 0.43; 95% CI, 0.19 to 0.94; p=0.04) and of CV events (hazard ratio, 0.41; 95% CI, 0.25 to 0.67; p<0.001).
- One patient in the intensive-therapy group had progression to end-stage renal disease, as compared with six patients in the conventional-therapy group (p=0.04). Fewer patients in the intensive-therapy group required revascularization (relative risk, 0.45; 95% CI, 0.23 to 0.86; p=0.02).

Conclusions:
- In-risk patients with Type 2 DM, intensive intervention with multiple drug combinations and behaviour modification had sustained beneficial effects with respect to vascular complications and on rates of death from any cause and from CV causes.
DIABETIC NEPHROPATHY (see Nephrology, NP28)

Epidemiology
• diabetes-induced renal failure is the most common cause of renal failure in North America
• 20-40% of persons with Type 1 DM (after 5-10 yr) and 4-20% with Type 2 DM have progressive nephropathy

Pathophysiology
• thickening of capillary basement membrane and glomerular mesangium resulting in glomerulosclerosis and renal insufficiency
• diffuse glomerulosclerosis is more common than nodular intercapillary glomerulosclerosis (Kimmelstiel-Wilson lesions)

Screening
• serum creatinine
• random urine test for albumin to creatinine ratio (ACR) plus urine dipstick test for all Type 2 DM patients at diagnosis, then annually, and for postpubertal Type 1 DM patients with ≥5 yr duration of DM

Clinical Features
• initial changes include microalbuminuria, increased GFR (up to 140%) from hyperfiltration, enlarged kidneys
• microalbuminuria: ACR of >2.0 mg/mmol (men) or >2.8 mg/mmol (women)
• macroalbuminuria: ACR of >20.0 mg/mmol (men) or >28.0 mg/mmol (women)
• progression over 15 yr to cause hypertension, persistent proteinuria (macroalbuminuria), nephrotic syndrome, and renal failure
• elevated HbA1c is an independent risk factor for progression to microalbuminuria

Treatment and Prevention
• tight glycemic control
• tight blood pressure control (<130/80 mmHg); can use either ACEI or ARB (often used first line for their CVD protection)
• even in the absence of glycemic control ACEIs or ARBs reduce the level of albuminuria and the rate of progression of renal disease in normotensive and hypertensive patients with Type 1 or Type 2 DM
• Type 1 DM → CKD with either hypertension or albuminuria → ACEIs 1st line; ARBs 2nd line
• Type 2 DM → CKD with hypertension and albuminuria → ACEIs or ARBs (dose adjust if creatinine clearance (CrCl) <60 mL/min)
• consider use of non-dihydropyridine calcium channel blocker (e.g. diltiazem) in those unable to tolerate both ACEIs and ARBs
• limit use of nephrotoxic drugs and dyes
• renal failure may necessitate hemodialysis and renal transplant

DIABETIC NEUROPATHY (see Neurology, N37)

Epidemiology
• approximately 50% of patients within 10 yr of onset of Type 1 DM and Type 2 DM

Pathophysiology
• can have peripheral sensory neuropathy, motor neuropathy or autonomic neuropathy
• mechanism poorly understood
• acute cranial nerve palsies and diabetic amyotrophy are thought to be due to ischemic infarction of peripheral nerve
• the more common motor and sensory neuropathies are thought to be related to metabolic or osmotic toxicity secondary to increased sorbitol and/or decreased myoinositol (possible mechanisms include accumulation of advanced glycation endproducts [AGE], oxidative stress, protein kinase C, nerve growth factor deficiency)

Screening
• 128 Hz tuning fork or 10 g monofilament at diagnosis and annually in people with Type 2 DM and after 5 yr duration of Type 1 DM
### Clinical Features

#### Table 13. Clinical Presentation of Diabetic Neuropathies

<table>
<thead>
<tr>
<th>Peripheral Sensory Neuropathy</th>
<th>Motor Neuropathy</th>
<th>Autonomic Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesias (tingling, itching), neuropathic pain, radicular pain, numbness, decreased tactile sensation</td>
<td>Less common than sensory neuropathy</td>
<td>Postural hypotension, tachycardia, decreased cardiovascular response to Valsalva maneuver</td>
</tr>
<tr>
<td>Bilateral and symmetric with decreased perception of vibration and pain/temperature; especially true in the lower extremities but may also be present in the hands</td>
<td>Delayed motor nerve conduction and muscle weakness/atrophy</td>
<td>Gastroparesis and alternating diarrhea and constipation</td>
</tr>
<tr>
<td>Decreased ankle reflex</td>
<td>May involve one nerve trunk (mononeuropathy) or more (mononeuropathy multiplex)</td>
<td>Urinary retention and erectile dysfunction</td>
</tr>
<tr>
<td>Symptoms may first occur in entrapment syndromes e.g. carpal tunnel</td>
<td>Some of the motor neuropathies spontaneously resolve after 6-8 wk</td>
<td></td>
</tr>
<tr>
<td>May result in neuropathic ulceration of foot</td>
<td>Reversible CN palsies: III (ptosis/ophthalmoplegia, pupil sparing), VI (inability to laterally deviate eye), and VII (Bell’s palsy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetic amyotrophy: refers to pain, weakness, and wasting of hip flexors or extensors</td>
<td></td>
</tr>
</tbody>
</table>

#### Treatment and Management

- tight glycemic control
- for neuropathic pain syndromes: tricyclic antidepressants (e.g. amitriptyline), pregabalin, duloxetine, anti-epileptics (e.g. carbamazepine, gabapentin), and capsaicin
- foot care education
- Jobst® fitted stocking and tilting of head of bed may decrease symptoms of orthostatic hypotension
- treat gastroparesis with domperidone and/or metoclopramide (dopamine antagonists), erythromycin (stimulates motilin receptors)
- medical, mechanical and surgical treatment for erectile dysfunction (see Urology, U30)

### Other Complications

#### Dermatologic
- diabetic dermopathy: atrophic brown spots commonly in pretibial region known as “skin spots”, secondary to increased glycosylation of tissue proteins or vasculopathy
- eruptive xanthomas secondary to increased triglycerides
- necrobiosis lipoidica diabeticorum: rare complication characterized by thinning skin over the shins allowing visualization of subcutaneous vessels

#### Bone and Joint Disease
- juvenile cheiroarthropathy: chronic stiffness of hand caused by contracture of skin over joints secondary to glycosylated collagen and other connective tissue proteins
- Dupuytren’s contracture
- bone demineralization: bone density 10-20% below normal
- frozen shoulder

#### Cataracts
- subcapsular and senile cataracts secondary to glycosylated lens protein or increased sorbitol causing osmotic change and fibrosis

#### Infections
- see Infectious Diseases, ID16

### Hypoglycemia

#### Etiology and Pathophysiology
- hypoglycemia occurs most frequently in people with diabetes receiving insulin or certain antihyperglycemic therapies (insulin secretagogues)
- in people without diabetes, care must be taken to distinguish fasting from post-prandial hypoglycemia as each invokes separate differential diagnoses
Table 14. Common Causes of Hypoglycemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Fasting</th>
<th>Without Hyperinsulinism</th>
<th>Post-Prandial (Nonfasting, Reactive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hyperinsulinism</td>
<td>• Severe hepatic dysfunction</td>
<td>• Exogenous insulin</td>
<td>• Alimentary</td>
</tr>
<tr>
<td></td>
<td>• Chronic renal insufficiency</td>
<td>• Sulfonylurea or meglitinide reaction</td>
<td>• Functional</td>
</tr>
<tr>
<td></td>
<td>• Hypocortisolism</td>
<td>• Autoimmune hypeglycemia (autoantibodies to insulin or insulin receptor)</td>
<td>• Noninsulinoma pancreatogenous</td>
</tr>
<tr>
<td></td>
<td>• Alcohol use</td>
<td>• Pancreatic β cell tumour</td>
<td>• hypoglycemic syndrome</td>
</tr>
<tr>
<td></td>
<td>• Non-pancreatic tumours</td>
<td>– insulinoma</td>
<td>• Occult diabetes</td>
</tr>
<tr>
<td></td>
<td>• Inborn error of carbohydrate metabolism, glycerogen storage disease, gluconeogenic enzyme deficiency</td>
<td></td>
<td>• Leucine sensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hereditary fructose intolerance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Galactosemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Newborn infant of diabetic mother</td>
</tr>
</tbody>
</table>

Clinical Features
- Whipple's triad
  1. serum glucose <2.5 mmol/L (45 mg/dL) in males and <2.2 mmol/L (40 mg/dL) in females
  2. neuroglycopenic symptoms
  3. rapid relief provided by administration of glucose
- adrenergic symptoms (typically occur first; caused by autonomic nervous system activity)
  - palpitations, sweating, anxiety, tremor, tachycardia
- neuroglycopenic symptoms (caused by decreased activity of CNS)
  - dizziness, headache, clouding of vision, mental dullness, fatigue, confusion, seizures, coma

Investigations
- electrolytes, creatinine, LFTs, drugs/toxins, cortisol
- if concerned about possible insulinoma:
  - bloodwork to be drawn when patient is hypoglycemic (e.g. during hospitalized 72-h fast) for glucose, serum ketones, insulin, pro-insulin, C-peptide, insulin antibodies

Treatment
- for fasting hypoglycemia, must treat underlying cause
- for post-prandial (reactive) hypoglycemia, frequent small feeds
- see Emergency Medicine, ER36
- treatment of hypoglycemic episode in the unconscious patient or patient NPO
  - D50W 50 mL (1 ampule) IV or 1 mg glucagon SC (if no IV available)
  - may need ongoing glucose infusion once BG >5 mmol/L (90 mg/dL)

Metabolic Syndrome
- several definitions, most widely used are National Cholesterol Education Program (NCEP/ATP III, updated by American Heart Association) and International Diabetes Federation (IDF) definitions (see sidebar)
- postulated syndrome related to insulin resistance associated with hyperglycemia, hyperinsulinemia, hypertension, central obesity, and dyslipidemia
- obesity aggravates extent of insulin resistance
- complications include diabetes, atherosclerosis, CAD, MI, and stroke
- women with PCOS are at increased risk for developing insulin resistance, hyperlipidemia, and metabolic syndrome
- not to be confused with syndrome X related to angina pectoris with normal coronary arteries (Prinzmetal angina)

Obesity
- see Family Medicine, FM7

Use C-peptide Levels to Distinguish between Exogenous and Endogenous Source of Hyperinsulinemia
- Increased = endogenous
- Decreased or normal = exogenous

Treatment of Acute Hypoglycemic Episode (Blood Glucose <4.0 mmol/L) in the Awake Patient (e.g. able to self-treat)
1) Eat 15 g of carbohydrates (CHO) (e.g. 3 packets sugar dissolved in water; 3/4 cup of juice)
2) Wait 15 min
3) Retest Blood Glucose (BG)
4) Repeat steps 1-3 until BG >5 mmol/L
5) Eat next scheduled meal. If next meal is >1 h away, eat snack including 15 g of CHO and protein.

Hypoglycemia Unawareness: (Type 1 DM >> > > Type 2 DM)
- Patient remains asymptomatic until severely hypoglycemic levels are reached
- Causes:
  - Decreased glucagon/epinephrine response
  - History of repeated hypoglycemia or low HbA1c
  - Autonomic neuropathy
  - Not safe to drive

Suggest that patient obtain a Medic-Alert bracelet if at risk for hypoglycemia, especially with hypoglycemia unawareness.

Features of Metabolic Syndrome

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>IDF (2005): to make diagnosis requires ≥2 of risk factors</th>
<th>ATP III (2005): requires ≥2 or 3 risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>WC ≥94 cm</td>
<td>WC ≥102 cm</td>
</tr>
<tr>
<td>Women</td>
<td>WC ≥80 cm</td>
<td>WC ≥88 cm</td>
</tr>
<tr>
<td></td>
<td>(37 inches)</td>
<td>(35 inches)</td>
</tr>
<tr>
<td></td>
<td>(38 inches)</td>
<td>(35 inches)</td>
</tr>
<tr>
<td></td>
<td>(88 cm)</td>
<td>(94 cm)</td>
</tr>
<tr>
<td></td>
<td>(34 inches)</td>
<td>(38 inches)</td>
</tr>
<tr>
<td></td>
<td>(35 inches)</td>
<td>(94 cm)</td>
</tr>
<tr>
<td>Triglyceride Level</td>
<td>≥1.7 mmol/L</td>
<td>≥1.7 mmol/L</td>
</tr>
<tr>
<td></td>
<td>(150 mg/dL)</td>
<td>(150 mg/dL)</td>
</tr>
<tr>
<td>HDL-C Level</td>
<td>&lt;1.0 mmol/L</td>
<td>&lt;1.0 mmol/L</td>
</tr>
<tr>
<td></td>
<td>(&lt;40 mg/dL)</td>
<td>(&lt;40 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>&lt;1.3 mmol/L</td>
<td>&lt;1.3 mmol/L</td>
</tr>
<tr>
<td></td>
<td>(&lt;50 mg/dL)</td>
<td>(&lt;50 mg/dL)</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>≥130/85 mmHg</td>
<td>≥130/85 mmHg</td>
</tr>
<tr>
<td></td>
<td>(≥180/100 mg/dL)</td>
<td>(≥180/100 mg/dL)</td>
</tr>
<tr>
<td>Fasting Glucose Level</td>
<td>≥5.6 mmol/L</td>
<td>≥5.6 mmol/L</td>
</tr>
<tr>
<td></td>
<td>(≥100 mg/dL)</td>
<td>(≥100 mg/dL)</td>
</tr>
</tbody>
</table>

WC = Waist circumference
Pituitary Gland

Pituitary Hormones

Figure 6. Hypothalamic-pituitary hormonal axes

**Hypothalamic Control of Pituitary**
- trophic and inhibitory factors control the release of pituitary hormones
- most hormones are primarily under trophic stimulation except prolactin which is primarily under inhibitory control by dopamine, as well as GH and TSH which are inhibited by SS (somatostatin)
- transection of the pituitary stalk (i.e. dissociation of hypothalamus and pituitary) leads to pituitary hypersecretion of prolactin and hyposecretion of all remaining hormones

**Anterior Pituitary Hormones**
- growth hormone (GH), luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and prolactin (PRL)

**Posterior Pituitary (Hypothalamic) Hormones**
- antidiuretic hormone (ADH) and oxytocin
- peptides synthesized in the supraoptic and paraventricular nuclei of the hypothalamus
- although ADH and oxytocin are produced in the hypothalamus these hormones are stored and released from the posterior pituitary

Table 15. The Physiology and Action of Pituitary Hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Function</th>
<th>Physiology</th>
<th>Inhibitory Stimulus</th>
<th>Secretory Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>Stimulates growth of adrenal cortex and secretion of its hormones</td>
<td>Polypeptide, Pulsatile and diurnal variation (highest in AM, lowest at midnight)</td>
<td>Dexamethasone, Cortisol</td>
<td>CRH, Metyrapone, Insulin-induced hypoglycemia, Vasopressin, Fever, pain, stress</td>
</tr>
<tr>
<td>GH</td>
<td>Needed for linear growth</td>
<td>Polypeptide, Acts indirectly through serum factors synthesized in the liver: IGF-1 (somatomedin-C), Serum GH undetectable for most of the day and suppressed after meals high in glucose, Sustained rise during sleep</td>
<td>Glucose challenge, Glucocorticoids, Hypothyroidism, Somatostatin, Dopamine D2 receptor agonists, IGF-1 (long-loop), Tonically by dopamine</td>
<td>GH, GH, Insulin-induced hypoglycemia, Exercise, REM sleep, Arginine, clonidine, propranolol, L-dopa</td>
</tr>
</tbody>
</table>
Table 15. The Physiology and Action of Pituitary Hormones (continued)

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Function</th>
<th>Physiology</th>
<th>Inhibitory Stimulus</th>
<th>Secretory Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH/FSH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Stimulate gonads via cAMP</td>
<td>• Polypeptide</td>
<td>• Estrogen</td>
<td>• Pulsatile GnRH</td>
</tr>
<tr>
<td></td>
<td>• Ovary:</td>
<td>• Glycoproteins (similar α subunit as TSH and hCG)</td>
<td>• Progesterone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– LH: production of androgens (thecal cells) which are converted to estrogens (granulosa cells); induces luteinization in follicles</td>
<td>• Secreted in pulsatile fashion</td>
<td>• Testosterone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– FSH: growth of granulosa cells in ovarian follicle; controls estrogen formation</td>
<td>• Inhibin</td>
<td>• Continuous (i.e. non-pulsatile) GnRH infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Testes:</td>
<td>• Continuous</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>– LH: production of testosterone (Leydig cells)</td>
<td></td>
<td>• Sleep</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– FSH: production of spermatozoa (Sertoli cells)</td>
<td></td>
<td>• Stress, hypoglycemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Pregnancy, breastfeeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mid-menstrual cycle</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Sexual activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• TRH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Drugs: psychotropics, antihypertensives, dopamine antagonists, opiates, high dose estrogen</td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td>• Promotes milk production</td>
<td>• Polypeptide</td>
<td>• Sleep</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Inhibits GnRH secretion</td>
<td>• Episodic secretion</td>
<td>• Hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>• Stimulates growth of thyroid and secretion of T3 and T4 via cAMP</td>
<td>• Glycoprotein</td>
<td>• Pregnancy, breastfeeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mid-menstrual cycle</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADH</td>
<td>• Acts at renal collecting ducts on V2 receptors to cause insertion of aquaporin channels and increases water reabsorption thereby concentrating urine</td>
<td>• Octapeptide</td>
<td>• Endogenous</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Secreted by posterior pituitary</td>
<td>• Opiates, dopamine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Osmoreceptors in hypothalamus detect serum osmolality</td>
<td>• TRH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Contracted plasma volume detected by baroreceptors is a more potent stimulus than T osmolality</td>
<td>• Epinephrine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Prostaglandins</td>
<td></td>
</tr>
<tr>
<td>ADH</td>
<td></td>
<td></td>
<td>• Lung or brain pathology</td>
<td></td>
</tr>
<tr>
<td>Oxytocin</td>
<td>• Causes uterine contraction</td>
<td>• Not a peptide</td>
<td>• Hypovolemia or ↓ effective circulatory volume</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Breast milk secretion</td>
<td>• Secreted by posterior pituitary</td>
<td>• ↑ serum osmolality</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Growth Hormone (GH)**

**GH DEFICIENCY**
- cause of short stature in children (see Pediatrics, P27)
- controversial significance in adults; often not clinically apparent, may present as fatigue

**GH EXCESS**
- in children (before epiphyseal fusion) leads to gigantism
- in adults (after epiphyseal fusion) leads to acromegaly

**Etiology**
- GH secreting pituitary adenoma, carcinoid or pancreatic islet tumours secreting ectopic GHRH resulting in excess GH

**Pathophysiology**
- normally GH is a catabolic hormone that acts to increase blood glucose levels
- in growth hormone excess states secretion remains pulsatile but there is loss of hypoglycemic stimulation, glucose suppression, and the nocturnal surge
- proliferation of bone, cartilage, soft tissues, organomegaly
- insulin resistance and IGT

**Clinical Features**
- enlargement of hands and feet, coarsening of facial features, thickening of calvarium, prognathism, thickening of skin, increased sebum production, sweating, acne, sebaceous cysts, fibromata mollusca, acanthosis nigricans, arthralgia, carpal tunnel syndrome, degenerative osteoarthritis, thyromegaly, renal calculi, hypertension, cardiomyopathy, obstructive sleep apnea, colonic polyps and DM
Investigations
- glucose suppression test is the most specific test (75 g of glucose PO suppresses GH levels in healthy individuals but not in patients with acromegaly)
- elevated serum insulin-like growth factor-1 (IGF-1) is usually first line diagnostic test

Treatment
- surgery, octreotide (somatostatin analogue), dopamine agonist (bromocriptine/cabergoline), growth hormone receptor antagonist (pegvisomant), radiation

**Prolactin (PRL)**

**HYPERPROLACTINEMIA**

**Etiology**
- pregnancy and breastfeeding
- prolactinoma: most common pituitary adenoma (prolactin-secreting tumours may be induced by estrogens and grow during pregnancy)
- pituitary masses with pituitary stalk compression causing reduced dopamine inhibition of prolactin release
- primary hypothyroidism (increased TRH)
- decreased clearance due to chronic renal failure or severe liver disease (prolactin is metabolized by both the kidney and liver)
- medications with anti-dopaminergic properties are a common cause of high prolactin levels: antipsychotics (common), antidepressants, antihypertensives, anti-migraine agents (triptans/ergotamines), bowel motility agents (metoclopramide/domperidone), H₂-blockers (ranitidine)
- macroprolactinemia (high molecular weight prolactin also known as big big prolactin)

**Clinical Features**
- galactorrhea (secretion of breast milk in women and, rarely, men), infertility, hypogonadism, amenorrhea, erectile dysfunction

**Investigations**
- serum PRL, TSH, liver enzyme tests, creatinine
- MRI

**Treatment**
- long-acting dopamine agonist: bromocriptine, cabergoline or quinagolide (Norprolac™)
- surgery ± radiation (rare)
- prolactin-secreting tumours are very slow-growing and sometimes require no treatment
- if medication-induced, consider stopping medication if possible
- in certain cases if microprolactinoma and not planning on becoming pregnant, may consider OCP

**Thyroid Stimulating Hormone (TSH)**
- see Thyroid, E20

**Adrenocorticotropic Hormone (ACTH)**
- see Adrenal Cortex, E29

**Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH)**
- see Gynecology, GY4

**HYPOGONADOTROPIC HYPOGONADISM**

**Clinical Features**
- hypogonadism, amenorrhea, erectile dysfunction (see Urology, U30), loss of body hair, fine skin, testicular atrophy, failure of pubertal development

**Treatment**
- Pergonal™ (combined FSH/LH hormone therapy), hCG, or pulsatile GnRH analogue if fertility desired
- symptomatic treatment with estrogen/testosterone

Approach to Nipple Discharge
- Differentiate between galactorrhea (fat droplets present) versus breast discharge (usually unilateral, may be bloody or serous)
- If galactorrhea, determine if physiologic (e.g. pregnancy, lactation, stress) versus pathologic
- If abnormal breast discharge, must rule out a breast malignancy
HYPERGONADOTROPIC HYPOGONADISM
• 2° hypersecretion in gonadal failure (e.g. in menopause)

**Antidiuretic Hormone (ADH)**

**DIABETES INSIPIDUS (DI)**

**Definition**
• disorder resulting from deficient ADH action causing passage of large volumes of dilute urine

**Etiology and Pathophysiology**
• central DI: insufficient ADH due to pituitary surgery, tumours, idiopathic/autoimmune, stalk lesion, hydrocephalus, histiocytosis X, trauma, familial central DI
• nephrogenic DI: collecting tubules in kidneys resistant to ADH due to drugs (e.g. lithium), hypercalcemia, hypokalemia, chronic renal disease, hereditary nephrogenic DI
• psychogenic polydipsia and osmotic diuresis must be ruled out

**Clinical Features**
• passage of large volumes of dilute urine, polydipsia, dehydration; hypernatremia can develop with lack of access to water or impaired thirst mechanism

**Diagnostic Criteria**
• fluid deprivation will differentiate true DI (high urine output persists, urine osmolality < plasma osmolality) from psychogenic DI (psychogenic polydipsia)
• response to exogenous ADH (DDAVP) will distinguish central from nephrogenic DI

**Treatment**
• DDAVP/vasopressin for central DI
• chlorpropamide, clofibrate, thiazides, NSAIDs or carbamazepine as second line or for partial DI
• nephrogenic DI treated with solute restriction NSAIDs and thiazide diuretics; DDAVP (if partial)

**SYNDROME OF INAPPROPRIATE ADH SECRETION (SIADH)**

**Diagnostic Criteria**
• hyponatremia with corresponding plasma hypo-osmolality, urine sodium concentration above 40 mEq/L, urine less than maximally diluted (>100 mOsm/kg), euvoolemia (edema absent), and absence of adrenal, renal or thyroid insufficiency

**Etiology and Pathophysiology**
• stress (pain, nausea, post-surgical)
• malignancy (lung, pancreas, lymphoma)
• CNS disease (inflammatory, hemorrhage, tumour, Guillain-Barré syndrome)
• respiratory disease (TB, pneumonia, empyema)
• drugs (SSRIs, vincristine, chlorpropamide, cyclophosphamide, carbamazepine, nicotine, morphine, DDAVP, oxytocin)

**Treatment**
• treat underlying cause, fluid restriction (800-1000 mL/day), vasopressin receptor antagonists (e.g. tolvaptan, conivaptan), and demeclocycline (antibiotic with anti-ADH properties, rarely-used) fluidocortisone, furosemide

**Pituitary Pathology**

**PITUITARY ADENOMA** (see Neurosurgery, NS14)

**Clinical Features**
• local mass effects
  - visual field defects (bitemporal hemianopia due to compression of the optic chiasm), diplopia (due to oculomotor nerve palsies), headaches; increased ICP is rare
• hypofunction
• hypopituitarism (see sidebar)
• hyperfunction
  - PRL (galactorrhea), GH (acromegaly in adults, gigantism in children), ACTH (Cushing’s disease = Cushing’s syndrome caused by a pituitary tumour)
  - tumours secreting LH, FSH and TSH are rare

**Presentations of Pituitary Lesions:**
• Mass effect (visual field deficits, diplopia, ptosis, headaches, CSF leak)
• Hyperfunction
• Hypofunction

**Important Deficiencies to Recognize**
• Adrenal insufficiency
• Hypothyroidism

Concurrent adrenal insufficiency and hypothyroidism should be treated with glucocorticoids first and then with thyroid hormone to avoid adrenal crisis.
Investigations
- radiological evaluation (MRI is imaging procedure of choice)
- formal visual field testing
- hypothalamic-pituitary hormonal function

HYPOPITUITARISM

Etiology (the eight Is)
- Invasive
  - pituitary tumours, craniopharyngioma, cysts (Rathke’s cleft, arachnoid or dermoid), metastases
- Infarction/hemorrhage
  - Sheehan’s syndrome (pituitary infarction due to excessive post-partum blood loss and hypovolemic shock)
  - pituitary apoplexy (acute hemorrhage/infarction of a pituitary tumour; presents with sudden loss of pituitary hormones, severe headache and altered level of consciousness; can be fatal if not recognized and treated early)
- Infiltrative/inflammatory
  - sarcoidosis, hemochromatosis, histiocytosis
- Infectious
  - syphilis, TB, fungal (histoplasmosis), parasitic (toxoplasmosis)
- Injury
  - severe head trauma
- Immunologic
  - autoimmune destruction
- Iatrogenic
  - following surgery or radiation
- Idiopathic
  - familial forms, congenital midline defects

Investigations
- triple bolus test
  - stimulates release of all anterior pituitary hormones in normal individuals
  - rapid sequence of IV infusion of insulin, GnRH and TRH
  - insulin (usual dose 0.1 unit/kg of human regular insulin) → hypoglycemia → increased GH and ACTH
  - GnRH (100 µg IV push) → increased LH and FSH
  - TRH (200 µg IV push over 60 s) → increased TSH and PRL (no longer available)

Thyroid

Thyroid Hormones

Figure 7. Thyroid hormone synthesis
Synthetic Function of Thyroid Gland
- the synthesis of thyroid hormones T₃ (triiodothyronine) and T₄ (thyroxine) by the thyroid gland involves trapping and oxidation of iodide, iodination of thyroglobulin, and release of T₃ and T₄
- free T₃ (0.03%) and free T₄ (0.3%) represent the hormonally active fraction of thyroid hormones
- the remaining fraction is bound to thyroxine binding globulin (TBG) and albumin and is biologically inactive
- T₃ is more biologically active (3-8x more potent), but T₄ has a longer half-life
- 85% of T₃ is converted to T₂ or reverse T₃ (RT₃) in the periphery by deiodinases
- RT₃ is metabolically inactive but produced in times of stress to decrease metabolic activity
- most of the plasma T₄ pool is derived from the peripheral conversion of T₃
- calcitonin, a hormone, is also produced in the thyroid, by the parafollicular cells or C cells
- it functions by inhibiting osteoclast activity and increasing renal calcium excretion

Role of Thyroid Hormones
- thyroid hormones act primarily through modifying gene transcription by binding to nuclear receptors
- action of these hormones is diffuse, affecting nearly every organ system
- they produce an increase in basal metabolic rate, including: increased Na'/K' ATPase activity, increased O₂ consumption, increased respiration, heat generation, and increased cardiovascular activity
- also play crucial role during fetal life in both neurological and somatic development

Regulation of Thyroid Function
- extrathyroid
  - stimulation of thyroid by TSH, epinephrine, prostaglandins (cAMP stimulators)
  - T₃ negatively feeds back on anterior pituitary to inhibit TSH and on hypothalamus to inhibit TRH
- intrathyroid (autoregulation)
  - increasing iodide supply inhibits iodide organification, thus decreasing T₃ and T₄ synthesis (Wolff-Chaikoff effect)
  - there is varying thyroid sensitivity to TSH in response to iodide availability
  - increased ratio of T₃ to T₄ in iodide deficiency
  - increased activity of peripheral 5' deiodinase in hypothyroidism increases T₃ production despite low T₄ levels

Tests of Thyroid Function and Structure
TSH
- sensitive TSH (sTSH) is the best test for assessing thyroid function
- hyperthyroidism
  - primary: TSH is low because of negative feedback from increased levels of circulating T₃ and T₄
  - secondary: increased TSH results in increased T₃ and T₄
- hypothyroidism
  - primary: increased TSH (most sensitive test) because of less negative feedback from T₃ and T₄
  - secondary: TSH is low or normal with variable response to TRH depending on the site of the lesion (pituitary or hypothalamic)

Free T₃ and Free T₄
- indications: if secondary or tertiary (hypothalamic) hyper/hypothyroidism is suspected, or if normal TSH levels despite symptoms of hyper/hypothyroidism
- standard assessment of thyroid function measures TSH and if necessary free T₃. Free T₃ should be measured if TSH is suppressed and free T₄ is normal to rule out T₃ toxicity

Thyroid Autoantibodies
- thyroglobulin antibodies (TgAb), thyroid peroxidase antibodies, TSH receptor inhibiting antibodies
  - increased in Hashimoto’s disease; normal variant in 10-20% of individuals
- thyroid stimulating immunoglobulin (TSI)
  - increased in Graves’ disease

Plasma Thyroglobulin
- used to monitor residual thyroid activity post-thyroidectomy, e.g. for thyroid cancer recurrence
- normal or elevated levels may suggest persistent, recurrent or metastatic disease, especially on stimulation

Serum Calcitonin
- not routinely done to investigate thyroid nodules
- ordered if suspicion of medullary thyroid carcinoma or family history of MEN IIa or IIb syndromes
Thyroid Imaging/Scans
- normal gland size 15-20 g (estimated by palpation)
- thyroid U/S
  - to measure size of gland, solid vs. cystic nodule, facilitate fine needle aspirate biopsy (FNAB)
- radioactive iodine thyroid scan (Technetium-99)
  - test of structure: order if there is a thyroid nodule and patient is hyperthyroid with low TSH
  - differentiates between hot (functioning \( \rightarrow \) excess thyroid hormone production) and cold (non-functioning) nodules
  - hot nodule \( \rightarrow \) very low chance malignancy; treat hyperthyroidism
  - cold nodule \( \rightarrow \) \(-5\%\) chance malignancy; further work-up required (U/S and FNAB)
- thyroid U/S
  - to measure size of gland, solid vs. cystic nodule, facilitate fine needle aspirate biopsy (FNAB)
- radioactive iodine uptake (RAIU)
  - test of function: order if patient is thyrotoxic
  - RAIU measures the turnover of iodine by thyroid gland in vivo
  - if \( ^{131}I \) uptake (i.e. incorporated) \( \rightarrow \) gland is overactive (hyperthyroid)
  - if \( ^{131}I \) uptake (i.e. not incorporated) \( \rightarrow \) gland is leaking thyroid hormone (e.g. thyroiditis), exogenous thyroid hormone use, or excess iodine intake (e.g. amiodarone or contrast dye, which has high iodine content)

Thyroid Biopsy
- fine needle aspiration (FNA) for cytology
  - differentiates between benign and malignant disease
  - best done under ultrasound guidance
  - accuracy decreased if nodule is greater than 50% cystic, or if nodule located posteriorly in the gland

Table 16. Summary of Diagnostic Testing in Hyperthyroidism and Hypothyroidism

<table>
<thead>
<tr>
<th>Disorder</th>
<th>TSH</th>
<th>Free T(_4/T_3)</th>
<th>Thyroid Antibodies</th>
<th>RAIU</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPERTHYROIDISM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves’ Disease</td>
<td>Decreased</td>
<td>Increased</td>
<td>TSI</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Toxic Nodular Goitre</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td>Heterogeneous uptake on scan</td>
</tr>
<tr>
<td>Toxic Nodule</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td>Hot nodule on scan</td>
</tr>
<tr>
<td>THYROIDITIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute, Silent, Postpartum</td>
<td>Decreased</td>
<td>Increased</td>
<td>Up to 50% of cases</td>
<td>Decreased</td>
<td>(becomes increased once entering hypothyroid phase, when TSH rises)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In classical subacute painful thyroiditis, ESR increased</td>
<td></td>
</tr>
<tr>
<td>EXTRATHYROIDAL SOURCES OF THYROID HORMONE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endogenous (struma ovariae, ovarian teratoma, metastatic follicular carcinoma)</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Exogenous (drugs)</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Decreased</td>
<td></td>
</tr>
</tbody>
</table>
Table 17. Differential Diagnosis of Thyrotoxicosis (continued)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>TSH</th>
<th>Free T4/T3</th>
<th>Thyroid Antibodies</th>
<th>RAIR</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EXCESSIVE THYROID STIMULATION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary thyrotrophoma</td>
<td>Increased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Pituitary thyroid hormone receptor resistance</td>
<td>Increased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Increased hCG (e.g. pregnancy)</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td>DO NOT DO THIS TEST IN PREGNANCY</td>
</tr>
</tbody>
</table>

Clinical Features

Table 18. Clinical Features of Thyrotoxicosis

<table>
<thead>
<tr>
<th>General</th>
<th>Fatigue, heat intolerance, irritability, fine tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVS</td>
<td>Tachycardia, atrial fibrillation, palpitations</td>
</tr>
<tr>
<td>GI</td>
<td>Weight loss with increased appetite, thirst, increased frequency of bowel movements (hyperdefecation)</td>
</tr>
<tr>
<td>Neurology</td>
<td>Proximal muscle weakness, hypokalemic periodic paralysis (more common in Asians)</td>
</tr>
<tr>
<td>GU</td>
<td>Oligomenorrhea, amenorrhea, decreased fertility</td>
</tr>
<tr>
<td>Dermatology</td>
<td>Fine hair, skin moist and warm, vitiligo, soft nails with onycholysis (Plummer’s nails), palmar erythema</td>
</tr>
<tr>
<td>Graves’ disease: clubbing (acropathy), pretibial myxedema (rare)</td>
<td></td>
</tr>
<tr>
<td>MSK</td>
<td>Decreased bone mass, proximal muscle weakness</td>
</tr>
<tr>
<td>Hematology</td>
<td>Graves’ disease: leukopenia, lymphocytosis, splenomegaly, lymphadenopathy (occasionally)</td>
</tr>
<tr>
<td>Eye</td>
<td>Graves’ disease: lid lag, retraction, proptosis, decreased acuity, puffiness, conjunctival injection</td>
</tr>
</tbody>
</table>

Treatment

- thionamides: PTU or MMI; MMI recommended (except in first trimester pregnancy)
- β-blockers for symptom control
- radioactive iodine thyroid ablation for Graves’ disease
- surgery in the form of hemi, sub-total, or complete thyroidectomy

Graves’ Disease

Definition

- syndrome characterized by hyperthyroidism with any of: diffuse goitre, ophthalmopathy, dermopathy

Epidemiology

- most common cause of thyrotoxicosis
- occurs at any age with peak in 3rd and 4th decade
- F > M = 7:1, 1.5-2% of U.S. women
- familial predisposition: 15% of patients have a close family member with Graves’ disease and 50% have family members with positive circulating antibodies
- association with HLA B8 and DR3
- may be associated with other inherited autoimmune disorders (e.g. pernicious anemia, Hashimoto’s disease)

Etiology and Pathophysiology

- autoimmune disorder due to a defect in T-suppressor cells
- B lymphocytes produce TSI that binds the TSH receptor and stimulates the thyroid gland
- immune response can be triggered by postpartum state, iodine excess, lithium therapy, viral or bacterial infections, glucocorticoid withdrawal
- ophthalmopathy a result of increased tissue volume due to inflammation and accumulation of glycosaminoglycans, stimulated by TSI, that increase osmotic pressure within the orbit. This leads to fluid accumulation and displacement of the eye ball forward
- dermopathy may be related to cutaneous glycosaminoglycan deposition

Clinical Features

- signs and symptoms of thyrotoxicosis
- diffuse thyroid goitre ± thyroid bruit secondary to increased blood flow through the gland
- ophthalmopathy: proptosis, diplopia, conjunctival injection, corneal abrasions, periorbital puffiness, lid lag, decreased visual acuity if Graves’ (plus signs of hyperthyroidism: lid retraction, characteristic stare)

Graves’ Ophthalmopathy

NO SPECS (in order of changes usually)
- No signs
- Only signs: lid lag, lid retraction
- Soft tissue: periorbital puffiness, conjunctival injection, chemosis
- Proptosis/Exophthalmos
- Extraocular (diplopia)
- Corneal abrasions (since unable to close eyes)
- Sight loss

Signs and Symptoms of HYPERthyroidism

- Tremor
- Heart rate up
- Yawning (fatigued)
- Restlessness
- Oligomenorrhea/amenorrhea
- Intolerance to heat
- Diarrhea
- Irritability
- Sweating
- Muscle wasting/weight loss

Caution with Thionamides

These drugs are effective in controlling hyperthyroidism and induce permanent remission in 20-30% of patients with Graves’ disease. They inhibit thyroid hormone synthesis. They are most often employed to achieve a euthyroid state before definitive treatment.

Adverse effects include teratogenicity, agranulocytosis, hepatotoxicity and ANCA-positive vasculitis.
• dermatopathy (rare): pretibial myxedema (thickening of dermis that manifests as non-pitting edema)
• acropachy: clubbing and thickening of distal phalanges

Investigations
• low TSH
• increased free \( T_4 \) (and/or increased \( T_3 \))
• positive for TSI
• increased radioactive iodine uptake
• diffuse high uptake on thyroid scan (only do this test in the presence of nodule)

Treatment
• thionamides
  ▪ propylthiouracil (PTU) or methimazole (MMI)
  ▪ inhibit thyroid hormone synthesis by inhibiting peroxidase-catalyzed reactions, thereby inhibiting organification of iodide, blocking the coupling of iodotyrosines. PTU also inhibits peripheral deiodination of \( T_4 \) to \( T_3 \)
  ▪ continue treatment until remission occurs (20–40% of patients achieve spontaneous remission at 6-18 mo of treatment)
  ▪ small goitre and recent onset are good indicators for long-term remission with medical therapy
  ▪ major side effects: hepatitis, agranulocytosis and fever/arthralgias
  ▪ minor side effects: rash
  ▪ iodinated contrast agents: sodium ipodate and iopanoic acid can inhibit conversion of \( T_4 \) to \( T_3 \) and are especially effective in combination with MMI
  ▪ MMI preferred vs. PTU due to longer duration of action (once daily for most), more rapid efficacy, and lower incidence of side effects
  ▪ MMI contraindicated in pregnancy (teratogenic), use PTU
• symptomatic treatment with \( \beta \)-blockers
• thyroid ablation with radioactive \( ^{131}I \) if PTU or MMI trial does not produce disease remission
  ▪ high incidence of hypothyroidism after \( ^{131}I \) requiring lifelong thyroid hormone replacement
  ▪ contraindicated in pregnancy
  ▪ subtotal or total thyroidectomy (indicated rarely for large goiters, suspicious nodule for CA, if patient is intolerant to thionamides and refusing RAI ablation)
    ▪ risks include hypoparathyroidism and vocal cord palsy
  ▪ ophthalmopathy/orbitopathy
    ▪ smoking cessation is most important
    ▪ prevent drying
    ▪ high dose prednisone in severe cases
    ▪ orbital radiation, surgical decompression

Prognosis
• course involves remission and exacerbation unless gland is destroyed by radioactive iodine or surgery
• lifetime follow-up needed
• risk of relapse is 37%, 21%, 6% in thionamides, radioiodine ablation, and surgery groups, respectively

Subacute Thyroiditis (Thyrotoxic Phase)

Definition
• acute inflammatory disorder of the thyroid gland characterized by an initial thyrotoxic state followed by hypothyroidism eventually followed by euthyroidism in most cases
• two subtypes: painful and painless

Etiology and Pathophysiology
• acute inflammation of the thyroid gland characterized by giant cells and lymphocytes
• disruption of thyroid follicles by inflammatory process results in the release of stored hormone rather than excessive production of new thyroid hormone
• painful = viral (usually preceded by URTI), De Quervain’s (granulomatous thyroiditis)
• painless = postpartum, auto-immune, lymphocytic
  ▪ occurs in 5-10% of postpartum mothers and is symptomatic in 1/3 of patients

Clinical Features
• thyroid gland enlargement
• two forms
  ▪ painful ("De Quervain’s") thyroid, ears, jaw and occiput
  ▪ painless ("Silent")
fever and malaise may be present, especially in De Quervain’s postpartum: thyrotoxicosis 2-3 mo postpartum with a subsequent hypothyroid phase at 4-8 mo postpartum may be mistakenly diagnosed as postpartum depression

Laboratory Investigations
- initial elevated free $T_4$, $T_3$, low TSH, RAIU markedly reduced
- marked elevation of ESR in painful variety only
- as disease progresses values consistent with hypothyroidism may appear
- rise in RAIU reflects gland recovery

Treatment
- painful – high dose NSAIDs, prednisone may be required for severe pain, fever, or malaise
- iodinated contrast agents (e.g. iopanoic acid, ipodate) to inhibit peripheral conversion of $T_4$ to $T_3$
- $\beta$-adrenergic blockade is usually effective in reversing most of the hypermetabolic and cardiac symptoms in both subtypes
- if symptomatically hypothyroid, may treat short-term with thyroxine

Prognosis
- full recovery in most cases, but permanent hypothyroidism in 10% of painless thyroiditis
- postpartum: most resolve spontaneously without need for supplementation, however may recur with subsequent pregnancies

Toxic Adenoma/Toxic Multinodular Goitre

Etiology and Pathophysiology
- autonomous thyroid hormone production from a functioning adenoma that is hypersecreting $T_3$ and $T_4$
- may be singular (toxic adenoma) or multiple (toxic multinodular goitre [Plummer’s disease])

Clinical Features
- goitre with adenomatous changes
- tachycardia, heart failure, arrhythmia, weight loss, nervousness, weakness, tremor, and sweats
- atrial fibrillation is a common presentation in the elderly
- seen most frequently in elderly people, often with presentation of atrial fibrillation

Investigations
- low TSH, high $T_3$ and $T_4$
- thyroid scan with increased uptake in nodule(s) and suppression of the remainder of the gland

Treatment
- initiate therapy with PTU or MMI to attain euthyroid state in order to avoid radiation thyroiditis
- use high dose radioactive iodine to ablate tissue over weeks
- $\beta$-blockers often necessary for symptomatic treatment prior to definitive therapy
- surgical excision may also be used as 1st line treatment

Thyrotoxic Crisis/Thyroid Storm

Definition
- acute exacerbation of all of the symptoms of thyrotoxicosis presenting in a life-threatening state secondary to uncontrolled hyperthyroidism – medical emergency!
- rare, but serious with mortality rate between 20-30%

Etiology and Pathophysiology
- often precipitated by infection, trauma, or surgery in a hyperthyroid patient

Differential Diagnosis
- sepsis, pheochromocytoma, malignant hyperthermia, drug overdose, neuroleptic malignant syndrome

Clinical Features
- hyperthyroidism
- extreme hyperthermia, tachycardia, vomiting, diarrhea, vascular collapse, hepatic failure with jaundice, and confusion
- tachyarrhythmia, congestive heart failure, shock
- mental status changes ranging from delirium to coma
Laboratory Investigations
• increased free T\(_3\) and T\(_4\), undetectable TSH
• ± anemia, leukocytosis, hyperglycemia, hypercalcemia, elevated LFTs

Treatment
• principles are the same as in hyperthyroidism except use higher doses and frequencies
• initiate prompt therapy; do not wait for confirmation from lab
• supportive: fluid and electrolytes, diuretics, vasopressors, cooling blanket, and acetaminophen for hyperthermia
• propranolol (IV) for tachycardia and to decrease peripheral conversion of T\(_4\) to T\(_3\) (watch for CHF)
• high dose PTU/MMI
• iodide (NaI, KI, Lugol’s solution) to inhibit release of thyroid hormone, given after PTU
• iodinated radiocontrast solutions such as iopanoic acid inhibit both peripheral conversion of T\(_4\) to T\(_3\) and release of thyroid hormone
• lithium to inhibit release of thyroid hormone
• dexamethasone to block peripheral conversion, to lower body temperature, and to treat possible underlying autoimmune condition
• if extreme plasmapheresis or dialysis to remove high circulating thyroid hormone
• treat precipitant

Prognosis
• probably <20% mortality rate if rapidly recognized and treated

Hypothyroidism

Definition
• clinical syndrome caused by cellular responses to insufficient thyroid hormone production

Epidemiology
• 2-3% of general population
• F:M = 10:1
• 10-20% of women over age 50 have subclinical hypothyroidism (normal T\(_4\), TSH mildly elevated)
• iodine deficiency most common cause worldwide, but not in North America

Etiology and Pathophysiology
• primary hypothyroidism (90%)
  ▪ inadequate thyroid hormone production secondary to intrinsic thyroid defect
  ▪ iatrogenic: post-ablative (\(^{131}\)I or surgical thyroidectomy)
  ▪ autoimmune: Hashimoto’s thyroiditis, chronic thyroiditis, idiopathic, burnt out Graves’
  ▪ hypothyroid phase of subacute thyroiditis
  ▪ drugs: goitrogens (iodine), PTU, MMI, lithium
  ▪ infiltrative disease (progressive systemic sclerosis, amyloid)
  ▪ iodine deficiency
  ▪ congenital (1/4000 births)
  ▪ neoplasia
• secondary hypothyroidism: pituitary hypothyroidism
  ▪ insufficiency of pituitary TSH
• tertiary hypothyroidism: hypothalamic hypothyroidism
  ▪ decreased TRH from hypothalamus (rare)
• peripheral tissue resistance to thyroid hormone (Refetoff syndrome)

Table 19. Interpretation of Serum TSH and Free T\(_4\) in Hypothyroidism

<table>
<thead>
<tr>
<th></th>
<th>Serum TSH</th>
<th>Free T(_4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overt Primary Hypothyroidism</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Subclinical Primary Hypothyroidism</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Secondary Hypothyroidism</td>
<td>Decreased or not appropriately elevated</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

Thyroid Hormone Replacement for Subclinical Hypothyroidism

Purpose: To assess the effects of thyroid hormone replacement for subclinical hypothyroidism.

Study Selection: RCTs comparing thyroid hormone replacement with placebo in adults with subclinical hypothyroidism. Minimum duration of follow-up was one month.

Results: No trial assessed (cardiovascular) mortality or morbidity. Seven studies evaluated symptoms, mood and quality of life with no statistically significant improvement. One study showed a statistically significant improvement in cognitive function. Six studies assessed serum lipids, there was a trend for reduction in some parameters following levothyroxine replacement. Some echocardiographic parameters improved after levothyroxine replacement therapy, like myocardial relaxation. Only four studies reported adverse events with no statistically significant differences between groups.

Conclusions: In current RCTs, levothyroxine replacement therapy for subclinical hypothyroidism did not result in improved survival or decreased cardiovascular morbidity. Data on health-related quality of life and symptoms did not demonstrate significant differences between intervention groups. Some evidence indicates that levothyroxine replacement improves some parameters of lipid profiles and left ventricular function.

Signs and Symptoms of Hypothyroidism
HIS FIRM CAP
Hypoventilation
Intolerance to cold
Slow HR
Fatigue
Impotence
Renal impairment
Menorrhagia/amenorrhea
Constipation
Anemia
Paresthesia
Clinical Features

Table 20. Clinical Features of Hypothyroidism

<table>
<thead>
<tr>
<th>Category</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Fatigue, cold intolerance, slowing of mental and physical performance, hoarseness, macroglossia</td>
</tr>
<tr>
<td>CVS</td>
<td>Pericardial effusion, bradycardia, hypotension, worsening CHF + angina, hypercholesterolemia, hyperhomocysteinemia, myxedema heart</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Decreased exercise capacity, hypoventilation secondary to weak muscles, decreased pulmonary responses to hypoxia, sleep apnea due to macroglossia</td>
</tr>
<tr>
<td>GI</td>
<td>Weight gain despite poor appetite, constipation</td>
</tr>
<tr>
<td>Neurology</td>
<td>Paresthesia, slow speech, muscle cramps, delay in relaxation phase of deep tendon reflexes (“hung reflexes”), carpal tunnel syndrome, asymptomatic increase in CK, seizures</td>
</tr>
<tr>
<td>GU</td>
<td>Menorrhagia, amenorrhea, impotence</td>
</tr>
<tr>
<td>Dermatology</td>
<td>Puffiness of face, periorbital edema, cool and pale, dry and rough skin, hair dry and coarse, eyebrows thinned (lateral 1/3), discolouration (carotenemia)</td>
</tr>
<tr>
<td>Hematology</td>
<td>Anemia: 10% pernicious due to presence of anti-parietal cell antibodies with Hashimoto’s thyroiditis</td>
</tr>
</tbody>
</table>

Treatment

- L-thyroxine (dose range: 0.05-0.2 mg PO OD – 1.6 µg/kg/d)
- usually require 1.6 times their weight in kg as the dose in µg/d
- elderly patients and those with CAD: start at 0.025 mg daily and increase gradually every 6 wk (start low, go slow)
- after initiating L-thyroxine, TSH needs to be evaluated in 6 wk; dose is adjusted until TSH returns to normal reference range
- once maintenance dose achieved, follow-up TSH with patient annually
- secondary/tertiary hypothyroidism:
  - need to rule out and/or treat adrenal insufficiency first
  - monitor via measurement of free T₄ (TSH is unreliable in this setting)

CONGENITAL HYPOTHYROIDISM

- see Pediatrics, P30

Hashimoto’s Thyroiditis

- most common form of primary hypothyroidism in North America
- chronic autoimmune thyroiditis characterized by both cellular and humoral factors in the destruction of thyroid tissue
- two major forms: goitrous and atrophic; both forms share same pathophysiology but differ in the extent of lymphocytic infiltration, fibrosis, and thyroid follicular cell hyperplasia
- goitrous variant usually presents with a rubbery goitre and euthyroidism, then hypothyroidism becomes evident
  - associated with fibrosis
- atrophic variant patients are hypothyroid from the start
  - associated with thyroid lymphoma

Etiology and Pathophysiology

- defect in clone of T-suppressors leads to cell-mediated destruction of thyroid follicles
- B lymphocytes produce antibodies against thyroid components including thyroglobulin, thyroid peroxidase, TSH receptor, Na⁺/I symporter

Risk Factors

- female gender
- genetic susceptibility: increased frequency in patients with Down’s syndrome, Turner’s syndrome, certain HLA alleles, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
- family Hx or personal Hx of other autoimmune diseases
- cigarette smoking
- high iodine intake
- stress and infection

Investigations

- high TSH, low T₄ (not necessary to measure T₃ as it will be low as well)
- presence of thyroid peroxidase and thyroglobulin antibodies in serum

Treatment

- if hypothyroid, replace with L-thyroxine (analog of T₄)
Myxedema Coma

Definition
- severe hypothyroidism complicated by trauma, sepsis, cold exposure, MI, inadvertent administration of hypnotics or narcotics, and other stressful events – medical emergency!
- rare, but serious mortality when it occurs (up to 60%, despite therapy)

Clinical Features
- hallmark symptoms of decreased mental status and hypothermia; hyponatremia, hypotension, hypoglycemia, bradycardia, hypoventilation, and generalized edema often present

Investigations
- decreased T₄, increased TSH, decreased glucose
- check ACTH and cortisol for evidence of adrenal insufficiency

Treatment
- aggressive treatment required
- ABCs: ICU admission
- corticosteroids (for risk of concomitant adrenal insufficiency): hydrocortisone 100 mg q8h
- L-thyroxine 0.2-0.5 mg IV loading dose, then 0.1 mg IV OD until oral therapy tolerated; also consider T₃ therapy
- supportive measures: mechanical ventilation, fluids, vasopressor drugs, passive rewarming, IV dextrose
- monitor for arrhythmia

Sick Euthyroid Syndrome (SES)

Definition
- changes in circulating thyroid hormones amongst patients with serious illness, trauma or stress
- not due to intrinsic thyroid or pituitary disease
- initially low free T₃ may be followed by low TSH and if severe illness low free T₄. With recovery of illness TSH may overshoot and become transiently high

Pathophysiology
- abnormalities in SES include alterations in
  - peripheral transport and metabolism of thyroid hormone
  - regulation of TSH secretion
  - thyroid function itself

Labs
- initially decreased free T₃ followed by decreased TSH and finally decreased free T₄

Treatment
- treat the underlying disease; thyroid hormone replacement worsens outcomes
- thyroid function tests normalize once patient is well (initially with a transient increase in TSH)

Non-Toxic Goitre

Definition
- generalized enlargement of the thyroid gland in a euthyroid individual that does not result from inflammatory or neoplastic processes

Pathophysiology
- the appearance of a goitre is more likely during adolescence, pregnancy, and lactation because of increased thyroid hormone requirements
  - early stages: goitre is usually diffuse
  - later stages: multinodular non-toxic goitre with nodule, cyst formation and areas of ischemia, hemorrhage, and fibrosis

Etiology
- iodine deficiency or excess
- goitrogens: brassica vegetables (e.g. turnip, cassava)
- drugs: iodine, lithium, para-aminosalicylic acid
- any disorder of hormone synthesis with compensatory growth
- peripheral resistance to thyroid hormone
Treatment
- remove goitrogens
- radioiodine therapy (need very high doses since non-toxic, used as last resort)
- suppression with L-thyroxine (rarely done)
- surgery may be necessary for severe compressive symptoms

Complications
- compression of neck structures causing stridor, dysphagia, pain and hoarseness
- multinodular goitre may become autonomous leading to toxic multinodular goitre and hyperthyroidism

Thyroid Nodules

Definition
- clearly defined discrete mass, separated from the thyroid parenchyma
- palpable nodules are found in approximately 5% of the population
- M:F = 1:4

Etiology
- benign tumours (e.g. colloid nodule, follicular adenoma)
- thyroid malignancy
- hyperplastic area in a multinodular goitre
- cyst: true thyroid cyst, area of cystic degeneration in a multinodular goitre

Investigations
- thyroid ultrasound to determine size and characteristics (cystic vs. solid vs. mixed)
- thyroid function tests (TSH)
- thyroid scan only if TSH is low to determine if nodule is hot (i.e. significant $^{131}$I uptake into nodule) which signifies very low malignant potential
- FNA for all nodules >1-1.5 cm, if not a hot nodule

Thyroid Malignancies
- see Otolaryngology OT37

Adrenal Cortex

Adrenocorticotropic Hormone (ACTH)
- a polypeptide (cleaved from prohormone POMC), secreted in a pulsatile fashion from the anterior pituitary with diurnal variability (peak: 0200-0400; trough: 1800-2400)
- secretion regulated by corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP)
- stimulates growth of adrenal cortex and release of glucocorticoids, androgens and, to a limited extent, mineralocorticoids
- some melanocyte stimulating activity

Adrenocortical Hormones

Aldosterone
- a mineralocorticoid which regulates extracellular fluid (ECF) volume through Na⁺ (and Cl⁻) retention and K⁺ (and H⁺) excretion (stimulates distal tubule Na⁺/K⁺ ATPase)
- regulated by the renin-angiotensin-aldosterone system (Figure 10)
- negative feedback to juxtaglomerular apparatus (JGA) by long loop (aldosterone → volume expansion) and short loop (angiotensin II → peripheral vasoconstriction)
Cortisol
- a glucocorticoid, regulated by the HPA axis
- involved in regulation of metabolism; counteracts the effects of insulin
- support blood pressure, vasomotor tone
- also involved in regulation of behaviour and immunosuppression

<table>
<thead>
<tr>
<th>Stimulatory Effects</th>
<th>Inhibitory Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulate hepatic glucose production (gluconeogenesis)</td>
<td>Inhibit bone formation; stimulate bone resorption</td>
</tr>
<tr>
<td>Increase insulin resistance in peripheral tissues</td>
<td>Inhibit fibroblasts, causing collagen and connective tissue loss</td>
</tr>
<tr>
<td>Increase protein catabolism</td>
<td>Suppress inflammation; impair cell-mediated immunity</td>
</tr>
<tr>
<td>Stimulate leukocytosis and lymphopenia</td>
<td>Inhibit growth hormone axis</td>
</tr>
<tr>
<td>Increase cardiac output, vascular tone, Na⁺ retention</td>
<td>Inhibit reproductive axis</td>
</tr>
<tr>
<td>Increase PTH release, urine calcium excretion</td>
<td>Inhibit vitamin D₃ and inhibit calcium uptake</td>
</tr>
</tbody>
</table>

Androgens
- sex steroids regulated by ACTH; primarily responsible for adrenarche (growth of axillary and pubic hair)
- principal adrenal androgens are dihydroepiandrosterone (DHEA), androstenedione and 11-hydroxyandrostenedione
- proportion of total androgens (adrenal to gonadal) increases in old age
Adrenocortical Functional Work-Up

STIMULATION TEST
- purpose: diagnosis of hormone deficiencies
- method: measure target hormone after stimulation with tropic (pituitary) hormone

1. Tests of Glucocorticoid Reserve
   - Cosyntropin (ACTH analogue) Stimulation Test
     - give 1 µg or 250 µg cosyntropin IV, then measure plasma cortisol levels at time 0, 30, and 60 min
     - physiologic response: stimulated plasma cortisol of >500 nmol/L (>18 µg/dL)
     - inappropriate response: inability to stimulate increased plasma cortisol
   - insulin tolerance test used to diagnose secondary or tertiary hypoadrenalism (see Pituitary Gland, E16)

SUPPRESSION TESTS
- purpose: diagnosis of hormone hypersecretion
- method: measure target hormone after suppression of its tropic (pituitary) hormone

1. Tests of Pituitary-Adrenal Suppressibility
   - Dexamethasone (DXM) Suppression Test
     - principle: DXM suppresses pituitary ACTH → plasma cortisol should be lowered if HPA axis is normal
     - Screening Test: Overnight DXM Suppression Test
       - oral administration of 1 mg DXM at midnight → measure plasma cortisol levels the following day at 8 am
       - physiologic response: plasma cortisol <50 nmol/L (1.8 µg/dL), with 50-140 nmol/L being a "grey zone" (cannot be certain if normal or not)
       - inappropriate response: failure to suppress plasma cortisol
       - <20% false positive results due to obesity, depression, alcohol, other medications
     - Confirmatory Test: Other testing is used to confirm the diagnosis, such as:
       - 24 h urine free cortisol (shows overproduction of cortisol)
       - midnight salivary cortisol (if available), shows lack of diurnal variation
       - inappropriate response: remains high (normally will be low at midnight)

2. Tests of Mineralocorticoid Suppressibility
   - principle: expansion of extracellular fluid volume (ECFV) → plasma aldosterone should be lowered if HPA axis were normal
   - ECFV Expansion with Normal Saline (NS)
     - IV infusion of 500 mL/h of NS for 4 h → then measure plasma aldosterone levels
     - plasma aldosterone >277 pmol/L (>10 ng/dL) is consistent with primary hyperaldosteronism, <140 pmol/L (<5 ng/dL) is normal
     - inappropriate response: failure to suppress plasma aldosterone
Mineralocorticoid Excess Syndromes

Figure 11. Approach to mineralocorticoid excess syndromes

Definition
- primary hyperaldosteronism (PH): excess aldosterone production (intra-adrenal cause)
- secondary hyperaldosteronism: aldosterone production in response to excess RAAS (extra-adrenal cause)

Etiology
- primary hyperaldosteronism
  - aldosterone-producing adrenal adenoma (Conn’s syndrome)
  - bilateral or idiopathic adrenal hyperplasia
  - glucocorticoid-remediable aldosteronism
  - aldosterone-producing adrenocortical carcinoma
  - unilateral adrenal hyperplasia
- secondary hyperaldosteronism (see Figure 11)

Clinical Features
- hypertension
- hypokalemia (may have mild hypernatremia), metabolic alkalosis
- normal K⁺, low Na⁺ in SH (low effective circulating volume leads to ↑ ADH release) → edema
- increased cardiovascular risk: LV hypertrophy, atrial fibrillation, stroke, MI
- fatigue, weakness, paresthesia, headache; severe cases with tetany, intermittent paralysis

Diagnosis
- investigate plasma aldosterone to renin ratio in patients with hypertension and hypokalemia
- confirmatory testing for PH: aldosterone suppression test (demonstrate inappropriate aldosterone secretion with ECFV expansion)
- imaging: CT adrenal glands

Table 22. Diagnostic Tests in Hyperaldosteronism

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary Hyperaldosteronism</th>
<th>Secondary Hyperaldosteronism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma aldosterone to renin ratio (PAC/PRA)</td>
<td>Elevated (↑ aldo, ↓ renin)</td>
<td>Normal (↑ aldo, ↓ renin)</td>
</tr>
<tr>
<td>Salt loading test:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A) Oral test:</td>
<td>↑ urine aldosterone</td>
<td></td>
</tr>
<tr>
<td>B) IV saline test:</td>
<td>↑ plasma aldosterone</td>
<td>Not performed if normal PAC/PRA</td>
</tr>
</tbody>
</table>

Treatment
- inhibit action of aldosterone: spironolactone, eplerenone, triamterene, amiloride (act on sodium channels)
- surgical excision of adrenal adenoma
- secondary hyperaldosteronism: treat underlying cause
Cushing's Syndrome

Definition
• results from chronic glucocorticoid excess (endogenous or exogenous sources)

Etiology
• ACTH-dependent (85%) – bilateral adrenal hyperplasia and hypersecretion due to:
  ▪ ACTH-secreting pituitary adenoma (Cushing's disease; 80% of ACTH-dependent)
  ▪ ectopic ACTH-secreting tumour (e.g. small cell lung carcinoma, bronchial, carcinoid, pancreatic islet cell, pheochromocytoma or medullary thyroid tumours)
• ACTH-independent (15%)
  ▪ long-term use of exogenous glucocorticoids
  ▪ primary adrenocortical tumours: adenoma and carcinoma (uncommon)
  ▪ bilateral adrenal nodular hyperplasia

Clinical Features
• symptoms: weakness, insomnia, mood disorders, impaired cognition, easy bruising, oligo-/amenorrhea, hirsutism and acne (ACTH dependent)
• signs: central obesity, round face, supraclavicular and dorsal fat pads, facial plethora, proximal muscle wasting, purple abdominal striae, skin atrophy, acanthosis nigricans, hypertension, hyperglycemia, osteoporosis, pathologic fractures, hyperpigmentation, hyperandrogenism if ACTH-dependent

Treatment
• adrenal
  ▪ adenoma: unilateral adrenalectomy (curative)
  ▪ carcinoma: adjunctive chemotherapy often not useful (frequent metastases, poor prognosis)
  ▪ medical treatment: mitotane, ketoconazole to reduce cortisol
• pituitary
  ▪ trans-sphenoidal resection, with glucocorticoid supplement post-operatively
• ectopic ACTH tumour (paraneoplastic syndrome): usually bronchogenic cancer (poor prognosis)
  ▪ surgical resection, if possible; chemotherapy/radiation for primary tumour
  ▪ agents blocking adrenal steroid synthesis: metyrapone or ketoconazole

Congenital Adrenal Hyperplasia
• see Pediatrics, P31
Hyperandrogenism

Definition
• state of having excessive secretion of androgens (DHEA, DHEA sulfate, testosterone)

Etiology and Pathophysiology

Table 23. Etiology of Hyperandrogenism

<table>
<thead>
<tr>
<th>Constitutional/Familial</th>
<th>Family history, predisposing ethnic background</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature adrenarche</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td>Anabolic steroids, ACTH, androgens, progestational agents</td>
</tr>
<tr>
<td>Androgen-mediated</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>PCOS</td>
</tr>
<tr>
<td></td>
<td>Ovarian hyperthecosis</td>
</tr>
<tr>
<td></td>
<td>Theca cell tumours</td>
</tr>
<tr>
<td></td>
<td>Pregnancy: placental sulfatase/aromatase deficiency</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Congenital adrenal hyperplasia (CAH, late-onset CAH)</td>
</tr>
<tr>
<td></td>
<td>Tumours (adenoma, carcinoma)</td>
</tr>
<tr>
<td>Pituitary</td>
<td>Cushing’s disease – high ACTH</td>
</tr>
<tr>
<td></td>
<td>Hyperprolactinemia</td>
</tr>
</tbody>
</table>

Clinical Features

Females:
• hirsutism
  ▪ male pattern growth of androgen-dependent terminal body hair in women: back, chest, upper abdomen, face, linea alba
  ▪ Ferriman-Gallwey scoring system is used to quantify severity of hirsutism
• virilization
  ▪ masculinization: hirsutism, temporal balding, clitoral enlargement, deepening of voice, acne
  ▪ increase in musculature
• defeminization
  ▪ loss of female secondary sex characteristics (i.e. amenorrhea, ↓ breast size, infertility)

Males:
• minimal effects on hair, muscle mass, etc.
• inhibition of gonadotropin secretion may cause reduction in: testicular size, testicular testosterone production and spermatogenesis

Investigations
• testosterone, DHEA-S as a measure of adrenal androgen production
• LH/FSH (commonly in PCOS > 2.5)
• 17-OH progesterone, elevated in CAH due to 21-OH deficiency
• for virilization: CT/MRI of adrenals and ovaries (identify tumours)
• if PCOS, check blood glucose, lipids, 75 g OGTT

Treatment
• discontinue causative medications
  ▪ antiandrogens, e.g. spironolactone
• oral contraceptives (e.g. cyproterone acetate – blocks androgen receptor; found in Diane 35°)
• surgical resection of tumour
• low dose glucocorticoid ± mineralocorticoid if CAH suspected
• treat specific causative disorders, e.g. tumours, Cushing’s, etc.
• cosmetic therapy (laser, electrolysis)
Adrenocortical Insufficiency

Definition
- a state of inadequate cortisol and aldosterone production by the adrenal glands

Etiology

PRIMARY (ADDISON’S DISEASE)

Table 24. Etiology of Primary Adrenocortical Insufficiency

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Description</th>
</tr>
</thead>
</table>
| Autoimmune (70-90%) | Isolated adrenal insufficiency  
Polyglandular autoimmune syndrome type I and II  
Antibodies often directed against adrenal enzymes and 3 cortical zones |
| Infection         | TB (7-20%) (most common in developing world)  
Fungal: histoplasmosis, panacoccidiomycosis  
HW, CMV  
Syphilis  
African trypanosomiasis |
| Infiltrative      | Metastatic cancer (lung>stomach>esophagus>colon>breast); lymphoma  
Sarcoidosis, amyloidosis, hemochromatosis |
| Vascular          | Bilateral adrenal hemorrhage  
Sepsis (meningococcal, Pseudomonas)  
Coagulopathy in adults or Waterhouse-Friderichsen syndrome in children  
Thrombosis, embolism, adrenal infarction |
| Drugs             | Inhibit cortisol: ketoconazole, megestrol acetate  
Increase cortisol metabolism: rifampin, phenytoin, barbiturates, heparin, coumadin |
| Others            | Adrenoleukodystrophy  
Congenital adrenal hypoplasia (impaired steroidogenesis)  
Familial glucocorticoid deficiency or resistance |

SECONDARY ADRENOCORTICAL INSUFFICIENCY
- inadequate pituitary ACTH secretion
- multiple etiologies (see Hypopituitarism, E20), including withdrawal of exogenous steroids

Clinical Features

Table 25. Clinical Features of Primary and Secondary Adrenal Insufficiency (AI)

<table>
<thead>
<tr>
<th></th>
<th>Primary AI (Addison’s or Acute AI)</th>
<th>Secondary AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and mucosa</td>
<td>Dark (palmar crease, extensor surface)</td>
<td>Pale</td>
</tr>
<tr>
<td>Potassium</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>Sodium</td>
<td>Low</td>
<td>Normal or Low</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Associated diseases</td>
<td>Primary hypothyroidism, Type 1 DM, vitiligo, neurological deficits</td>
<td>Central hypogonadism or hypothyroidism, growth hormone deficiency, diabetes insipidus, headaches, visual abnormalities</td>
</tr>
</tbody>
</table>
| Associated symptoms  | Weakness, fatigue, weight loss, hypotension, salt craving, postural dizziness, myalgia, arthralgia  
GI: nausea, vomiting, abdominal pain, diarrhea | Same except:  
NO salt craving  
GI less common |
| Diagnostic test      | Cosyntropin Stimulation Test  
High morning plasma ACTH | Insulin tolerance test  
Cosyntropin Stimulation Test  
Low morning plasma ACTH |

Adapted from: Salvatori R. JAMA 2005;294:2481-2488

Treatment
- acute condition – can be life-threatening
  - IV NS in large volumes (2-3 L); add D5W if hypoglycemic from adrenal insufficiency
  - hydrocortisone 50-100 mg IV q6-8h for 24h, then gradual tapering
  - identify and correct precipitating factors
- maintenance
  - hydrocortisone 15-20 mg total daily dose, in 2-3 divided doses, highest dose in the AM
  - Florinef® (fludrocortisone, synthetic mineralocorticoid) 0.05-0.2 mg PO daily if mineralocorticoid deficient increase dose of steroids 2-3 fold for a few days during moderate-severe illness (e.g. with vomiting, fever)
  - major stress (e.g. surgery, trauma) requires 150-300 hydrocortisone IV daily divided into 3 doses
  - medical alert bracelet and instructions for emergency hydrocortisone/dexamethasone IM/SC injection
Adrenal Medulla

Catecholamine Metabolism

• catecholamines are synthesized from tyrosine in postganglionic sympathetic nerves (norepinephrine) and chromaffin cells of adrenal medulla (epinephrine)
• broken down into metanephrines and other metabolites (VMA, HVA) and excreted in urine

Pheochromocytoma

Definition
• rare catecholamine secreting tumour derived from chromaffin cells of the sympathetic system

Epidemiology
• most commonly a single tumour of adrenal medulla
• rare cause of hypertension (<0.2% of all hypertensives)

Etiology and Pathophysiology
• most cases sporadic (80%)
• familial: associated with multiple endocrine neoplasia II (MEN IIA and IIB) (50% penetrance; i.e. 50% of people with the mutation get pheochromocytoma), von Hippel-Lindau (10-20% penetrance), paraganglioma (20% penetrance), or neurofibromatosis type 1 (0.1-5.7% penetrance)
• tumours, via unknown mechanism, able to synthesize and release excessive catecholamines

Clinical Features
• 50% suffer from paroxysmal HTN; the rest have sustained HTN
• classic triad: episodic “pounding” headache, palpitations/tachycardia, diaphoresis
• other symptoms: tremor, anxiety, chest or abdominal pain, nausea/vomiting, visual blurring, weight loss, polyuria, polydipsia
• other signs: orthostatic hypotension, papilledema, hyperglycemia, dilated cardiomyopathy
• symptoms may be triggered by stress, exertion, anesthesia, abdominal pressure, certain foods (especially tyramine containing foods)

Investigations
• urine catecholamines
  ▪ increased catecholamine metabolites (metanephrines) and free catecholamines
  ▪ plasma metanephrines if available (most sensitive)
  ▪ cut-off values will depend on assay used
• CT abdomen
  ▪ if negative, whole body CT and meta-iodo-benzoguanidine (MIBG) scintigraphy, Octreoscan, or MRI

Treatment
• surgical removal of tumour (curative) with careful pre- and post-operative ICU monitoring
• adequate pre-operative preparation
  ▪ α-blockade for BP control; phenoxybenzamine (10-21 d pre-operative), IV phentolamine (peri-operative, if required)
  ▪ β-blockade for HR control once α blocked for a few days
  ▪ metyrosine (catecholamine synthesis inhibitor) + phenoxybenzamine or prazosin
  ▪ volume restoration with vigorous salt-loading and fluids
• rescreen urine 1-3 mo post-operatively
• screen urine in first degree relatives; genetic testing in patients <50 yr old

Disorders of Multiple Endocrine Glands

Multiple Endocrine Neoplasm (MEN)

• neoplastic syndromes involving multiple endocrine glands
• tumours of neuroectodermal origin
• autosomal dominant inheritance with variable penetrance
• genetic screening for RET proto-oncogene on chromosome 10 has long-term benefit in MEN II
  ▪ early cure and prevention of medullary thyroid cancer
Table 26. MEN Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Tissues Involved</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN I (chromosome 11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wermer’s Syndrome</strong></td>
<td>Pituitary, Ant. pituitary adenoma</td>
<td>Headache, visual field defects. Often non-secreting but may secrete GH (acromegaly) and PRL (galactorrhea, erectile dysfunction, decreased libido, amenorrhea)</td>
</tr>
<tr>
<td></td>
<td>Parathyroid</td>
<td>Nephrolithiasis, bone abnormalities, MSK complaints, symptoms of hypercalcaemia</td>
</tr>
<tr>
<td></td>
<td>Entero-pancreatic endocrine</td>
<td>Epi gastric pain (peptic ulcers and esophagitis)</td>
</tr>
<tr>
<td></td>
<td>Gastrinoma</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Insulinomas</td>
<td>Secretory diarrhea</td>
</tr>
<tr>
<td></td>
<td>Vasoactive intestinal peptide (VIP)-omas</td>
<td>Rash, anorexia, anemia, diarrhea, glossitis</td>
</tr>
<tr>
<td></td>
<td>Glucagonoma</td>
<td>Carcinoid syndrome</td>
</tr>
<tr>
<td></td>
<td>Carcinoid syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAN II (chromosome 10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1. IIa Sipple’s Syndrome</strong></td>
<td>Thyroid (&gt;90%)</td>
<td>Physical signs are variable and often subtle</td>
</tr>
<tr>
<td></td>
<td>Medullary thyroid cancer (MTC)</td>
<td>Neck mass or thyroid nodule; non-tender, anterior lymph nodes</td>
</tr>
<tr>
<td></td>
<td>Adrenal medulla (40-50%)</td>
<td>HTN, palpitations, headache, sweating</td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma</td>
<td>Symptoms of hypercalcaemia</td>
</tr>
<tr>
<td></td>
<td>Parathyroid (10-20%)</td>
<td>Scaly skin rash</td>
</tr>
<tr>
<td></td>
<td>1st parathyroid hyperplasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cutaneous lichen amyloidosis</td>
<td></td>
</tr>
<tr>
<td><strong>2. Familial Medullary Thyroid Ca</strong></td>
<td>Thyroid</td>
<td>MTC without other clinical manifestations of MEN IIa or IIb</td>
</tr>
<tr>
<td><strong>(a variant of IIa)</strong></td>
<td>MTC</td>
<td></td>
</tr>
<tr>
<td><strong>3. IIb</strong></td>
<td>Thyroid</td>
<td>MTC: most common component, more aggressive and earlier onset than MEN IIa</td>
</tr>
<tr>
<td></td>
<td>MTC</td>
<td>HTN, palpitations, headache, sweating</td>
</tr>
<tr>
<td></td>
<td>Adrenal medulla</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma</td>
<td>Chronic constipation; megacolon</td>
</tr>
<tr>
<td></td>
<td>Neurons</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mucosal neuroma, intestinal ganglioneuromas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MSK</td>
<td>Marfanoid habitus (no aortic abnormalities)</td>
</tr>
</tbody>
</table>

Investigations

- **MEN I**
  - laboratory
    - may consider genetic screening for MEN-1 mutation in index patients
      - if a mutation is identified, screen family members who are at risk
    - gastrinoma: elevated serum gastrin level (>200 ng/mL) after IV injection of secretin
    - insulinoma: reduced fasting blood glucose (hypoglycemia) with elevated insulin and C-peptide levels
    - glucagonoma: elevated blood glucose and glucagon levels
    - pituitary tumours: assess GH, IGF-1 and prolactin levels (for over-production), TSH, free T<sub>3</sub>, 8 AM cortisol, LH, FSH, bioavailable testosterone or estradiol (for underproduction due to mass effect of tumour)
    - hyperparathyroidism: serum Ca<sup>2+</sup> and albumin, PTH levels; bone density scan (DEXA)
  - imaging
  - MRI for pituitary tumours, gastrinoma, insulinoma

- **MEN II**
  - laboratory
    - genetic screening for RET mutations in all index patients
      - if a mutation is identified screen family members who are at risk
    - calcitonin levels (MTC); urine catecholamines and metanephrines (pheochromocytoma); serum Ca<sup>2+</sup>, albumin and PTH levels (hyperparathyroidism)
    - pentagastrin ± calcium stimulation test if calcitonin level is within reference range
    - FNA for thyroid nodules → cytology
  - imaging
    - CT or MRI of adrenal glands, metaiodobenzylguanidine (MIBG) scan for pheochromocytoma
    - octreoscan and/or radionuclide scanning for determining the extent of metastasis

Treatment

- **MEN I**
  - medical
    - proton pump inhibitor (PPI) for acid hypersecretion in gastrinoma
    - cabergoline or other dopamine agonists to suppress prolactin secretion
    - somatostatin for symptomatic carcinoid tumours

- **MEN II**
  - medical
    - surgery for thyrotoxicosis
    - radioactive iodine (131I) with or without total thyroidectomy
    - total thyroidectomy (less common than 131I) for thyroid nodules and DTC

- surgery for hyperparathyroidism, insulinoma, glucagonoma, pituitary tumours (if medical treatment fails for the latter)
- trans-sphenoidal approach with prn external radiation
- MEN II
- surgery for MEN IIa with pre-operative medical therapy:
  - prostaglandin inhibitors to alleviate diarrhea associated with thyroid cancer
  - α-blocker for at least 10-21 d for pheochromocytoma pre-op
  - hydration, calcitonin, IV bisphosphonates for hypercalcemia

### Calcium Homeostasis

- normal total serum Ca\(^{2+}\): 2.2-2.6 mmol/L (8.5-10.5 mg/dL)
- ionic/free Ca\(^{2+}\) levels: 1.15-1.31 mmol/L (4.6-5.25 mg/dL)
- serum Ca\(^{2+}\) is about 50% protein bound (mostly albumin)
- regulated mainly by two factors: parathyroid hormone (PTH) and vitamin D
- actions mainly on three organs: GI tract, bone, and kidney

#### Table 27. Major Regulators in Calcium Homeostasis

<table>
<thead>
<tr>
<th>Major Regulators</th>
<th>Source</th>
<th>Regulation</th>
<th>Net Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH</td>
<td>Parathyroid glands</td>
<td>Stimulated by low serum Ca(^{2+}) and high serum PO(_4)(^{3-}); inhibited by chronic low serum Mg(^{2+}), high serum Ca(^{2+}), and calcitriol</td>
<td>↑ Ca(^{2+}); ↓ Calcitriol</td>
</tr>
<tr>
<td>Calcitriol (1,25-(OH)(_2)D(_3))</td>
<td>Dietary intake</td>
<td>Synthesized from cholesterol: UV on skin makes cholecalciferol (VitD3) → liver makes calcidiol (25-(OH)D(_3)) → kidneys make calcitriol</td>
<td>↑ Ca(^{2+}); ↓ PO(_4)(^{3-}); ↓ Ca(^{2+}) (in pharmacologic doses)</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Thyroid C cells</td>
<td>Stimulated by pentagastrin (GI hormone) and high serum Ca(^{2+}); inhibited by low serum Ca(^{2+}); kidneys make calcitriol</td>
<td>↓ Ca(^{2+})</td>
</tr>
<tr>
<td>Mg(^{2+})</td>
<td>Major intracellular divalent cation</td>
<td>See section on Magnesium (E42)</td>
<td>Cofactor for PTH secretion</td>
</tr>
<tr>
<td>PO(_4)(^{3-})</td>
<td>Intracellular anion found in all tissues</td>
<td>See section on Phosphate (E41)</td>
<td>↓ Ca(^{2+})</td>
</tr>
</tbody>
</table>
**Hypercalcemia**

**Definition**
- total corrected serum Ca\(^{2+}\) >2.6 mmol/L (10.5 mg/dL) OR ionized Ca\(^{2+}\) >1.35 mmol/L (5.4 mg/dL)

**Approach to Hypercalcemia** (Figure 15)
1. Is the patient hypercalcemic? (correct for albumin – see sidebar)
2. Is the PTH high/normal or low?
3. If PTH is low, is phosphate high/normal or low? If phosphate is high/normal is the level of vitamin D metabolites high or low?

**Clinical Features**
- symptoms depend on the absolute Ca\(^{2+}\) value and the rate of its rise (may be asymptomatic)

**Table 28. Symptoms of Hypercalcemia**

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>GI</th>
<th>Renal</th>
<th>Rheumatological</th>
<th>MSK</th>
<th>Psychiatric</th>
<th>Neurologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Constipation</td>
<td>Polyuria (Nephrogenic Di)</td>
<td>Gout</td>
<td>Weakness &gt;3 mmol/L (12 mg/dL)</td>
<td>Hypotonia</td>
<td>Hyporeflexia</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Anorexia</td>
<td>Polydipsia</td>
<td>Pseudogout</td>
<td>Bone pain (bones)</td>
<td>Hypoventilation</td>
<td>Myopathy</td>
</tr>
<tr>
<td>Short QT</td>
<td>Nausea</td>
<td>Nephrolithiasis (stones)</td>
<td>Chondrocalcinosis</td>
<td>Increased alertness (Anxiety)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deposition of Ca(^{2+}) on valves, coronary arteries, myocardial fibres</td>
<td>Vomiting (groans)</td>
<td>Renal failure (irreversible)</td>
<td>Cytokines in multiple myeloma</td>
<td></td>
<td>Cognitive dysfunction</td>
<td>Sydenham's</td>
</tr>
<tr>
<td></td>
<td>PUD pancreatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Syndrome</td>
</tr>
</tbody>
</table>

**High Ca\(^{2+}\)**
- Initial investigations: PTH, PO\(_4\), Mg\(^{2+}\), Urine Ca\(^{2+}\), creatinine
- Drugs: Lithium, Oral Calcidiol (25-OH Vit D), Oral Calcitriol (1,25-(OH)\(_2\) Vit D)

**Low Vit D metabolites**
- Hyperparathyroidism: Solitary adenoma (81%), Hyperplasia (15%), Carcinoma (4%), MEN I and IIa
- Tertiary Hyperparathyroidism: Increased PTH after prolonged secondary hyperparathyroidism due to renal failure

**Hypervitaminosis D:** Excessive intake of Vit D or its metabolites
- Nephrotic syndrome, metabolic alkalosis and renal insufficiency
- Drugs: theophylline, thiazide diuretics, estrogen/tamoxifen

**Granulomatous disease:** e.g. TB, sarcoid, lymphoma (esp. Hodgkins) which causes extra-renal production of calcitriol by macrophages in the lung and lymph nodes

**Immobilization**
- Malignancy
  - High bone turnover: e.g. hyperparathyroidism A, thyrotoxicosis, Paget’s disease
  - Milk alkali syndrome: (hypercalcemia, metabolic alkalosis and renal insufficiency)
- Drugs: theophylline, thiazide diuretics, estrogen/tamoxifen

**Hypervitaminosis D:** Excessive intake of Vit D or its metabolites

**Clinical Features**
- symptoms depend on the absolute Ca\(^{2+}\) value and the rate of its rise (may be asymptomatic)

**Table 28. Symptoms of Hypercalcemia**

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>GI</th>
<th>Renal</th>
<th>Rheumatological</th>
<th>MSK</th>
<th>Psychiatric</th>
<th>Neurologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Constipation</td>
<td>Polyuria (Nephrogenic Di)</td>
<td>Gout</td>
<td>Weakness &gt;3 mmol/L (12 mg/dL)</td>
<td>Hypotonia</td>
<td>Hyporeflexia</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Anorexia</td>
<td>Polydipsia</td>
<td>Pseudogout</td>
<td>Bone pain (bones)</td>
<td>Hypoventilation</td>
<td>Myopathy</td>
</tr>
<tr>
<td>Short QT</td>
<td>Nausea</td>
<td>Nephrolithiasis (stones)</td>
<td>Chondrocalcinosis</td>
<td>Increased alertness (Anxiety)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deposition of Ca(^{2+}) on valves, coronary arteries, myocardial fibres</td>
<td>Vomiting (groans)</td>
<td>Renal failure (irreversible)</td>
<td>Cytokines in multiple myeloma</td>
<td></td>
<td>Cognitive dysfunction</td>
<td>Sydenham's</td>
</tr>
<tr>
<td></td>
<td>PUD pancreatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Syndrome</td>
</tr>
</tbody>
</table>

**Treatment**
- treatment depends on the Ca\(^{2+}\) level and the symptoms
- treat acute, symptomatic hypercalcemia aggressively

**Hypercalcemic crisis (usually >4 mmol/L or 16 mg/dL):** primary symptoms include oliguria/anuria and mental status changes (including somnolence and eventually coma) → this is a medical emergency and should be treated immediately!
**Table 29. Treatment of Acute Hypercalcemic Crisis**

<table>
<thead>
<tr>
<th>Increase Urinary Ca²⁺ Excretion</th>
<th>Diminish Bone Resorption</th>
<th>Decrease GI Ca²⁺ Absorption</th>
<th>Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotonic saline (4-5 L) over 24 h ± loop diuretic (e.g. furosemide) but only if hypovolemic</td>
<td>Bisphosphonates (Tx of choice)</td>
<td>Corticosteroids in hypervitaminosis D and hematologic malignancies</td>
<td>Treatment of last resort</td>
</tr>
<tr>
<td>Calcium: 4 IU/kg IM/SC q12h</td>
<td>Inhibits osteoclastic bone resorption and promotes renal excretion of calcium</td>
<td>Anti-tumour effects: decreased calcitriol production by the activated mononuclear cells in lung and lymph node</td>
<td></td>
</tr>
<tr>
<td>8 IU/kg IM/SC q6h</td>
<td>Acts rapidly but often transient response (decreased by 0.3-0.5 mmol/L (1.2-2.0 mg/dL) beginning within 4-6 h) max effect usually in 7 d</td>
<td>Slow to act (5-10 d); need high dose</td>
<td></td>
</tr>
<tr>
<td>Only works for 48 h</td>
<td>Combination of calcitriol and steroids may prolong reduction in calcium</td>
<td>Corticosteroids: most useful in Vit D toxicity, granulomatous disease, some malignancies</td>
<td></td>
</tr>
<tr>
<td>Rapid onset within 4-6 h</td>
<td>Tachyphylaxis may occur</td>
<td>Saline diuresis + loop diuretic (for volume overload): temporary measure</td>
<td></td>
</tr>
</tbody>
</table>

**Hypocalcemia**

**Definition**
- total corrected serum Ca²⁺ <2.2 mmol/L (8.5 mg/dL)

**Table 30. Clinical Features of Hypocalcemia**

<table>
<thead>
<tr>
<th>Acute Hypocalcemia</th>
<th>Chronic Hypocalcemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesia</td>
<td>CNS: lethargy, seizures, psychosis, basal ganglia calcification, Parkinson’s, dystonia, hemiballismus, papilledema, pseudotumour cerebri</td>
</tr>
<tr>
<td>Laryngospasm (with stridor)</td>
<td>CVS: prolonged QT interval → Torsades de pointes (ventricular tachycardia)</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>Gl: steatorrhea</td>
</tr>
<tr>
<td>Tetany</td>
<td>ENDO: impaired insulin release</td>
</tr>
<tr>
<td>Chvostek’s sign (tap CN VII)</td>
<td>SKIN: dry, scaling, alopecia, brittle and transversely fissured nails, candidiasis, abnormal dentition</td>
</tr>
<tr>
<td>Trousseau’s sign (carpal spasm)</td>
<td>Ocular: cataracts</td>
</tr>
<tr>
<td>ECG changes</td>
<td>MUSC: generalized muscle weakness and wasting</td>
</tr>
<tr>
<td>Delirium</td>
<td>Psychiatric Sc: emotional instability, anxiety and depression</td>
</tr>
</tbody>
</table>

**Approach to Hypocalcemia** (Figure 16)
1. Is the patient hypocalcemic?
2. Is the PTH high or low?
3. If PTH is high, is phosphate low or normal?
4. Is the Mg²⁺ level low?

**Approach to Treatment**
- correct underlying disorder
- mild/asymptomatic (ionized Ca²⁺ >0.8 mmol/L, 3.2 mg/dL)
  - treat by increasing dietary Ca²⁺ by 1000 mg/d |
  - calcitriol 0.25 µg/d |
- acute/asymptomatic hypocalcemia (ionized Ca²⁺ <0.7 mmol/L, 2.8 mg/dL)
  - immediate treatment required |
  - IV calcium gluconate 1-2 g over 10-20 min followed by slow infusion if necessary |
  - goal is to raise Ca²⁺ to low normal range (2.0-2.1 mmol/L, 8.0-8.4 mg/dL) to prevent symptoms but allow maximum stimulation of PTH secretion |
  - if PTH recovery not expected, requires long-term therapy with calcitriol and calcium |
- do not correct hypocalcemia if asymptomatic and suspected to be transient

**Differential Diagnosis of Hypercalcemia**
- Primary hyperparathyroidism |
- Malignancy: hematologic, humoral, skeletal metastases (>90% from 1 or 2) |
- Renal disease: tertiary hyperparathyroidism |
- Drugs: calcium carbonate, milk-alkali syndrome, thiazide, lithium, theophylline, vitamin A/D intoxication |
- Familial hypercalcemic hypercalciuria |
- Granulomatous disease: sarcoidosis, TB, Hodgkin’s lymphoma |
- Thyroid disease: thyrotoxicosis |
- Adrenal disease: adrenal insufficiency, pheochromocytoma |
- Immobilization

**Acute Management of Hypercalcemia/Hypercalcemic Crisis**
- Volume expansion (e.g. NS IV 300-500 cc/h) initial therapy |
- Calcitriol: transient, partial response |
- Bisphosphonate: treatment of choice |
- Corticosteroid: most useful in Vit D toxicity, granulomatous disease, some malignancies |
- Saline diuresis + loop diuretic (for volume overload): temporary measure

**Hypomagnesemia can impair PTH secretion and action.**

**Differential Diagnosis of Tetany**
- Hypocalcemia |
- Metabolic alkalosis (with hyperventilation) |
- Hypokalemia |
- Hypomagnesemia

**Signs and Symptoms of Acute Hypocalcemia**
- Paresthesias: perioral, hands and feet |
- Chvostek’s sign: percussion of the facial nerve just anterior to the external auditory meatus elicits ipsilateral spasm of the orbicularis oculi or orbicularis oris muscles |
- Trousseau’s sign: inflation of a blood pressure cuff above systolic pressure for 3 min elicits carpal spasm and paresthesia
**Hyperphosphatemia**

**Definition**
- serum phosphate $>1.45$ mmol/L (4.1 mg/dL)

**Table 31. Etiology of Hyperphosphatemia**

<table>
<thead>
<tr>
<th>Increased Phosphate Load</th>
<th>Reduced Renal Clearance</th>
<th>Pseudohyperphosphatemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI intake (rectal enema, GI bleeding)</td>
<td>Acute/chronic renal failure</td>
<td>Hyperglibulinemia</td>
</tr>
<tr>
<td>IV phosphate load (K-Phos®, blood transfusion)</td>
<td>Hypoparathyroidism</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Endogenous phosphate (tumour lysis syndrome, rhabdomyolysis, hemolysis, lactic and ketoacidosis)</td>
<td>Acromegaly</td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td>Drugs (Phenytoin, phenobarbital, carbamazepine)</td>
<td>Tumour calcinosis (ability of kidney to specifically clear phosphate is defective)</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Features**
- non-specific, include ectopic calcification, renal osteodystrophy

**Treatment**
- acute: hemodialysis if symptomatic
- chronic: low PO$_4^{3-}$ diet, phosphate binders (e.g. CaCO$_3$)

**Hypophosphatemia**

**Definition**
- serum phosphate $<0.85$ mmol/L (2.4 mg/dL)

**Table 32. Etiology of Hypophosphatemia**

<table>
<thead>
<tr>
<th>Inadequate Intake</th>
<th>Renal Losses</th>
<th>Excessive Skeletal Mineralization</th>
<th>Shift into ICF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starvation</td>
<td>Hyperparathyroidism</td>
<td>Osteoblastic metastases</td>
<td>Recovery from metabolic acidosis</td>
</tr>
<tr>
<td>Malabsorption (diarrhea, steatorrhea)</td>
<td>Duretics</td>
<td>Post-parathyroidectomy (referred to as ‘hungry bone syndrome’)</td>
<td>Respiratory alkalosis</td>
</tr>
<tr>
<td>Antacid use</td>
<td>X-linked or AD hypophosphatemic rickets</td>
<td></td>
<td>Starvation refeeding (stimulated by insulin)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Fanconi syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Symptoms usually present when phosphate $<0.32$ mmol/L (1.0 mg/dL)
- Treat asymptomatic patients if phosphate $<0.84$ mmol/L (2.0 mg/dL)
Clinical Features  
- non-specific (CHF, coma, hypotension, weakness, defective clotting)

Treatment  
- treat underlying cause  
  - Oral PO₄³⁻: 2-4 g/d divided bid-qid (start at 1 g/d to minimize diarrhea)  
  - IV PO₄³⁻: only for severely symptomatic patients or inability to tolerate oral therapy

Hypermagnesemia  

Definition  
- serum magnesium >0.85 mmol/L (2.1mg/dL)

Etiology  
- AKI/CRF  
- Mg²⁺-containing antacids or enemas  
- IV administration of large doses of MgSO₄ (e.g. for preeclampsia; see Obstetrics, OB16)

Clinical Features  
- drowsiness, hyporeflexia, respiratory depression, heart block, cardiac arrest

Treatment  
- discontinue Mg²⁺-containing products  
- IV calcium (Mg²⁺-antagonist) for acute reversal of magnesium toxicity  
- dialysis if renal failure

Hypomagnesemia  

Definition  
- serum magnesium <0.70 mmol/L (1.7 mg/dL)

Etiology  
- GI losses  
  - starvation/malabsorption  
  - vomiting/diarrhea  
  - alcoholism  
  - acute pancreatitis  
- excess renal loss  
  - 2° hyperaldosteronism due to cirrhosis and CHF  
  - hyperglycemia  
  - hypokalemia  
  - hypercalcemia  
  - loop and thiazide-type diuretics  
  - nephrotoxic medications  
  - proton-pump inhibitors

Clinical Features  
- seizures, paresis, Chvostek and Trousseau signs, ECG changes (widened QRS, prolonged PR, T-wave abnormalities) and arrhythmias including Torsades de pointes

Treatment  
- treat underlying cause  
- Mg²⁺ 1M/IV; cellular uptake of Mg²⁺ is slow, therefore repletion requires sustained correction  
- discontinue diuretics  
  - in patients requiring diuretics, use a K⁺-sparing diuretic to minimize magnesuria

Metabolic Bone Disease  

Osteoporosis  

Definition  
- a condition characterized by decreased bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture  
- bone mineral density (BMD) ≥2.5 standard deviations below the peak bone mass for young adults (i.e. T-score ≤–2.5)  
- osteopenia: BMD with T-score between -1.0 and -2.5

Etiology and Pathophysiology  

Primary Osteoporosis  
- primary type 1: most common in post-menopausal women, due to decline in estrogen, worsens with age  
- primary type 2: occurs after age 75, seen in females and males at 2:1 ratio, possibly due to zinc deficiency
Secondary Osteoporosis
- gastrointestinal diseases
- gastrectomy
- malabsorption (e.g. celiac disease)
- chronic liver disease
- bone marrow disorders
- multiple myeloma
- lymphoma
- leukemia
- endocrinopathies
- Cushing's syndrome
- hyperparathyroidism
- hyperthyroidism
- premature menopause
- diabetes
- malignancy
- secondary to chemotherapy
- myeloma

Clinical Features
- commonly asymptomatic
- height loss due to collapsed vertebrae
- fractures: most commonly in hip, vertebrae, humerus and wrist
  - fragility fractures: fracture with fall from standing height
  - Dowager's hump: collapse fracture of vertebral bodies in mid-dorsal region
  - x-ray: vertebral compression and crush fractures, wedge fractures, "codfishing" sign
    (weakening of subchondral plates and expansion of intervertebral discs)
- pain, especially backache, associated with fractures

Approach to Osteoporosis
1. Assess risk factors for osteoporosis on history and physical
2. Decide if patient requires BMD testing with dual-energy x-ray absorptiometry (DEXA): men and women ≥65 yr or younger if presence of risk factors (Table 33)
3. Initial investigations:
   - all patients with osteoporosis: calcium corrected for albumin, CBC, creatinine, ALP, TSH
   - also consider serum and urine protein electrophoresis, celiac workup and 24 h urinary Ca²⁺ excretion to rule out additional secondary causes
   - 25-OH-Vitamin D level should only be measured after 3-4 mo of adequate supplementation and should not be repeated if an optimal level ≥75 nmol/L is achieved
   - lateral thoracic and lumbar x-ray if clinical evidence of vertebral fracture
4. Assess 10-yr fracture risk by combining BMD result and risk factors (only if ≥50 yr)
   1) WHO Fracture Risk Assessment Tool (FRAX);
   2) Canadian Association of Radiologists and Osteoporosis Canada Risk Assessment Tool (CAROC)
   - approach to management guided by 10-yr risk stratification into low, medium, high risk
5. For all patients being assessed for osteoporosis, encourage appropriate lifestyle changes (see Table 35)

Table 33. Osteoporosis Risk Stratification

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>10-yr Fracture Risk</th>
<th>Management Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>&lt;10%</td>
<td>Unlikely to benefit from pharmacotherapy; encourage lifestyle changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reassess risk in 5 yr</td>
</tr>
<tr>
<td>Medium Risk</td>
<td>10-20%</td>
<td>Discuss patient preference for management and consider additional risk factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Factors that warrant consideration for pharmacological therapy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Additional vertebral fracture(s) identified on vertebral fracture assessment (VFA) or lateral spine x-ray</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Previous wrist fracture in individuals ≥65 or with T-score ≤-2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lumbar spine T-score much lower than femoral neck T-score</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rapid bone loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Men receiving androgen-deprivation therapy for prostate cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Women receiving aromatase-inhibitor therapy for breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Long-term or repeated systemic glucocorticoid use (oral or parenteral) that does not meet the conventional criteria for recent prolonged systemic glucocorticoid use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recurrent falls (defined as falling 2 or more times in the past 12 mo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Other disorders strongly associated with osteoporosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discuss patient preference for management and consider additional risk factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Factors that warrant consideration for pharmacological therapy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Additional vertebral fracture(s) identified on vertebral fracture assessment (VFA) or lateral spine x-ray</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Previous wrist fracture in individuals ≥65 or with T-score ≤-2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lumbar spine T-score much lower than femoral neck T-score</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rapid bone loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Men receiving androgen-deprivation therapy for prostate cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Women receiving aromatase-inhibitor therapy for breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Long-term or repeated systemic glucocorticoid use (oral or parenteral) that does not meet the conventional criteria for recent prolonged systemic glucocorticoid use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recurrent falls (defined as falling 2 or more times in the past 12 mo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Other disorders strongly associated with osteoporosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repeat BMD and reassess risk every 1-3 yr initially</td>
</tr>
<tr>
<td>High Risk</td>
<td>&gt;20%; OR</td>
<td>Start pharmacotherapy</td>
</tr>
<tr>
<td></td>
<td>Prior fragility fracture of hip or spine; OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>More than one fragility fracture</td>
<td></td>
</tr>
</tbody>
</table>
Table 34. Indications for BMD Testing

<table>
<thead>
<tr>
<th>Table 34. Indications for BMD Testing</th>
<th>Older Adults (age ≥50 yr)</th>
<th>Younger Adults (age &lt;50 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women and men age ≥55 yr</td>
<td>Fracture</td>
<td>Fracture</td>
</tr>
<tr>
<td>Menopausal women, and men aged 50-64 yr</td>
<td>Fracture after age 40</td>
<td>Fracture</td>
</tr>
<tr>
<td>with clinical risk factors for fracture:</td>
<td>Prolonged use of glucocorticoids</td>
<td>Use of other high-risk medications</td>
</tr>
<tr>
<td>• Fragility fracture after age 40</td>
<td>(aromatase inhibitors, androgen deprivation therapy)</td>
<td>(aromatase inhibitors, androgen deprivation therapy)</td>
</tr>
<tr>
<td>• Prolonged glucocorticoid use</td>
<td>Hypogonadism or premature menopause</td>
<td>Hypogonadism or premature menopause</td>
</tr>
<tr>
<td>• Other high-risk medication use (aromatase inhibitors, androgen deprivation therapy)</td>
<td>Primary hyperparathyroidism</td>
<td>Primary hyperparathyroidism</td>
</tr>
<tr>
<td>Other disorders strongly associated with osteoporosis: primary hyperparathyroidism, Type 1 diabetes, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (&lt;45 yr), Cushing’s disease, chronic malnutrition or malabsorption, chronic liver disease, COPD and chronic inflammatory conditions (e.g. inflammatory bowel disease)</td>
<td>Other disorders strongly associated with rapid bone loss and/or fracture</td>
<td></td>
</tr>
</tbody>
</table>

Table 35. Treatment of Osteoporosis in Women and Men

<table>
<thead>
<tr>
<th>Treatment of Osteoporosis</th>
<th>Table 35. Treatment of Osteoporosis in Women and Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment for both men and women</td>
<td><strong>Drug Therapy</strong></td>
</tr>
<tr>
<td>Diet: Elemental calcium 1000-1200 mg/d; Vit D 1000 IU/d</td>
<td>Bisphosphonate: Inhibitors of osteoclast binding</td>
</tr>
<tr>
<td>Exercise: 3x30 min weight-bearing exercises/wk</td>
<td>1st line in prevention of hip, nonvertebral and vertebral # (Grade A): alendronate, risedronate, zoledronic acid</td>
</tr>
<tr>
<td>Cessation of smoking, reduce caffeine intake</td>
<td>2nd line (Grade B): etidronate</td>
</tr>
<tr>
<td>Stop/avoid osteoporosis-inducing medications</td>
<td>Parathyroid Hormone</td>
</tr>
<tr>
<td>YES fragility #: 18-24 mo duration</td>
<td>Calcitonin (2nd line): osteoclast receptor binding</td>
</tr>
<tr>
<td>YES fragility #: 200 IU nasally OD with Calcitriol 0.25 µg bid</td>
<td></td>
</tr>
</tbody>
</table>

**Lifestyle**

<table>
<thead>
<tr>
<th>Osteoporosis</th>
<th>Bisphosphonate: Inhibitors of osteoclast binding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SERM (selective estrogen-receptor modulator): agonistic effect on bone but antagonistic effect on uterus and breast</strong></td>
<td>1st line in prevention of vertebral # (Grade A): raloxifene</td>
</tr>
<tr>
<td>+ve: prevents osteoporotic # (Grade A to B evidence), improves lipid profile, decreased breast ca risk</td>
<td>+ve: increased risk of DVT/PE, stroke mortality, hot flashes, leg cramps</td>
</tr>
<tr>
<td>-ve: combined estrogen/progestin prevents hip, vertebral, total #</td>
<td>For most women, risks &gt; benefits</td>
</tr>
<tr>
<td><strong>HRT: combined estrogen + progesterone (see Gynecology, CY53)</strong></td>
<td>+ve: increased risks of breast ca, cardiovascular events and DVT/PE</td>
</tr>
</tbody>
</table>

**Drug Therapy**

| Bisphosphonate: Inhibitors of osteoclast binding | 1st line in prevention of hip, nonvertebral and vertebral # (Grade A): alendronate, risedronate, zoledronic acid |
| Parathyroid Hormone | YES fragility #: 18-24 mo duration |
| Calcitonin (2nd line): osteoclast receptor binding | YES fragility #: Calcitonin 200 IU nasally OD with Calcitriol 0.25 µg bid |

**Treatment specific to post-menopausal women**

| SERM (selective estrogen-receptor modulator): agonistic effect on bone but antagonistic effect on uterus and breast | 1st line in prevention of vertebral # (Grade A): raloxifene |
| +ve: prevents osteoporotic # (Grade A to B evidence), improves lipid profile, decreased breast ca risk | +ve: increased risk of DVT/PE, stroke mortality, hot flashes, leg cramps |
| -ve: combined estrogen/progestin prevents hip, vertebral, total # | For most women, risks > benefits |
| **HRT: combined estrogen + progesterone (see Gynecology, CY53)** | +ve: increased risks of breast ca, cardiovascular events and DVT/PE |

**Clinical Signs of Fractures or Osteoporosis**

- **Height loss ≥3 cm (Sn 92%)**
- **Weight <51 kg**
- **Kyphosis (Sp 92%)**
- **Tooth count <20 (Sp 92%)**
- **Grip strength**
- **Armspan-height difference >5 cm (Sp 76%)**
- **Wall-occpit-height difference >0 cm (Sp 87%)**
- **Rib-pelvis distance ≤2 fingerbreadth (Sn 88%)**
**Osteomalacia and Rickets**

- **rickets**: osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue *prior* to epiphyseal closure (in childhood)
- **osteomalacia**: osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue *after* epiphyseal closure (in adulthood)

**Etiology and Pathophysiology**

**Vitamin D Deficiency**
- deficient uptake or absorption
  - nutritional deficiency
  - malabsorption: post-gastrectomy, small bowel disease (e.g. Celiac sprue), pancreatic insufficiency
- defective 25-hydroxylation
  - liver disease
  - anticonvulsant therapy
- loss of vitamin D binding protein
- defective 1-α-25 hydroxylation
  - hypoparathyroidism
  - renal failure
- pathophysiology: leads to secondary hyperparathyroidism and hypophosphatemia

**Mineralization Defect**
- abnormal matrix
  - osteogenesis imperfecta
  - fibrogenesis imperfecta
  - axial osteomalacia
- enzyme deficiency
  - hypophosphatasia (inadequate ALP bioactivity)
  - presence of calcification inhibitors
  - bisphosphonates, aluminum, high dose fluoride, anticonvulsants

**Table 36. Clinical Presentations of Rickets and Osteomalacia**

<table>
<thead>
<tr>
<th>Rickets</th>
<th>Osteomalacia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal pain and deformities, bow legged</td>
<td>Not as dramatic</td>
</tr>
<tr>
<td>Fracture susceptibility</td>
<td></td>
</tr>
<tr>
<td>Weakness and hypotonia</td>
<td></td>
</tr>
<tr>
<td>Disturbed growth</td>
<td></td>
</tr>
<tr>
<td>Ricketic rosary (prominent costochondral junctions)</td>
<td></td>
</tr>
<tr>
<td>Harrison’s groove (indentation of lower ribs)</td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td></td>
</tr>
</tbody>
</table>

**Investigations**

**Table 37. Laboratory Findings in Osteomalacia and Rickets**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Serum Phosphate</th>
<th>Serum Calcium</th>
<th>Serum ALP</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiency</td>
<td>Decreased</td>
<td>Decreased to normal</td>
<td>Increased</td>
<td>Decreased calcitriol</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Decreased</td>
<td>Normal</td>
<td>Decreased to normal</td>
<td></td>
</tr>
<tr>
<td>Proximal RTA</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal</td>
<td>Associated with hyperchloremic metabolic acidosis</td>
</tr>
<tr>
<td>Conditions associated with abnormal matrix formation</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

- radiologic findings
  - pseudofractures, fissures, narrow radiolucent lines – thought to be healed stress fractures or the result of erosion by arterial pulsation
  - loss of distinctness of vertebral body trabeculae; concavity of the vertebral bodies
  - changes due to secondary hyperparathyroidism: subperiosteal resorption of the phalanges, bone cysts, resorption of the distal ends of long bones
  - others: bowing ofibia, coxa profunda hip deformity
- bone biopsy: usually not necessary but considered the gold standard for diagnosis

**Treatment**
- definitive treatment depends on the underlying cause
- vitamin D supplementation
- PO43− supplements if low serum PO43−, Ca2+ supplements for isolated calcium deficiency
- bicarbonate if chronic metabolic acidosis
Renal Osteodystrophy

- changes to mineral metabolism and bone structure secondary to chronic kidney disease
- represents a mixture of four types of bone disease:
  - osteomalacia: low bone turnover combined with increased unmineralized bone (osteoid)
  - adynamic bone disease: low bone turnover due to excessive suppression of parathyroid gland
  - osteitis fibrosa cystica: increased bone turnover due to secondary hyperparathyroidism
  - mixed uremic osteodystrophy: both high and low bone turnover, characterized by marrow fibrosis and increased osteoid
- metastatic calcification secondary to hyperphosphatemia may occur

Pathophysiology

- metabolic bone disease secondary to chronic renal failure
- combination of hyperphosphatemia (inhibits 1,25(OH)$_2$-Vit. D synthesis) and loss of renal mass (reduced 1-α-hydroxylase)

Clinical Features

- soft tissue calcifications → necrotic skin lesions if vessels involved
- osteodystrophy → generalized bone pain and fractures
- pruritus
- neuromuscular irritability and tetany may occur
- radiologic features of osteitis fibrosa cystica, osteomalacia, osteosclerosis, osteoporosis

Investigations

- serum Ca$^{2+}$ corrected for albumin, PO$_4^{3-}$, PTH, ALP, ± imaging (x-ray, BMD), ± bone biopsy

Treatment

- prevention
  - maintenance of normal serum Ca$^{2+}$ and PO$_4^{3-}$ by restricting PO$_4^{3-}$ intake to 1 g OD
  - Ca$^{2+}$ supplements; PO$_4^{3-}$ binding agents (calcium carbonate, aluminum hydroxide)
  - vitamin D with close monitoring to avoid hypercalcemia and metastatic calcification

Paget’s Disease of Bone

Definition

- a metabolic disease characterized by excessive bone destruction and repair

Epidemiology

- a common disease: 5% of the population, 10% of population >80 yr old

Etiology and Pathophysiology

- postulated to be related to a slow progressing viral infection of osteoclasts, possibly paramyxovirus
- strong familial incidence
- initiated by increased osteoclastic activity leading to increased bone resorption; osteoblastic activity increases in response to produce new bone that is structurally abnormal and fragile

Differential Diagnosis

- primary bone lesions
  - osteogenic sarcoma
  - multiple myeloma
  - fibrous dysplasia
- secondary bone lesions
  - osteitis fibrosa cystica
  - metastases

Clinical Features

- usually asymptomatic (routine x-ray finding or elevated ALP)
- severe bone pain (e.g. pelvis, femur,ibia) is often the presenting complaint
- skeletal deformities: bowed tibias, kyphosis, frequent fractures
- skull involvement: headaches, increased hat size, deafness
- increased warmth over involved bones due to increased vascularity
- high output congestive heart failure
- hypercalcemia with immobilization
- osteosarcoma

Comparison of a Single Infusion of Zoledronic Acid with Risedronate for Paget’s Disease

Study: Two identical, randomized, double-blind, actively controlled trials (combined for analysis).
Patients: 357 men and women who were older than 30 yr of age and had radiologically confirmed Paget’s disease. All but 4 patients had alkaline phosphatase levels that were more than twice the upper limit of normal.
Intervention: One 15-min infusion of 5 mg of zoledronic acid compared with 60 d of oral risedronate (50 mg/d) with follow up at 6 mo.
Primary Outcome: Rate of therapeutic response at 6 mo, defined as a normalization of alkaline phosphatase levels or a reduction of at least 75% in the total alkaline phosphatase excess.
Results: At 6 mo, 96% of patients receiving zoledronic acid had a therapeutic response (169 of 176), as compared with 74.3% of patients receiving risedronate (127 of 171, P<0.001). Alkaline phosphatase levels normalized in 86.6% of patients in the zoledronic acid group and 57.9% of patients in the risedronate group (P<0.001). Zoledronic acid was associated with a shorter median time to a first therapeutic response (169 of 176) as compared with 74.3% of patients receiving risedronate (127 of 171, P<0.001). Alkaline phosphatase levels normalized in 86.6% of patients in the zoledronic acid group and 57.9% of patients in the risedronate group (P<0.001). Zoledronic acid was associated with a shorter median time to a first therapeutic response (64 vs. 89 d, P<0.001). Quality of life increased significantly from baseline at both 3 and 6 mo in the zoledronic acid group and differed significantly from those in the risedronate group at 3 mo. Pain scores improved in both groups. During post-trial follow-up (median, 190 d), 21 of 82 patients in the risedronate group had a loss of therapeutic response, as compared with 1 of 113 patients in the zoledronic acid group (P<0.001).
Conclusions: A single infusion of zoledronic acid produces more rapid, more complete, and more sustained responses in Paget’s disease than does daily treatment with risedronate.
Investigations
- laboratory
  - ↑↑ serum ALP (unless burnt out), Ca\(^{2+}\) normal or ↑, PO\(_4^{3-}\) normal
  - urinary hydroxyproline ↑ (indicates resorption)
- imaging
  - bone scan to evaluate the extent of disease
  - skeletal survey: involved bones are denser and expanded with cortical thickening
    - initial lesion may be destructive and radiolucent
    - multiple fissure fractures in long bones

Complications
- local
  - fractures; osteoarthritis
  - cranial nerve compression and palsies (e.g. deafness), spinal cord compression
  - osteosarcoma/sarcomatous change in 1-3%
    - indicated by marked bone pain, new lytic lesions and sudden increased ALP
- systemic
  - hypercalcemia and nephrolithiasis
  - high output congestive heart failure due to increased vascularity

Treatment
- symptomatic therapy (pain management)
- weight-bearing exercise
- adequate calcium and vitamin D intake to prevent development of secondary hyperparathyroidism
- treat medically if ALP > 3x normal
  - bisphosphonates, e.g. alendronate 40 mg PO OD x 6 mo OR risedronate 30 mg PO OD x 3 mo OR zoledronic acid 5 mg IV per year
  - calcitonin 50-100 U/d SC
- surgery for fractures, deformity, degenerative changes

Male Reproductive Endocrinology

Androgen Regulation
- negative feedback may occur by androgens directly or after conversion to estrogen
  - testosterone (from Leydig cells) primarily involved in negative feedback on LH and GnRH, whereas inhibin (from Sertoli cells) suppresses FSH secretion

Tests of Testicular Function
- testicular size (lower limit = 4 cm x 2.5 cm)
- LH, FSH, total and/or bioavailable testosterone
- human chorionic gonadotropin (hCG) stimulation test
  - assesses ability of Leydig cell to respond to gonadotropin
- semen analysis
  - semen volume, sperm count, morphology and motility
- testicular biopsy
  - indicated with normal FSH and azoospermia/oligospermia

Hypogonadism and Infertility
- see Urology, U34
- deficiency in gametogenesis or testosterone production

Etiology
- causes include primary (testicular failure), secondary (hypothalamic-pituitary failure) and idiopathic
- primary hypogonadism is more common than secondary
Table 38. Classification and Features of Hypogonadism

<table>
<thead>
<tr>
<th>Hypogonadotropic Hypogonadism (Primary Hypogonadism)</th>
<th>Hypogonadotropic Hypogonadism (Secondary Hypogonadism)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td></td>
</tr>
<tr>
<td>Primary testicular failure</td>
<td>Hypothalamic-pituitary axis failure</td>
</tr>
<tr>
<td>↑ LH and FSH, ↑ FSH:LH ratio</td>
<td>↓ LH + FSH</td>
</tr>
<tr>
<td>↓ testosterone and sperm count</td>
<td>↓ testosterone and sperm count</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
</tr>
<tr>
<td>Congenital:</td>
<td></td>
</tr>
<tr>
<td>• Chromosomal defects (Klinefelter’s, Noonan)</td>
<td></td>
</tr>
<tr>
<td>• Cryptorchidism</td>
<td></td>
</tr>
<tr>
<td>• Male pseud thermaphrodism</td>
<td></td>
</tr>
<tr>
<td>• Bilateral anorchia (vanishing testicle syndrome)</td>
<td></td>
</tr>
<tr>
<td>• Myotonic dystrophy</td>
<td></td>
</tr>
<tr>
<td>• Mutation of FSH or LH receptor gene</td>
<td></td>
</tr>
<tr>
<td>• Disorders of androgen synthesis</td>
<td></td>
</tr>
<tr>
<td>Germ cell defects</td>
<td></td>
</tr>
<tr>
<td>• Sertoli cell only syndrome</td>
<td></td>
</tr>
<tr>
<td>• Leydig cell aplasia/failure</td>
<td></td>
</tr>
<tr>
<td>Infection/Inflammation</td>
<td></td>
</tr>
<tr>
<td>• Orchitis – TB, lymphoma, mumps, leprosy</td>
<td></td>
</tr>
<tr>
<td>• Genital tract infection</td>
<td></td>
</tr>
<tr>
<td>Physical factors</td>
<td></td>
</tr>
<tr>
<td>• Trauma, heat, irradiation, testicular torsion, varicocele</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>• Marijuana, alcohol, chemotherapty, ketocortizone, spironolactone</td>
<td></td>
</tr>
<tr>
<td>Autoimmune (antispem antibodies)</td>
<td></td>
</tr>
<tr>
<td>Chronic systemic diseases (AIDS)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Testicular size and consistency (soft/firm)</td>
<td></td>
</tr>
<tr>
<td>Sperm count</td>
<td></td>
</tr>
<tr>
<td>LH, FSH, total and/or bioavailable testosterone</td>
<td></td>
</tr>
<tr>
<td>hCG stimulation</td>
<td></td>
</tr>
<tr>
<td>Karyotype</td>
<td></td>
</tr>
<tr>
<td>Testicular size and consistency (soft/firm)</td>
<td></td>
</tr>
<tr>
<td>Sperm count</td>
<td></td>
</tr>
<tr>
<td>LH, FSH, total and/or bioavailable testosterone</td>
<td></td>
</tr>
<tr>
<td>Prolactin levels</td>
<td></td>
</tr>
<tr>
<td>MRI of hypothalamic-pituitary region</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment**
- testosterone replacement (improve libido, muscle mass, strength, hair growth, bone mass)
- IM injection, transdermal testosterone patch/gel, oral
- side effects: acne, fluid retention, erythrocytosis, sleep apnea, benign prostatic hypertrophy
- contraindicated if history of prostate cancer
- GnRH agonist to restore fertility, if hypothalamic dysfunction with intact pituitary
- administered SC in pulsatile fashion using an external pump
- hCG ± human menopausal gonadotropin (hMG) (to supply FSH) can be used to restore fertility in cases of either hypothalamic or pituitary lesions
- surgery – only if testicular tissues are not functioning

**Other Causes of Male Infertility**
- hereditary disorders: Kartagener syndrome, cystic fibrosis
- anatomy: hypospadias, retrograde ejaculation
- obstruction: vasal occlusion, vasal aplasia, vasectomy, seminal vesicle disease
- sexual dysfunction: erectile dysfunction, premature ejaculation, infrequent coitus
- surgery: TURP, radical prostatectomy, orchietomy

**DEFECTS IN ANDROGEN ACTION**

**Etiology**
- complete androgen insensitivity (testicular feminization)
- incomplete androgen insensitivity
  - 5α-reductase deficiency
  - mixed gonadal dysgenesis
  - defects in testosterone synthesis
- infertile male syndrome
- undervirilized fertile male syndrome

**Clinical Features**
- depends on age of onset
Table 39. Effects of Testosterone Deficiency

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester in utero</td>
<td>Incomplete virilization of external genitalia (ambiguous genitalia)</td>
</tr>
<tr>
<td></td>
<td>Incomplete development of Wolffian ducts to form male internal genitalia (male pseudohermaphrodism)</td>
</tr>
<tr>
<td>Third trimester in utero</td>
<td>Micropenis</td>
</tr>
<tr>
<td></td>
<td>Cryptorchidism (failure of normal testicular descent)</td>
</tr>
<tr>
<td>Prepuberty</td>
<td>Incomplete pubertal maturation (high pitch voice, sparse pubic + axillary hair, absence of facial hair)</td>
</tr>
<tr>
<td></td>
<td>Eunuchoidal body habitus (greater growth of extremity long bones relative to axial bones)</td>
</tr>
<tr>
<td></td>
<td>Poor muscle development, reduced peak bone mass</td>
</tr>
<tr>
<td>Postpuberty</td>
<td>Decrease in energy, mood, and libido</td>
</tr>
<tr>
<td></td>
<td>Fine wrinkles in corners of mouth and eyes</td>
</tr>
<tr>
<td></td>
<td>Decrease in pubic/axillary hair, hematocrit, muscle mass, strength and BMD</td>
</tr>
</tbody>
</table>

Adapted from UptoDate, 2010 + Cecil's Essentials of Medicine

Treatment
- appropriate gender assignment in the newborn
- hormone replacement or supplementation
- psychological support
- gonadectomy for cryptorchidism (due to increased risk for testicular cancer)
- reduction mammoplasty for gynecomastia

Erectile Dysfunction

- see Urology, U30

Gynecomastia

Definition
- true gynecomastia refers to benign proliferation of the glandular component of the male breast, resulting in the formation of a concentric, rubbery, firm mass extending from the nipple(s)
- pseudogynecomastia or lipomastia refers to enlargement of soft adipose tissue, especially seen in obese individuals and does not warrant further evaluation

Etiology

Physiologic
- puberty
- elderly (involutional)
- neonatal (maternal hormone)

Pathologic
- endocrinopathies: primary or secondary hypogonadism, hyperthyroidism, extreme hyperprolactinemia, adrenal disease
- tumours: pituitary, adrenal, testicular, breast, ectopic production of hCG
- chronic diseases: cirrhosis, renal, malnutrition (with refeeding)
- drugs: estrogens and estrogen agonists, spironolactone, ketoconazole, cimetidine, digoxin, chemotherapy, marijuana, alcohol
- congenital/genetic: Klinefelter’s syndrome, androgen insensitivity
- other: idiopathic, familial

Pathophysiology
- decreased androgen production + increased estrogen production
- increased availability of estrogen precursors for peripheral conversion to estrogen
- androgen receptor blockage + binding of androgen to sex hormone binding globulin (SHBG)

History
- recent change in breast characteristics
- trauma to testicles
- mumps
- alcohol and/or drug use
- FHx
- sexual dysfunction

Occurrence of Gynecomastia

<table>
<thead>
<tr>
<th>Time Period</th>
<th>% Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infancy</td>
<td>60-90</td>
</tr>
<tr>
<td>Puberty</td>
<td>4-69</td>
</tr>
<tr>
<td>Ages 50-80</td>
<td>24-65</td>
</tr>
</tbody>
</table>

Causes of Gynecomastia

DOC TECH
- Drugs
- Other
- Congenital
- Tumour
- Endocrine
- CHronic disease
Physical Exam
• signs of feminization
• breast
  ▪ must differentiate from breast cancer (unilateral, eccentric, hard/firm mass, fixed to
    underlying tissue) with possible skin changes (dimpling, retraction) or nipple changes
    (discharge, crusting)
  ▪ gynecomastia occurs concentrically around nipple, is not fixed to underlying tissue, and no
    discrete mass is palpable
• genito-urinary exam
• stigmata of liver or thyroid disease

Investigations
• laboratory: serum TSH, PRL, LH, FSH, testosterone, estradiol, LFTs, creatinine, hCG (if hCG is
  elevated need to locate the primary tumour)
• CXR and CT of chest/abdomen/pelvis (to locate neoplasm)
• testicular U/S to rule out testicular mass
• MRI of hypothalamic-pituitary region if pituitary adenoma suspected

Treatment
• initial observation for most men with gynecomastia
• medical
  ▪ correct the underlying disorder, discontinue responsible drug
  ▪ androgens for hypogonadism
  ▪ anti-estrogens: tamoxifen, clomiphene
• surgical
  ▪ usually required for macromastia; gynecomastia present for >1 yr (fibrosis is unresponsive to
    medication); or failed medical treatment and for cosmetic purposes

Female Reproductive Endocrinology

• see Gynecology, GY4
Paraneoplastic Syndrome

- clinical syndromes involving non-metastatic systemic effects that accompany malignant disease
- triggered by antibodies against neoplasm cross-reacting with normal tissue or by production of a physiologically active substance by the neoplasm
- commonly present with cancers of lung, breast, ovaries, or lymphatic system

Table 40. Clinical Presentation

<table>
<thead>
<tr>
<th>Syndrome Class</th>
<th>Symptoms/Syndrome</th>
<th>Associated Malignancies</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>Cushing's syndrome</td>
<td>Small-cell lung cancer, Pancreatic carcinoma, Neural tumours, Thymoma</td>
<td>Ectopic ACTH and ACTH-like substance secretion</td>
</tr>
<tr>
<td></td>
<td>SIADH</td>
<td>Small-cell lung cancer, CNS malignancies</td>
<td>Anti-diuretic hormone secretion</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia</td>
<td>Lung cancer, Breast carcinoma, Renal cell carcinoma, Multiple myeloma, Ovarian carcinoma</td>
<td>PTH-related protein, TGF-α, TNF secretion</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
<td>Hepatocellular carcinoma, Fibrosarcoma</td>
<td>Insulin or insulin-like substance secretion</td>
</tr>
<tr>
<td></td>
<td>Carcinoid</td>
<td>Pancreatic carcinoma, Gastric carcinoma</td>
<td>Serotonin, bradykinin secretion</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Lambert-Eaton myasthenic syndrome (LEMS)</td>
<td>Small-cell lung cancer</td>
<td>Ab interferes with ACh release</td>
</tr>
<tr>
<td></td>
<td>Myasthenia gravis</td>
<td>Thymoma</td>
<td>Ab interferes with ACh release</td>
</tr>
<tr>
<td></td>
<td>Paraneoplastic limbic encephalitis</td>
<td>Small-cell lung cancer</td>
<td>Unknown</td>
</tr>
<tr>
<td>Renal</td>
<td>Hypokalemic nephropathy</td>
<td>Small-cell lung cancer</td>
<td>Ectopic ACTH and ACTH-like substance secretion</td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
<td>Lymphoma, Melanomas</td>
<td>Immunocomplex sedimentation in nephrons</td>
</tr>
<tr>
<td>GI</td>
<td>Watery diarrhea</td>
<td>Medullary thyroid carcinomas</td>
<td>Prostaglandin secretion</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Erythrocytosis</td>
<td>Renal cell carcinoma, Hepatocellular carcinoma</td>
<td>EPO production</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>SLE</td>
<td>Lymphomas, Lung cancer, Breast carcinoma, Gonadal carcinoma</td>
<td>Anti-nuclear Ab production</td>
</tr>
<tr>
<td></td>
<td>Scleroderma</td>
<td>Breast carcinoma, Lung cancer, Uterine cancer</td>
<td>Anti-nuclear Ab production</td>
</tr>
</tbody>
</table>

Investigations
- CBC, electrolytes, creatinine, LFTs, ALP, ESR, C-reactive protein, serum/urine electrophoresis, 
- serum autoantibodies, lumbar puncture 
- imaging: skeletal survey, CT, MRI, PET scan 
- ± endoscopy

Treatment
- treat underlying tumour: surgery, radiation, chemotherapy 
- treat immune-mediated disorder: IVIG, steroids, immunosuppressive drugs, plasmapheresis (reserved for patients with identifiable antibodies in serum)
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>Canada Name</th>
<th>US Name (if different)</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide</td>
<td>Sensitizes peripheral tissues to insulin • Increases glucose uptake • Decreases hepatic glucose production by simulation of hepatic AMP-activated protein kinase (AMPK) • Use in nonobese Type 2 DM</td>
<td>metformin</td>
<td>Glucophage®</td>
<td>Glumetza®</td>
<td>500 mg OD titrated to 2000 mg/d maximum</td>
<td>Useful in obese Type 2 DM • Improves both fasting and postprandial hyperglycemia • Also ↓ TG</td>
<td>• GI upset (abdo discomfort, nausea) • Absolute: HbA1c 1.0-2.0%</td>
<td>• Hypoglycemia • Weight gain</td>
<td>↓ HbA1c 1.0-2.0%</td>
</tr>
<tr>
<td>Insulin secretagogue</td>
<td>Stimulates insulin release from β-cells by causing K+ channel closure • Depolarization • Ca2+ mediated insulin release</td>
<td>sulfonylureas: glyburide</td>
<td>Diabeta®</td>
<td>Micronase®</td>
<td>2.5-5.0 mg/d titrated to 50-200 mg/d</td>
<td>• Absolut: Moderate to severe liver dysfunction • RELATIVE (glyburide and glimepiride): Adjust dose in mild to moderate kidney dysfunction • Do not combine with insulin</td>
<td>Hypoglycemia, fluid retention and congestive heart failure • Increased risk of bladder cancer with pioglitazone (requires written informed consent when prescribing)</td>
<td>↓ HbA1c 1.0-1.5% for nateglinide and 0.5-1.0% for nateglinide</td>
<td></td>
</tr>
<tr>
<td>Insulin sensitizers (thiazolidinedione)</td>
<td>Sensitizes peripheral tissues to insulin • Increases glucose uptake • Decreases FFA release from adipose • BINDS to nuclear receptor PPAR-γ</td>
<td>rosiglitazone</td>
<td>Avandia®</td>
<td></td>
<td>2-8 mg OD</td>
<td>• Rosiglitazone – indicated only in patients with type 2 diabetes mellitus for whom all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance</td>
<td>• Peripheral edema • CHF • Anemia • Fluid retention and congestive heart failure • Increased risk of cardiac events with rosiglitazone (requires written informed consent when prescribing)</td>
<td>↓ HbA1c 1.0-1.5%</td>
<td></td>
</tr>
<tr>
<td>α-glucosidase inhibitor</td>
<td>α-carbohydrate GI absorption by inhibiting brush border α-glucosidase</td>
<td>acarbose</td>
<td>Glucobay®</td>
<td></td>
<td>25 mg OD titrated to 100 mg t.i.d</td>
<td>↓ postprandial hyperglycemia • • ↑ postprandial hyperglycemia</td>
<td>Flatulence • Abdominal cramps • Diarrhea</td>
<td>↓ HbA1c 0.5-1.0%</td>
<td></td>
</tr>
<tr>
<td>Dipetidyl peptidase-IV (DPP-IV) inhibitor</td>
<td>Inhibits degradation of endogenous antihyperglycemic incretin hormones • Incretin hormones stimulate insulin secretion, inhibit glucagon release, and delay gastric emptying</td>
<td>sitagliptin</td>
<td>Januvia®</td>
<td></td>
<td>100 mg OD</td>
<td>• • RELATIVE (sitagliptin and saxagliptin): Use with dose reduction in kidney dysfunction</td>
<td>• Nasopharyngitis • URTI • Headache • Pancreatitis • Steven-Johnson syndrome</td>
<td>↓ HbA1c 0.5-1.0%</td>
<td></td>
</tr>
<tr>
<td>Glucagon-like peptide (GLP)-1 analogue</td>
<td>BINDS to GLP-1 receptor to promote insulin release • Insulinotropic effect suppressed as plasma glucose &lt;4 mmol/L • Slows gastric emptying, suppress inappropriately elevated glucagon levels • Causes β-cell regeneration and differentiation in vitro</td>
<td>Exenatide</td>
<td></td>
<td></td>
<td>5-10 µg SC bid 1 h before meals</td>
<td>• Absolute: Type 1 DM • DKA • Acute pancreatitis hx</td>
<td>• Nausea, vomiting, diarrhea • Distress, headache • Muscle weakness • Anti-insulin antibodies • Pancreatitis</td>
<td>↓ HbA1c 1.0-1.5%</td>
<td></td>
</tr>
</tbody>
</table>
## Dyslipidemia Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>Canada Name</th>
<th>US Name (if different)</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG CoA reductase inhibitor</td>
<td>• Inhibits cholesterol biosynthesis, ↓ LDL synthesis, ↑ LDL clearance, modest ↑ HDL, limited ↓ VLDL</td>
<td>atorvastatin</td>
<td>Lipitor®</td>
<td>10-80 mg/d</td>
<td>• 1st line monotherapy</td>
<td>• Active liver disease</td>
<td>• GI symptoms</td>
<td>1st liver enzymes, Mysolix (1 risk if combined with fibrates)</td>
</tr>
<tr>
<td></td>
<td>• Inhibits cholesterol biosynthesis, ↓ LDL synthesis, ↑ LDL clearance, modest ↑ HDL, limited ↓ VLDL</td>
<td>fluvastatin</td>
<td>Lescol®</td>
<td>20-80 mg/d</td>
<td>• Used for ↑ LDL, ↑ TG</td>
<td>Persistent ↑ in AST, ALT unexplained</td>
<td>Rhabdomyolysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Inhibits cholesterol biosynthesis, ↓ LDL synthesis, ↑ LDL clearance, modest ↑ HDL, limited ↓ VLDL</td>
<td>lovastatin</td>
<td>Mevercor®</td>
<td>20-80 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Inhibits cholesterol biosynthesis, ↓ LDL synthesis, ↑ LDL clearance, modest ↑ HDL, limited ↓ VLDL</td>
<td>rosuvastatin</td>
<td>Crestor®</td>
<td>10-40 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Inhibits cholesterol biosynthesis, ↓ LDL synthesis, ↑ LDL clearance, modest ↑ HDL, limited ↓ VLDL</td>
<td>simvastatin</td>
<td>Zocor®</td>
<td>10-80 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrates</td>
<td>• Uregulates lipoprotein lipase = apo A1, ↓ VLDL, ↓ TG, modest ↓ LDL, modest ↑ HDL</td>
<td>bezafibrate</td>
<td>Bezalip®</td>
<td>400 mg/d</td>
<td>• Used for ↑ TG, hyperchylomicronaemia</td>
<td>• Hepatic disease</td>
<td>• GI upset</td>
<td>1st risk of gallstone formation, ↑ risk of rhabdomyolysis when combined with statins</td>
</tr>
<tr>
<td></td>
<td>• Uregulates lipoprotein lipase = apo A1, ↓ VLDL, ↓ TG, modest ↓ LDL, modest ↑ HDL</td>
<td>fenofibrate</td>
<td>Lipid®</td>
<td>48-200 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Uregulates lipoprotein lipase = apo A1, ↓ VLDL, ↓ TG, modest ↓ LDL, modest ↑ HDL</td>
<td>gemfibrozil</td>
<td>Lipid®</td>
<td>600-1200 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niacin</td>
<td>• Inhibits secretion of hepatic VLDL via lipoprotein lipase (LPL) pathway → decreased VLDL and LDL, decreased clearance of HDL</td>
<td>nicotinic acid</td>
<td>Niaspan®</td>
<td>0.5-2 g/d</td>
<td>• Used for ↑ LDL, ↑ VLDL</td>
<td>• Hyperlipidemia</td>
<td>• GI upset</td>
<td>Abnormal liver enzymes, Pruritus, IGT, Constipation, Flatulence, Bloating, Rise in TG</td>
</tr>
<tr>
<td></td>
<td>• Inhibits secretion of hepatic VLDL via lipoprotein lipase (LPL) pathway → decreased VLDL and LDL, decreased clearance of HDL</td>
<td>generic niacin</td>
<td>Niacor®</td>
<td>1-3 g/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>• Resins that bind bile acids in intestinal lumen and prevent absorption thereby ↓ LDL</td>
<td>cholestyramine</td>
<td>Questran®</td>
<td>2-24 g/d</td>
<td>• Used for ↑ LDL</td>
<td>• Complete biliary obstruction</td>
<td>• Hepatic disease, Hypersensitivity, Hepatic dysfunction, Active PUD, Hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Resins that bind bile acids in intestinal lumen and prevent absorption thereby ↓ LDL</td>
<td>colestipol</td>
<td>Colestid®</td>
<td>5-30 g/d</td>
<td>• Use as adjunct with statins or fibrates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol absorption inhibitors</td>
<td>• Inhibits cholesterol absorption at the small intestine brush border</td>
<td>ezetimibe</td>
<td>Ezetrol®</td>
<td>10 mg/d</td>
<td>• Used for ↑ LDL, apo B</td>
<td>• Hypersensitivity</td>
<td>• Fatigue, Pharyngitis, Sinusitis, Abdominal pain, Diarrhea, Arthralgia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Inhibits cholesterol absorption at the small intestine brush border</td>
<td>generic ezetimibe</td>
<td>Zeria®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Thyroid Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>Canada Name</th>
<th>US Name (if different)</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithyroid Agent (thionamides)</td>
<td>• Decreases thyroid hormone production by inhibiting iodine and peroxidase from interacting with thyroglobulin to form T3 and T4; ↓ PTU also interferes with conversion of T4 to T3</td>
<td>propylthiouracil (PTU)</td>
<td>Propyl-Thyracil®</td>
<td>Start 100 mg PO tid, then adjust accordingly</td>
<td>• Hyperthyroidism</td>
<td>• Hyperreactivity</td>
<td>• Recent MI, thyrotoxicosis</td>
<td>If wrong dosing: symptoms of hypothyroidism or hyperthyroidism, Skin rash from dye in pill</td>
</tr>
<tr>
<td></td>
<td>• Decreases thyroid hormone production by inhibiting iodine and peroxidase from interacting with thyroglobulin to form T3 and T4; ↓ PTU also interferes with conversion of T4 to T3</td>
<td>methimazole (MMI)</td>
<td>Tapazole®</td>
<td>Start 5-20 mg PO OD, then adjust accordingly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Decreases thyroid hormone production by inhibiting iodine and peroxidase from interacting with thyroglobulin to form T3 and T4; ↓ PTU also interferes with conversion of T4 to T3</td>
<td>methimazole (MMI)</td>
<td>Tapazole®</td>
<td>Up to 60 mg OD may be required</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>• Synthetic form of thyroxine (T4)</td>
<td>levothyroxine</td>
<td>Synthroid®</td>
<td>0.05-2.0 mg/d, usually 1.6 times weight in kg is dose in micrograms</td>
<td>• Hypothyroidism</td>
<td>• Recent MI, thyrotoxicosis</td>
<td>• If wrong dosing: symptoms of hypothyroidism or hyperthyroidism, Skin rash from dye in pill</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Synthetic form of thyroxine (T4)</td>
<td>Synthroid®</td>
<td>Levoxyl®</td>
<td>0.05-2.0 mg/d, usually 1.6 times weight in kg is dose in micrograms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Synthetic form of thyroxine (T4)</td>
<td>levothyroxine</td>
<td>Synthroid®</td>
<td>0.05-2.0 mg/d, usually 1.6 times weight in kg is dose in micrograms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Synthetic form of thyroxine (T4)</td>
<td>levothyroxine</td>
<td>Synthroid®</td>
<td>0.05-2.0 mg/d, usually 1.6 times weight in kg is dose in micrograms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Synthetic form of thyroxine (T4)</td>
<td>levothyroxine</td>
<td>Synthroid®</td>
<td>0.05-2.0 mg/d, usually 1.6 times weight in kg is dose in micrograms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Synthetic form of thyroxine (T4)</td>
<td>levothyroxine</td>
<td>Synthroid®</td>
<td>0.05-2.0 mg/d, usually 1.6 times weight in kg is dose in micrograms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Synthetic form of thyroxine (T4)</td>
<td>levothyroxine</td>
<td>Synthroid®</td>
<td>0.05-2.0 mg/d, usually 1.6 times weight in kg is dose in micrograms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithyroid Agent</td>
<td>• Radioactive isotope of iodine that is incorporated into the thyroid gland irritating the area and destroying local glandular tissue</td>
<td>sodium iodide 1-131</td>
<td>Iodotope®</td>
<td>Dose corrected for 24 h radioactive iodine uptake, Hyperthyroidism 4-12 mCi Thyroid Ca 50-150 mCi</td>
<td>• Hyperthyroidism</td>
<td>• Thyroid malignancy</td>
<td>• Nausea, vomiting</td>
<td>Nausea, vomiting, Bone marrow suppression, Sialadenitis, Thyroiditis</td>
</tr>
<tr>
<td>Drug Class</td>
<td>Mechanism of Action</td>
<td>Generic Drug Name</td>
<td>Canada Name</td>
<td>US Name (if different)</td>
<td>Dosing</td>
<td>Indications</td>
<td>Contraindications</td>
<td>Side Effects</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>------------------</td>
<td>--------------</td>
<td>------------------------</td>
<td>-----------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>• Inhibits osteoclast-mediated bone resorption</td>
<td>alendronate</td>
<td>Fosamax®</td>
<td>Osteoporosis: 5-10 mg OD 70 mg once weekly Paget’s: 40 mg OD for 8 mo</td>
<td>• Prevention of postmenopausal osteoporosis • Treatment of osteoporosis • Glucocorticoid-induced osteoporosis • Paget’s disease</td>
<td>• Esophageal stricture or achalasia (oral) • Unable to stand or sit upright for &gt; 30 min (oral) • Hypersensitivity • Hypocalcemia • Renal insufficiency</td>
<td>• GI • NSP pain • Headache • Osteonecrosis of the jaw</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Prevention of postmenopausal osteoporosis</td>
<td>risedronate</td>
<td>Actonel®</td>
<td>Osteoporosis: 5 mg OD 35 mg once weekly Paget’s: 30 mg OD for 2 mo</td>
<td>• Treatment and prevention of postmenopausal osteoporosis • Treatment and prevention of glucocorticoid-induced osteoporosis • Paget’s disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Treatment of osteoporosis</td>
<td>etidronate</td>
<td>Didronel®</td>
<td>Paget’s: 5-10 mg/kg OD x 6 mo</td>
<td>• Symptomatic Paget’s disease • Prevention and treatment of heterotopic ossification after total hip replacement or spinal cord injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Glucocorticoid-induced osteoporosis</td>
<td>ibandronate</td>
<td>Boniva®</td>
<td>2.5 mg OD or 150 mg once monthly</td>
<td>• Treatment and prevention of postmenopausal osteoporosis (US only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Paget’s disease</td>
<td>pamidronate</td>
<td>Aredia®</td>
<td>Hypercalcemia of malignancy 60-90 mg IV over 2-24 h Wait at least 7 d before considering retreatment</td>
<td>• Hypercalcemia of malignancy • Paget’s disease • Osteolytic bone metastases of breast cancer • Osteolytic lesions of multiple myeloma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Osteolytic bone metastases of breast cancer</td>
<td>zoledronate</td>
<td>Zometa® Adalsta®</td>
<td>5 mg IV once yearly IV</td>
<td>• Treatment of osteoporosis • Hypercalcemia of malignancy • Treatment and prevention of skeletal complications related to cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Osteolytic lesions of multiple myeloma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective Estrogen Receptor Modulators</td>
<td>• Decreases resorption of bone through binding to estrogen receptors</td>
<td>raloxifene</td>
<td>Evista®</td>
<td>60 mg OD</td>
<td>• Treatment and prevention of postmenopausal osteoporosis (2nd line)</td>
<td>• Lactation • Pregnancy • Active or past history of DVT, PE or retinal vein thrombosis</td>
<td>• Hot flashes • Leg cramps • Increased risk of fatal stroke, venous thromboembolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hot flashes</td>
<td>calcitonin</td>
<td>Miacalcin®</td>
<td>One spray (200 IU) per day, alternating nostrils</td>
<td>• Treatment of postmenopausal osteoporosis, greater than 5 yr postmenopause</td>
<td>• Clinical allergy to salmon-calcitonin</td>
<td></td>
<td>• Rhinitis • Epistaxis • Sinusitis • Nasal dryness</td>
</tr>
<tr>
<td></td>
<td>• Hot flashes</td>
<td>denosumab</td>
<td>Proka™ Xgeva™</td>
<td>60 mg SC q6mo</td>
<td>• Treatment of postmenopausal women at high risk of fracture • Prevent skeletal-related events in patients with bone metastasis from solid tumours</td>
<td>• Hypocalcemia • Fatigue/headache • Dermatitis/rash • Hypophosphatemia/hypocalcemia • Hypercholesterolemia • GI discomfort</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hot flashes</td>
<td>teriparatide</td>
<td>Forteo®</td>
<td>20 μg SC OD X 18-24 mo</td>
<td>• Treatment of postmenopausal women with osteoporosis who are at high risk for fracture • Treatment of men with primary or hyperparathyroid osteoporosis who are at high risk for fracture</td>
<td>• Paget’s disease • Prior external beam or implant radiation therapy involving the skeleton • Bone metastases • Metabolic bone diseases other than osteoporosis</td>
<td>• Orthostatic hypotension • Hypercalcemia • Dizziness • Leg cramps</td>
<td></td>
</tr>
</tbody>
</table>
# Metabolic Bone Disease Medications (continued)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>Canada Name</th>
<th>US Name (if different)</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>• Inhibits PTH secretion</td>
<td>Calcitriol (1,25(OH)2-D)</td>
<td>Rocaltrol® Calcijex®</td>
<td>Start 0.25 µg/d Titrating up by 0.25 µg/d at 4-8 wk intervals to 0.5-1 µg/d</td>
<td>• Hypoparathyroidism</td>
<td>• Caution in patients on digoxin (risk of hypercalcemia which may precipitate arrhythmia)</td>
<td>• Hypercalcemia</td>
<td>• Headache, nausea, vomiting, constipation</td>
</tr>
<tr>
<td>vitamin D</td>
<td>• Regulation of calcium and phosphate homeostasis</td>
<td>ergocalciferol (vitamin D2)</td>
<td>Drisdol® Erdol®</td>
<td>50,000 IU/wk</td>
<td>• Hypercalcemia</td>
<td>• Decreased renal function</td>
<td>• Hypocalcemia</td>
<td>• Headache, nausea, vomiting, constipation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>calcitriol (1,25(OH)2-D)</td>
<td>Recaltril® Calcijex®</td>
<td>Start 0.25 µg/d Titrating up by 0.25 µg/d at 2-4 wk intervals to 0.5-2 µg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# Adrenal Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mineralocorticoid Activity</th>
<th>Generic Drug Name</th>
<th>Potency (relative to Cortisol)</th>
<th>Equivalent Dose (mg)</th>
<th>Duration of Action (t1/2 in h)</th>
<th>Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>Yes</td>
<td>Cortef Solu-Cortef</td>
<td>1.0</td>
<td>20</td>
<td>8</td>
<td>Adrenal Crisis: 50-100 mg IV bolus, then 50-100 mg q8h (continuous infusion x 24-48 h) PO once stable (50 mg q8h x 48 h, then taper over 14 d) Chronic: 15-20 mg PO OD (2/3 AM, 1/3 PM)</td>
<td>• In high doses, mineralocorticoid side effects may emerge (salt + water retention, ECF volume expansion, HTN, low K+ metabolic alkalosis)</td>
</tr>
<tr>
<td>Cortisone acetate</td>
<td>Yes</td>
<td>Cortisone Acetate</td>
<td>0.8</td>
<td>25</td>
<td>oral = 8 IM = 18+</td>
<td>Adrenal Crisis: 75-300 mg/d PO/IM divided q12-24h Chronic: 15 mg daily</td>
<td>• Pre-drug which is converted to active form as hydrocortisone • High doses can result in mineralocorticoid side effects (see above)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>No</td>
<td>Prednisone</td>
<td>4</td>
<td>5</td>
<td>16-36</td>
<td>Adrenal Crisis: 15-60 mg/d PO qd or divided bid/qid Chronic: 5 mg daily</td>
<td>• Pre-drug which is converted to active form as prednisolone</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>No</td>
<td>Dexamethasone</td>
<td>30</td>
<td>0.7</td>
<td>36-54</td>
<td>Adrenal Crisis: 4 mg IV; repeat q2-6h if necessary</td>
<td>• Used for undiagnosed adrenal insufficiency (won’t interfere with measurement of serum cortisol levels)</td>
</tr>
</tbody>
</table>
## Landmark Endocrinology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIABETES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>NEJM 2008; 358:2560-72</td>
<td>Compared with standard therapy the use of intensive therapy to target normal HbA1c levels (&lt;6%) for 3.5 yr increased mortality and did not significantly reduce major cardiovascular events</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>NEJM 2008; 358:2545-59</td>
<td>Intensive glucose control that lowered the HbA1c value to 6.5% reduced the incidence of nephropathy but did not significantly reduce major macrovascular events, death from cardiovascular events or death from any cause. Hypoglycemia was more common in the intensive control group</td>
</tr>
<tr>
<td>BARI-2D</td>
<td>NEJM 2009; 360:2503-15</td>
<td>In patients with both Type 2 DM and coronary artery disease no significant difference was found in the rates of death and major cardiovascular events in patients undergoing prompt revascularization and those undergoing medical therapy or between strategies of insulin sensitization and insulin</td>
</tr>
<tr>
<td>DCCT</td>
<td>NEJM 1993; 329:977-86</td>
<td>Intensive blood glucose control delayed the onset and reduced the progression of microvascular complications (retinopathy, nephropathy and neuropathy) in Type 1 DM</td>
</tr>
<tr>
<td>EDIC</td>
<td>NEJM 2005; 353:2644-53</td>
<td>Compared with conventional therapy intensive diabetes therapy early on without macrovascular disease (goal HbA1c &lt; 6.05%) has long-term beneficial effects on the risk of cardiovascular disease in patients with Type 1 DM</td>
</tr>
<tr>
<td>NAVIGATOR</td>
<td>NEJM 2010; 362:1463-90</td>
<td>In patients with impaired glucose tolerance, nateglinide did not reduce progression to diabetes or risk of cardiovascular events while valsartan only reduced progression to diabetes</td>
</tr>
<tr>
<td>Steno-2</td>
<td>NEJM 2008; 358:580-91</td>
<td>In at-risk patients with Type 2 DM intensive intervention with multiple drug combinations and behaviour modification had sustained significant beneficial effects with respect to vascular complications and mortality. Multifactorial intervention is critical in the management of Type 2 DM</td>
</tr>
<tr>
<td>UKPDS</td>
<td>Lancet 1998; 352:837-53</td>
<td>Intensive blood glucose control reduces microvascular but not macrovascular complications in Type 2 DM</td>
</tr>
<tr>
<td>UKPDS extension</td>
<td>NEJM 2008; 359:1577-89</td>
<td>Continued risk reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause 10 yr post UKPDS trial follow up in Type 2 DM</td>
</tr>
<tr>
<td>VADT</td>
<td>NEJM 2009; 360:1-11</td>
<td>In patients with longstanding poorly controlled Type 2 DM intensive glucose control had no significant effect on the rates of major cardiovascular events, death or microvascular complications. Adverse events, predominantly hypoglycemia, were more common in the intensive control group</td>
</tr>
<tr>
<td><strong>LIPIDS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S</td>
<td>Lancet 1994; 344:1383-89</td>
<td>In patients with angina or previous MI and high total cholesterol simvastatin reduced: all-cause mortality, fatal and nonfatal coronary events, and need for coronary artery bypass surgery or angioplasty</td>
</tr>
<tr>
<td>FIELD</td>
<td>Lancet 2005; 366:1849-61</td>
<td>In patients with Type 2 DM not previously on statin therapy fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. It did reduce non-fatal myocardial infarctions and revascularizations</td>
</tr>
<tr>
<td>HPS</td>
<td>Lancet 2002; 360:7-22</td>
<td>In high-risk patients with various cholesterol values simvastatin reduced all-cause mortality, coronary deaths and major vascular events</td>
</tr>
<tr>
<td>Jupiter</td>
<td>NEJM 2008; 359:2195-207</td>
<td>Rosuvastatin significantly reduced the incidence of major cardiovascular events in patients with elevated high-sensitivity C-reactive protein levels and no hyperlipidemia</td>
</tr>
<tr>
<td>TNT</td>
<td>NEJM 2005; 352:1425-35</td>
<td>Lipid-lowering therapy with atorvastatin 80 mg/d in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/d</td>
</tr>
</tbody>
</table>
References


Four Principles of Family Medicine ................ 2

Periodic Health Examination (PHE) ............... 2
Purpose of the PHE
Breast Cancer Screening Guidelines
Colorectal Cancer Screening Guidelines
Cervical Cancer Screening

Health Promotion and Counselling
Motivational Strategies for Behavioural
Change ........................................... 5
Nutrition .......................................... 5
Obesity ........................................... 7
Dyslipidemia ..................................... 8
Exercize .......................................... 10
Smoking Cessation ............................... 10
Alcohol ........................................... 12

Common Presenting Problems
Abdominal Pain ................................... 13
Allergic Rhinitis .................................. 13
Amenorrhea ...................................... 14
Anxiety .......................................... 15
Asthma/COPD ................................... 16
Benign Prostatic Hyperplasia (BPH) ............ 17
Bronchitis (Acute) ................................ 18
Chest Pain ...................................... 18
Common Cold (Acute Rhinitis) .................. 19
Contraception .................................... 20
Cough .......................................... 21
Dementia ........................................ 21
Depression ...................................... 21
Diabetes Mellitus (DM) .......................... 22
Diarrhea ........................................ 22
Dizziness ........................................ 26

Domestic Violence/Elder Abuse ................. 28
Dyspepsia ......................................... 29
Dyspnea .......................................... 29
Dysuria .......................................... 30
Epistaxis ......................................... 31
Erectile Dysfunction (ED) ........................ 31
Eye Complaints .................................. 32
Falls in the Elderly ............................... 32
Fatigue .......................................... 32
Fever ........................................... 34
Joint Pain ........................................ 35
Headache ........................................ 36
Hearing Impairment ............................. 37
Hypertension .................................... 37
Low Back Pain ................................... 41
Menopause/Hormone Replacement Therapy
(HRT) ............................................. 42
Osteoarthritis .................................... 43
Osteoporosis ..................................... 43
Rash ............................................. 45
Rhinorhoea ....................................... 46
Sexually Transmitted Infections (STIs) ......... 46
Sinusitis ......................................... 47
Sleep Disorders .................................. 48
Sore Throat (Pharyngitis) ...................... 50

Complementary and Alternative Medicine (CAM) .......... 52

Primary Care Models ............................. 53

Antimicrobial Quick Reference .................. 53

References ..................................... 56

Acronyms
AAA  abdominal aortic aneurysm
ACR  albumin:creatinine ratio
AIU  anal intraepithelial neoplasia
BMI  body mass index
ABG  arterial blood gas
AR  absolute reduction
BPPV  benign paroxysmal positional vertigo
CA  cancer
CADG  coronary artery bypass graft
CAD  coronary artery disease
C8T  cognitive behavioural therapy
CF  cystic fibrosis
CHF  congestive heart failure
CPAP  continuous positive airway pressure
CRC  colorectal cancer
DHP  diptheridypine
DMPA  depot medroxyprogesterone
DRE  digital rectal exam
DG  double strength
ER  emergency room
ER  extended release
F/U  follow-up
FBG  fasting blood glucose
FGBT  fecal occult blood test
FRS  Framingham Risk Score
GAD  generalized anxiety disorder
gastroesophageal reflux disease
general medical condition
glucose intolerance
high density lipoprotein cholesterol
high-grade squamous intraepithelial
lesion
human papillomavirus
inflammation
inflammaotry bowel disease
irritable bowel syndrome
inhaled corticosteroids
impaired fasting glucose
impaired glucose tolerance
ischemic heart disease
ischemic stroke
intravenous pyelogram
kidneys, ureter, bladder x-ray
low density lipoprotein cholesterol
low grade squamous intraepithelial
lesion
left ventricle
left ventricle hypertrophy
metered dose inhaler
monoamine oxidase inhibitor
MMSE  mini mental status examination
Montreal cognitive assessment
men who sleep with men
nausea/vomiting
insulin human sophane
neural tube defects
nitrugycin
ova and parasites
obesessive compulsive disorder
oral contraceptive pill
obsessive compulsive personality
disorder
once a day
oral glucose challenge test
oral glucose tolerance test
over the counter
polycystic ovarian syndrome
pulmonary function test
pelvic inflammatory disease
premenstrual syndrome
paroxysmal nocturnal dyspnea
proton pump inhibitor
purified protein derivative
post-traumatic stress disorder
PUD  peptic ulcer disease
PVD  peripheral vascular disease
RCT  randomized controlled trial
SAH  subarachnoid hemorrhage
SDBI  selective serotonin reuptake inhibitor
SERM  selective estrogen receptor modulator
SIDS  sudden infant death syndrome
SLE  systemic lupus erythematosis
SNRI  serotonin noradrenaline reuptake inhibitor
SSRI  selective serotonin reuptake inhibitor
transient ischemic attack
total cholesterol
TC  total cholesterol
TCA  tricylic antidepressant
glucocorticoid
TNF  tissue necrosis factor
TM  tympanic membrane
TMJ  temporomandibular joint
UC  ulcerative colitis
URTI  upper respiratory tract infection
UTI  urinary tract infection
VAIN  vaginal intraepithelial neoplasia
VIN  vulvar intraepithelial neoplasia
VSI  vertebral insufficiency
WSIB  Workplace Safety and Insurance Board
Four Principles of Family Medicine

College of Family Physicians of Canada Guidelines
1. The family physician is a skilled clinician
   - in diagnosing and managing diseases common to the population served
   - recognizes importance of early diagnosis of serious life-threatening illnesses
2. Family medicine is a community-based discipline
   - provides information and access to community services
   - responds/adapts to changing needs and circumstances of the community
3. The family physician is a resource to a defined practice population
   - serves as a health resource
   - advocates for public policy to promote health
4. The patient-physician relationship is central to the role of the family physician
   - committed to the person, not just the disease
   - promotes continuity of patient care

Periodic Health Examination (PHE)

- Canadian Task Force on Preventive Health Care established in 1976, first published in 1979, last updated in 2005
- mandate: to develop and disseminate clinical practice guidelines for primary and preventive care
- recommendations are based on systematic analysis of scientific evidence
  - most notable recommendation is the abolition of the annual physical exam; replaced by the PHE

Purpose of the PHE

- primary prevention: identify risk factors for common diseases; counsel patients to promote healthy behaviour
- secondary prevention: presymptomatic detection of disease to allow early treatment and to prevent disease progression
- update clinical data
- enhance patient-physician relationship

Table 1. Periodic Health Exam

<table>
<thead>
<tr>
<th>General Population</th>
<th>Special Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DISCUSSION</strong></td>
<td></td>
</tr>
<tr>
<td>Dental hygiene (community fluoridation, brushing, flossing) (A)</td>
<td>Pediatrics: Home visits for high risk families (A)</td>
</tr>
<tr>
<td>Noise control and hearing protection (A)</td>
<td>Inquiry into developmental milestones (B)</td>
</tr>
<tr>
<td>Screen for poverty</td>
<td>Adolescents: Counsel on sexual activity and contraceptive methods (B)</td>
</tr>
<tr>
<td>Smokers: counsel on smoking cessation, provide:</td>
<td>Counsel to prevent smoking reduction (B)</td>
</tr>
<tr>
<td>- Nicotine replacement therapy (A)</td>
<td>Perimenopausal women:</td>
</tr>
<tr>
<td>- Referral to smoking cessation program (B)</td>
<td>Adults &gt;50: Assess for risk factors for osteoporosis and fracture (A)</td>
</tr>
<tr>
<td>- Dietary advice on leafy green vegetables and fruits (B)</td>
<td>Counsel on osteoporosis</td>
</tr>
<tr>
<td>- Seat belt use (B)</td>
<td>Counsel on risks/benefits of hormonereplacement therapy (B)</td>
</tr>
<tr>
<td>- Injury prevention (bicycle helmets, smoke detectors) (B)</td>
<td>(see <a href="http://www.canadiantaskforce.ca">www.canadiantaskforce.ca</a> - for up to date guideline)</td>
</tr>
<tr>
<td>- Moderate physical activity (B)</td>
<td>Adults &gt;65: Follow-up on caregiver concern of cognitive impairment (A)</td>
</tr>
<tr>
<td>- Avoid sun exposure and wear protective clothing (B)</td>
<td>Multidisciplinary post-fall assessment (A)</td>
</tr>
<tr>
<td>- Problem drinking screening and counselling (B)</td>
<td>Pediatrics: Repeated examinations of hips, eyes and hearing (especially in first year of life) (A)</td>
</tr>
<tr>
<td>- Counselling to protect against STIs (B)</td>
<td>Serial height, weight and head circumference (B)</td>
</tr>
<tr>
<td>- Nutritional counseling and dietary advice on fat and cholesterol (B)</td>
<td>Visual acuity testing after age 2 (B)</td>
</tr>
<tr>
<td>- Dietary advice on calcium and vitamin D requirements (see <a href="http://www.canadiantaskforce.ca">www.canadiantaskforce.ca</a> - for up to date guideline)</td>
<td>Adults &gt;85: Visual acuity (Snellen sight chart) (B)</td>
</tr>
<tr>
<td><strong>PHYSICAL</strong></td>
<td></td>
</tr>
<tr>
<td>Blood pressure measurement (B)</td>
<td>Pediatric: Hearing impairment (inquiry, whispered voice test, audiogram) (B)</td>
</tr>
<tr>
<td>BMI measurement in obese adults (B)</td>
<td>First degree relative with melanoma: Full body skin exam (B)</td>
</tr>
</tbody>
</table>
### Breast Cancer Screening Guidelines

**2011 Recommendations on screening for breast cancer in average-risk women** *(The Canadian Task Force on Preventative Health Care)* *(Weak recommendations with low-moderate quality evidence)*

- average-risk women: women age 40-74 with no personal history of breast cancer, history of breast cancer in 1st degree relatives, known mutations of the *BRCA1/BRCA2* genes or previous exposures of the chest wall to radiation

#### Mammography
- age 40-49: no routine screening
- age 50-69: routine screening q2-3yr
- age 70-74: routine screening q2-3yr

#### Magnetic Resonance Imaging (MRI)
- no routine screening with MRI scans

#### Clinical Breast Examination (CBE)
- no routine CBE alone or in conjunction with mammography to screen for breast cancer

#### Breast self-examination
- recommend not advising women to routinely practice breast self-examination

---

<table>
<thead>
<tr>
<th>TESTS</th>
<th>General Population</th>
<th>Special Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Multiphase screening with the Hemocult® test (adults age 50-75 q1-2yr)</td>
<td>Pediatrics: Routine hemoglobin for high risk infants (B) Blood lead screening of high risk infants (B)</td>
<td>Diabetics: Urine dipstick (A) Fundoscopy (B)</td>
</tr>
<tr>
<td>• Sigmoidoscopy (adults &gt; 50)</td>
<td>Tub high risk groups: Mantoux skin testing (A)</td>
<td>STI high risk groups: Voluntary HIV antibody screening (A) Gonorrhea screening (A) Chlamydia screening in women (B) Syphilis screen (A)</td>
</tr>
<tr>
<td>• Bone mineral density: age ≥84 if at risk (see FM44 in risk factors), otherwise age ≥65</td>
<td>Colon cancer high risk groups: Colonoscopy (A)</td>
<td>FAP: Genetic testing and sigmoidoscopy annually, begin at age 10-12 (B)</td>
</tr>
<tr>
<td>• Fasting lipid profile (C):</td>
<td>HNPPC: Colonoscopy q1-2yr; begin at age 20 or 10 yr younger than earliest case in the family (B)</td>
<td>Syphilis risk group: VDRL test (A)</td>
</tr>
<tr>
<td>• Women:</td>
<td>• Prostate cancer screening with PSA and DRE (A)</td>
<td>• For men &gt;50 with at least 10-yr life expectancy q2-yr</td>
</tr>
<tr>
<td>• For men &gt; 50 or post-menopausal; earlier if at risk</td>
<td>• If family history of prostate CA or African descent</td>
<td>• If age 70 after ≥3 negative tests in 10 yr prior (2012 Ontario guidelines). See FM4</td>
</tr>
<tr>
<td>• Men:</td>
<td>• Prostate cancer screening with PSA and DRE (A)</td>
<td>• See Urology, U25</td>
</tr>
<tr>
<td>• Age 80</td>
<td>• Prostate cancer screening with PSA and DRE (A)</td>
<td>• See Urology, U25</td>
</tr>
<tr>
<td>• Women:</td>
<td>• Prostate cancer screening with PSA and DRE (A)</td>
<td>• See Urology, U25</td>
</tr>
<tr>
<td>• Age 70 after</td>
<td>• Prostate cancer screening with PSA and DRE (A)</td>
<td>• See Urology, U25</td>
</tr>
<tr>
<td>• Age 60</td>
<td>• Prostate cancer screening with PSA and DRE (A)</td>
<td>• See Urology, U25</td>
</tr>
<tr>
<td>• Age 50 after</td>
<td>• Prostate cancer screening with PSA and DRE (A)</td>
<td>• See Urology, U25</td>
</tr>
<tr>
<td>• Age 40 after</td>
<td>• Prostate cancer screening with PSA and DRE (A)</td>
<td>• See Urology, U25</td>
</tr>
<tr>
<td>• Age 30 after</td>
<td>• Prostate cancer screening with PSA and DRE (A)</td>
<td>• See Urology, U25</td>
</tr>
<tr>
<td>• Age 20 after</td>
<td>• Prostate cancer screening with PSA and DRE (A)</td>
<td>• See Urology, U25</td>
</tr>
<tr>
<td>• Age 10 after</td>
<td>• Prostate cancer screening with PSA and DRE (A)</td>
<td>• See Urology, U25</td>
</tr>
<tr>
<td>• Age 0 after</td>
<td>• Prostate cancer screening with PSA and DRE (A)</td>
<td>• See Urology, U25</td>
</tr>
<tr>
<td>• Age 0 after</td>
<td>• Prostate cancer screening with PSA and DRE (A)</td>
<td>• See Urology, U25</td>
</tr>
</tbody>
</table>

---

**Classification of recommendation in brackets. See sidebar on FM3.**
**Reference:** Canadian Task Force on Preventative Health Care, 2005

---

**Folic Acid Supplementation in Pregnancy (Joint SOGC-Motherisk clinical guideline)**
- To prevent neural tube defects in all women capable of becoming pregnant
- Low risk women (no personal health risks, planned pregnancy): 0.4-1.0 mg daily folic acid supplementation for at least 2-3 mo before conception and throughout pregnancy and postpartum period
- High risk women (health risks including epilepsy, insulin dependent diabetes, BMI >35, family history of NTD, high risk ethnic group): at least 3 mo prior to conception until 10-12 wk post conception
- For women ≥50 yr: daily folic acid supplementation for at least 2-3 mo before conception and throughout pregnancy and postpartum period
- High risk women (health risks including epilepsy, insulin dependent diabetes, BMI >35, family history of NTD, high risk ethnic group): at least 3 mo prior to conception until 10-12 wk post conception
- For women ≥50 yr: daily folic acid supplementation for at least 2-3 mo before conception and throughout pregnancy and postpartum period
- High risk women (health risks including epilepsy, insulin dependent diabetes, BMI >35, family history of NTD, high risk ethnic group): at least 3 mo prior to conception until 10-12 wk post conception
- For women ≥50 yr: daily folic acid supplementation for at least 2-3 mo before conception and throughout pregnancy and postpartum period
- High risk women (health risks including epilepsy, insulin dependent diabetes, BMI >35, family history of NTD, high risk ethnic group): at least 3 mo prior to conception until 10-12 wk post conception
- For women ≥50 yr: daily folic acid supplementation for at least 2-3 mo before conception and throughout pregnancy and postpartum period

---

**Prostate-Cancer Mortality at 11 Years of Follow-up**

**NEJM 2011;364:911-920**

**Study:** Updated “ERSPC” study – multicentre randomised trial of screening for prostate cancer using PSA.

**Patients:** 162,388 men, ages 55-69 from 8 different European countries.

**Intervention:** PSA-based screening.

**Main Outcome:** mortality from prostate cancer

**Results:** After median follow up of 11 yr, the RR of death from prostate cancer was 21%. The ARR was 1.07 deaths/1000 men. NNT=1055 – therefore to prevent one death from prostate cancer at 11 yr follow up, 1055 men would need to be screened.

---

**Appropriate Use of Screening and Diagnostic Tests to Foster High-Value, Cost-Conscious Care**

Aims: Improving value of health care, reduce cost, improve patient outcomes

- Suggested principles for providing high-value, cost-conscious care (see article Table 1 for specific examples):

  1. Diagnostic tests should not be performed if the results will not change management.
  2. If the pretest probability of disease is low, the likelihood of a false-positive test result is higher than the likelihood of a true-positive result. False-positive results often lead to further testing, which may be expensive and potentially harmful (e.g. anxiety for patient, inappropriate treatment).
  3. The true cost of a test includes not only the cost of the test itself but also the downstream costs incurred because the test was performed. These include the costs of subsequent testing, treatment, or follow-up.
Colorectal Cancer Screening Guidelines

- recommendations for average risk individuals (asymptomatic, no history of UC, polyps, or CRC):
  - Canadian Association of Gastroenterology (2010):
    - FOBT q1-2yr
    - flexible sigmoidoscopy q10yr
    - flexible sigmoidoscopy + FOBT q5yr
    - for UC patients, colonoscopy q1-2yr after 8 yr of disease

![Diagram of colorectal cancer screening guidelines]

Cervical Cancer Screening

- either conventional Papanicolaou (Pap) smear or liquid based cytology testing
- endocervical and exocervical cell sampling (aim is to sample the transitional zone)
- best identifies squamous cell abnormalities, less reliable for glandular abnormalities
  - false positives 5-10%, false negatives 10-40% (for single test)
  - false negative rate 50% for existing cervical cancer
- cervical cancer screening guidelines differ by Canadian jurisdiction (see The Society of Obstetricians and Gynaecologists of Canada updated guidelines)

- Canadian guidelines:
  - screen all women age ≥25 q3yr
  - women age ≥70: if 3 normal tests in a row and no abnormal tests in last 10 yr, can discontinue screening

- Ontario guidelines:
  - screen all women age ≥21 who are or have ever been sexually active (includes intercourse or digital/oral activity with partner of either gender)
  - if cytology is normal, can screen every 3 yr
  - women age ≥70: if 3 successive negative Pap tests in last 10 yr, can discontinue screening

- pregnant women and women who have sex with women should follow the routine cervical screening regimen
- women who have had a hysterectomy:
  - total: discontinue screening if hysterectomy was for benign disease and no history of cervical dysplasia or HPV infection
  - subtotal: continue screening according to guidelines
- exceptions to guidelines:
  - immunocompromised (transplant, steroids, diethylstilbestrol exposure, HIV)
  - adolescent women
  - previously unscreened patients

Figure 1. Approach to higher risk screening

AAPC = attenuated adenomatous polyposis; FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colorectal cancer; 1st degree relatives: parents, siblings, children; 2nd degree relatives: grandparents, aunts, uncles; 3rd degree relatives: great grandparents or cousins

Printed with permission from Can J Gastroenterol 2004;18:93-99
Health Promotion and Counselling

- Health promotion is the most effective preventative strategy.
- 40-70% of productive life lost annually is preventable.
- There are several effective ways to promote healthy behavioural change, such as discussions appropriate to a patient's present stage of change.

Motivational Strategies for Behavioural Change

<table>
<thead>
<tr>
<th>Patient's Stage of Change</th>
<th>Physician's Aim</th>
<th>Physician's Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-contemplation</td>
<td>Encourage patient to consider the possibility of change</td>
<td>Raise issue in a sensitive manner</td>
</tr>
<tr>
<td></td>
<td>Assess readiness for change</td>
<td>Offer (not impose) a neutral exchange of information to avoid resistance</td>
</tr>
<tr>
<td></td>
<td>Increase patient’s awareness of the problem and its risks</td>
<td></td>
</tr>
<tr>
<td>Contemplation</td>
<td>Understand patient’s ambivalence and encourage change</td>
<td>Offer opportunity to discuss pros and cons of change using reflective listening</td>
</tr>
<tr>
<td></td>
<td>Build confidence and gain commitment to change</td>
<td></td>
</tr>
<tr>
<td>Preparation</td>
<td>Explore options and choose course most appropriate to patient</td>
<td>Offer realistic options for change and opportunity to discuss inevitable difficulties</td>
</tr>
<tr>
<td></td>
<td>Identify high-risk situations and develop strategies to prevent relapse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continue to strengthen confidence and commitment</td>
<td></td>
</tr>
<tr>
<td>Action</td>
<td>Help patients design rewards for success</td>
<td>Offer positive reinforcement and explore ways of coping with obstacles</td>
</tr>
<tr>
<td></td>
<td>Develop strategies to prevent relapse</td>
<td>Encourage self-rewards to positively reinforce change</td>
</tr>
<tr>
<td></td>
<td>Support and reinforce convictions towards long-term change</td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>Help patient maintain motivation</td>
<td>Discuss progress and signs of impending relapse</td>
</tr>
<tr>
<td></td>
<td>Review identified high-risk situations and strategies for preventing relapse</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>Help patient view relapse as a learning experience</td>
<td>Offer a non-judgmental discussion about circumstances surrounding relapse and how to avoid relapse in the future</td>
</tr>
<tr>
<td></td>
<td>Provide support appropriate to present level of readiness post-relapse</td>
<td>Reassess patient’s readiness to change</td>
</tr>
</tbody>
</table>


Nutrition

General Population
- Canada's Food Guide is appropriate for individuals age ≥2.
- Counsel on variety, portion size, and plate layout (see Figure 3).

Table 3. Canada's Food Guide 2007 Recommendations for Adults

<table>
<thead>
<tr>
<th>Food Group</th>
<th>Servings/day</th>
<th>Choose More Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grain products</td>
<td>6-8</td>
<td>Whole grain and enriched grain products</td>
</tr>
<tr>
<td>Vegetables and fruit</td>
<td>7-10</td>
<td>Dark green vegetables, orange vegetables and fruit</td>
</tr>
<tr>
<td>Milk products</td>
<td>2-3</td>
<td>Lower-fat dairy products</td>
</tr>
<tr>
<td>Children age 2-8: 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Youth age 9-18: 3-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant/breastfeeding: 3-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meat and alternatives</td>
<td>2-3</td>
<td>Lean meat, poultry, fish, peas, beans, lentils</td>
</tr>
</tbody>
</table>

Figure 2. Decision making chart for cervical cancer screening (not applicable for adolescents)
TZ = transitional zone; ASCUS = abnormal squamous cells of unknown significance; LSIL = low grade squamous intraepithelial lesion; HSIL = high grade squamous intraepithelial lesion; ASC-H = abnormal squamous cells cannot rule out HSIL; AGUS = atypical glandular cells of unknown significance
Adapted from Ontario Cervical Screening Cytology Guidelines. May 2012

Figure 3. Plate layout
Vegetables 50%
Meat and Alternatives 25%
Grain Products 25%
## Cardiovascular Disease Prevention

### Table 4. Dietary Guidelines for Reducing Risk of Cardiovascular Disease in General Population

<table>
<thead>
<tr>
<th>Food Item</th>
<th>Recommendations</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fat</strong></td>
<td>Fat intake &lt;30% of total energy, saturated fat &lt;7% of total energy, trans fat &lt;1% of total energy, cholesterol &lt;300 mg/d</td>
<td>Lower LDL</td>
</tr>
<tr>
<td><strong>Omega-3 fatty acid rich foods</strong></td>
<td>≥2 servings/wk of fish (esp. oily fish like salmon)</td>
<td>Decreased sudden death, death from CAD Lower TG</td>
</tr>
<tr>
<td><strong>Salt</strong></td>
<td>≤2300 g/d</td>
<td>Lower BP</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td>≤2 drinks/d for men, &lt;1 drink/d for women</td>
<td>Decreased risk of hypertriglyceridemia, HTN</td>
</tr>
</tbody>
</table>


---

### Table 5. Introduction to Vitamins and Minerals

<table>
<thead>
<tr>
<th>Vitamin/Mineral</th>
<th>Dietary Source</th>
<th>Signs of Deficiency</th>
<th>Signs of Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Folate (vit B9)</strong></td>
<td>Green leafy vegetables, organ meats, dried yeast, dried beans, legumes, citrus, fortified grains</td>
<td>Macrocytic anemia, diarrhea, glossitis, lethargy, stomatitis</td>
<td>None known from foods, seizures</td>
</tr>
<tr>
<td><strong>Cyanocobalamin (vit B12)</strong></td>
<td>Organ meats, beef, pork, milk, cheese, fish</td>
<td>Megablastic anemia, glossitis, leukopenia, weakness, peripheral neuropathy (esp. foot drop)</td>
<td>None known from foods</td>
</tr>
<tr>
<td><strong>Ascorbic acid (vit C)</strong></td>
<td>Citrus fruits, tomatoes, potatoes, red berries, peppers</td>
<td>Scurvy, keratosis of hair follicles, impaired wound healing, anemia, depression, lethargy, bleeding</td>
<td>Osmotic diarrhea, N/V, oxalate kidney stones, interference with anticoagulation therapy</td>
</tr>
<tr>
<td><strong>Vitamin A</strong></td>
<td>Fish liver oils, egg yolk, dairy products, green leafy or orange/ yellow vegetables and fruit</td>
<td>Dermatitis, night blindness, keratomalacia, xerophthalmia</td>
<td>N/V, headache, dizziness, deep bone pain, peeling skin, gingivitis, alopecia, hepatotoxicity</td>
</tr>
<tr>
<td><strong>Vitamin D</strong></td>
<td>Fish, fish liver oils, fortified milk, egg yolk, sunlight</td>
<td>Osteoporosis, osteomalacia, muscle weakness, bone pain, hypophosphatemia, hypocalemia</td>
<td>Excess bone and soft tissue calcification, kidney stones, hypercalcemia, anorexia, renal failure</td>
</tr>
<tr>
<td><strong>Vitamin E</strong></td>
<td>Polyunsaturated vegetable oils, nuts, eggs, wheat germ, whole grains</td>
<td>Rare hemolysis, anemia, neuronal axonopathy, myopathy</td>
<td>Prolonged clotting time, impaired neutrophil function</td>
</tr>
<tr>
<td><strong>Vitamin K</strong></td>
<td>Green leafy vegetables, liver, vegetable oils, intestinal flora</td>
<td>Bleeding, purpura, bruising, prolonged clotting time</td>
<td>Jaundice</td>
</tr>
<tr>
<td><strong>Calcium</strong></td>
<td>Dairy products, dark green and leafy vegetables, fortified soy, fortified orange juice</td>
<td>Tetany, arrhythmias, congestive heart failure, altered nerve conduction, osteomalacia</td>
<td>Metastatic calcification, weakness, renal failure, psychosis</td>
</tr>
<tr>
<td><strong>Magnesium</strong></td>
<td>Soy, clams, wheat germ, almonds, dairy products, green leaves, nuts, cereal grains, seafood</td>
<td>Weakness, convulsions, neuromuscular irritability and dysfunction, failure to thrive</td>
<td>Hypotension, cardiac disturbances, respiratory failure</td>
</tr>
<tr>
<td><strong>Potassium</strong></td>
<td>Meat, milk, bananas, prunes, raisins, oranges, grapefruits, potatoes, legumes</td>
<td>Polyuria, impaired muscle contraction, ECG changes (prolonged QT interval, prominent U-waves), peritoneal distention, dyspnea, paralysis, cardiac disturbances</td>
<td>Mental confusion, hypotension, weakness, ECG changes (flattened P-waves, wide QRS, peaked T-waves), paralysis, cardiac disturbances</td>
</tr>
<tr>
<td><strong>Iron</strong></td>
<td>Meat, fish, poultry, organ meats, eggs, prunes, peas, beans, lentils, soy, raisins, fortified grain products</td>
<td>Glossitis, fatigue, tachycardia, microcytic hypochromic anemia, koilonychia, enteropathy</td>
<td>Nutritional hemosiderosis, organ damage</td>
</tr>
</tbody>
</table>

Adapted from Mosby’s Family Practice Sourcebook: An Evidence-Based Approach to Care, 4th edition, edited by Dr. Michael Evans (pp. 343-345). Copyright © 2006 Elsevier Canada, a division of Reed Elsevier Canada, Ltd. All rights reserved. Reprinted by permission of Elsevier Canada, 2009
Table 6. Macronutrient Distribution Ranges

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Protein as % of Daily Calories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Protein</td>
</tr>
<tr>
<td>1 to 3</td>
<td>5-20</td>
</tr>
<tr>
<td>4 to 18</td>
<td>10-30</td>
</tr>
<tr>
<td>19 and older</td>
<td>10-35</td>
</tr>
</tbody>
</table>


### Obesity

- body mass index (BMI) = weight (kg)/height (m)^2 = weight (lbs)/height (inch)^2 x 703; BMI is a poor predictor of obesity
- waist circumference (WC)
  - should be measured in all adults to assess obesity-related health risks
  - specific cutoff points exist for different ethnic backgrounds (as recommended by the 2006 Canadian Clinical Practice Guidelines on obesity)
  - measurement of waist-hip ratio has no advantage over waist circumference alone

Table 7. Classification of Weight by BMI, Waist Circumference, and Associated Disease Risks in Adults

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Underweight</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obesity</th>
<th>Men ≤102 cm (40 in)</th>
<th>Women ≤88 cm (35 in)</th>
<th>Men &gt;102 cm (40 in)</th>
<th>Women &gt;88 cm (35 in)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>18.5-24.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
<td>Increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>30.0-34.9</td>
<td>I</td>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35.0-39.9</td>
<td>II</td>
<td>Very High</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme</td>
<td>40.0 +</td>
<td>III</td>
<td>Extremely High</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Epidemiology

- 16% (4 million) of people ≥18 yr old are obese, 32% (8 million) are overweight in Canada, according to StatsCan (2007)
- obesity rate in people of aboriginal origin is 1.6 times higher than the national average
- proportion of children aged 6-11 who are overweight has more than doubled in the last 25 yr; percentage of overweight adolescents has tripled
- overweight and obesity rates in children are directly proportional to screen time (see Exercise, FM10)
- only 10-15% of population consume <30% fat daily
- obese persons generally consume more energy-dense food which tends to be highly processed, micronutrient poor, and high in fats, sugars, or starch

### Adverse Medical Consequences of Obesity

- Type 2 DM
- CAD
- Stroke
- HTN
- Gallbladder disease
- Non-alcoholic steatohepatitis
- Complications of pregnancy
- Dyslipidemia
- Osteoarthritis
- Sleep apnea
- Certain cancers
- CHF
- Low back pain
- Increased total mortality

### Losing Weight

- Aim for caloric intake 500-1000 kcal/d less than total daily energy expenditure (TDEE)
- Results in 1-2 lb (0.5-1 kg) weight loss per wk
- Achieved by combination of increased activity and/or decreased caloric intake

### Low BMI is associated with:

- Osteoporosis
- Eating disorders
- Under-nutrition
- Pregnancy complications

- Burning Fat
  - 3500 kcal of energy are used for every pound of human fat burned during activity.

- Low BMI is associated with:
  - Osteoporosis
  - Eating disorders
  - Undernutrition
  - Complications of pregnancy
Dyslipidemia

- see Endocrinology, E2
- defined as abnormal elevation of plasma cholesterol or triglyceride levels
- increased risk associated with obesity, DM, alcohol use

Assessment
- measure fasting serum TC, LDL-C, HDL-C, and TG
- screen with full fasting lipid profile q1-3yr in males over age 40, females over age 50 or who are menopausal, or any adults with additional CAD risk factors
- assess for presence of other CAD risk factors
- screen for secondary causes: hypothyroidism, chronic kidney disease, DM, nephrotic syndrome, liver disease
- risk category
  - estimate using the model for 10-yr CAD risk developed from the Framingham data (Framingham Risk Score – FRS)
  - FRS calculated based on the following factors: gender, age, HDL-C, total cholesterol, sBP, smoking, diabetes
    - to be completed for men age 40-75, and women age 50-75 q3-5yr
• cardiovascular age calculated as patient’s age ± the difference between his or her estimated remaining life expectancy
  used to increase adherence to therapy and reaffirm positive effect of following therapy
• primary target of therapy is LDL-C levels; the alternate primary targets are apolipoprotein B (apo B) and non-HDL-C (not used widely yet) (see Table 8)
• optional secondary targets once LDL-C/apo B is at target include TCHDL-C ratio, apo B:apo AI ratio, hs-CRP (used more for risk stratification of CAD), non-HDL-C and serum TG levels
• emerging risk factors (from Framingham group)
  ▪ lipoprotein a
  ▪ metabolic syndrome
  ▪ genetic risk
  ▪ hormone replacement therapy
  ▪ infectious agents

Table 8. Target Lipid Values for Primary Prevention of CAD (2012 Canadian Cholesterol Guidelines)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Initiate Treatment if:</th>
<th>Primary Targets</th>
<th>Alternate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Consider treatment in all patients</td>
<td>LDL-C &lt; 2 mmol/L or ≥50% decrease in LDL-C</td>
<td>apo B &lt; 0.80 g/L or ≤2.6mmol/L</td>
</tr>
<tr>
<td>Moderate (FRS 10-19%)</td>
<td>LDL-C ≥ 3.5 mmol/L</td>
<td>apo B ≥ 1.2 g/L or ≤50% decrease in LDL-C</td>
<td>non-HDL-C ≥ 4 mmol/L</td>
</tr>
<tr>
<td>Low (FRS ≤ 10%)</td>
<td>LDL-C ≥ 5.0 mmol/L</td>
<td>Familial hypercholesterolemia</td>
<td>≥50% decrease in LDL-C</td>
</tr>
</tbody>
</table>


Management
• intensity and type of treatment is guided by “risk category” assigned
  1. health behaviours (can decrease LDL-C by up to 10%)
     ▪ smoking cessation: probably the most important for preventing CAD
     ▪ dietary modification: reduce saturated fats, refined sugars, alcohol; increase fruits, vegetables and fibres
     ▪ physical activity: at least 150 min of moderate to vigorous intensity aerobic exercise per week
     ▪ employ consistent lifestyle modifications for at least 3 mo before considering drug therapy; high risk patient should start treatment immediately with concurrent health behaviour interventions
  2. pharmacologic therapy (can decrease LDL-C by up to 40%)
     ▪ for a comparison of dyslipidemia medications, see Endocrinology, E5
     ▪ statins (HMG-CoA reductase inhibitors)
       ▪ currently recommended as 1st line monotherapy following unsuccessful lifestyle modifications
       ▪ risks: myopathy and hepatotoxicity – must follow LFTs q6-12mo
     ▪ other agents: bile acid sequestrants, nicotinic acid, fibrates, psyllium, cholesterol absorption inhibitors (e.g. ezetimibe)
     ▪ after initiating drug therapy
       ▪ monitor ALT, AST, CK at baseline then 6 wk later for signs of transaminitis or myositis; tolerate rise in CK up to 10 times upper limit of normal (2-3 times upper limit of normal if symptomatic), or serum creatinine of ≤25%; repeat ALT, AST and CK with lipid bloodwork
       ▪ fasting lipids should be measured at 3 mo
       ▪ if adequate response is achieved, evaluate fasting lipids q6-12mo
     ▪ isolated hypertriglyceridemia (does not increase your cardiovascular risk!)
       ▪ normal HDL-C and TC, elevated TG
       ▪ mild ≥2.2 mmol/L (≥200 mg/dL); marked ≥5.6 mmol/L (≥500 mg/dL)
       ▪ principal therapy is lifestyle modification
       ▪ weight loss, exercise, avoidance of smoking and alcohol, effective blood glucose control in diabetics, increased omega-3 fatty acid intake
     ▪ drug therapy
       ▪ nicotinic acid
       ▪ fibrates

Clinical Definition of Metabolic Syndrome
• Central obesity:
  Men – waist circumference ≥94 cm
  Women – waist circumference ≥80 cm
• Plus any TWD of the following four factors:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG level</td>
<td>≥1.7 mmol/L (150 mg/dL)</td>
</tr>
<tr>
<td>LDL-C level</td>
<td>≤2.6mmol/L</td>
</tr>
<tr>
<td>Men</td>
<td>&lt; 1.0 mmol/L (40 mg/dL)</td>
</tr>
<tr>
<td>Women</td>
<td>&lt; 1.3 mmol/L (50 mg/dL)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/85 mmHg</td>
</tr>
<tr>
<td>Fasting glucose level</td>
<td>≤5.6 mmol/L (100 mg/dL)</td>
</tr>
</tbody>
</table>

To calculate Framingham Risk Score, go to http://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease-10-year-risk.php#

With use caution when prescribing combined statin and fibrate therapy as there has been concern regarding the safety of certain combinations.

Statin-Related Adverse Events: A Meta-analysis
Clin Ther 2008;29:26-35
Study: Meta-analysis of 18 RCTs (N=71,108) focused on adverse effects of statins.
Patients: Those taking statin monotherapy for primary or secondary prevention of CVD.
Intervention: Statin vs. placebo.
Main outcome: Adverse events (AE) including elevated liver enzymes or myopathy (myalgias, elevated CK, rhabdomyolysis).
Results: Statin therapy increased the risk of any AE by 39% (OR = 1.39, 95% CI, 1.09-1.80, P = 0.008) compared with placebo. Treating 1000 patients with a statin would cause 5 AE. Serious events (CK >10 times the upper limit of normal or rhabdomyolysis) are infrequent (NNH = 4300) and rhabdomyolysis, although serious, is rare (NNH = 4300).
Conclusion: Statin therapy was associated with greater odds of AEs compared with placebo but with substantial clinical benefit. Similar rates of serious AEs were observed between statin and placebo.

The Benefits of Statins in People without Established Cardiovascular Disease but with Cardiovascular Risk Factors: Meta-Analysis of Randomized Controlled Trials
Study: Meta-analysis of 10 RCTs.
Population: 70,388 participants (minimum of 80% without established cardiovascular (CV) disease).
Intervention: Statins, placebo, active control, usual care.
Main outcome: All-cause mortality. Other outcomes: major coronary events, major cerebrovascular events.
Results: Statin use significantly reduced the incidence of all-cause mortality (OR 0.88; 95% CI 0.81-0.96), major coronary events (OR 0.70; 95% CI 0.63-0.81) and major cerebrovascular events (OR 0.81; 95% CI 0.71-0.93).
Conclusion: Statins largely reduce the risk of major CV events and improve survival in patients with CV risk factors without established CV disease.

To ronto Notes 2014

Use with caution when prescribing combined statin and fibrate therapy as there has been concern regarding the safety of certain combinations.

The Benefits of Statins in People without Established Cardiovascular Disease but with Cardiovascular Risk Factors: Meta-Analysis of Randomized Controlled Trials
Study: Meta-analysis of 10 RCTs.
Population: 70,388 participants (minimum of 80% without established cardiovascular (CV) disease).
Intervention: Statins, placebo, active control, usual care.
Main outcome: All-cause mortality. Other outcomes: major coronary events, major cerebrovascular events.
Results: Statin use significantly reduced the incidence of all-cause mortality (OR 0.88; 95% CI 0.81-0.96), major coronary events (OR 0.70; 95% CI 0.63-0.81) and major cerebrovascular events (OR 0.81; 95% CI 0.71-0.93).
Conclusion: Statins largely reduce the risk of major CV events and improve survival in patients with CV risk factors without established CV disease.
Exercise

Epidemiology
- 25% of the population exercises regularly, 50% occasionally, 25% are sedentary
- screen time (time spent watching TV/movies, playing video games, or using the computer) has been increasing steadily in the last several yr, while time spent being physically active has been decreasing
- current recommendation from international pediatric societies is that children (>2 yr old) should limit their screen time to less than 2 h/d

Management
- assess current level of fitness, motivation and access to exercise
- encourage warm up and cool down periods to allow transition between rest and activity and to avoid injuries
- exercise with caution for patients with CAD, diabetes (risk of hypoglycemia), exercise-induced asthma
- patients with known CAD should have cardiac assessment prior to commencing exercise
- Canadian Physical Activity Guidelines for adults age 18-64 (ParticipACTION)
  - ≥150 min of moderate- to vigorous-intensity aerobic physical activity per wk, in bouts of ≥10 min
  - moderate-intensity: brisk walking, bike riding
  - vigorous-intensity: jogging, cross-country skiing
- muscle and bone strengthening activities using major muscle groups, ≥2 d/wk
- benefits of exercise
  - reduces risk of premature death, heart disease, stroke, HTN, certain types of cancer, type 2 diabetes, osteoporosis, overweight/obesity
  - leads to improved fitness, strength, and mental health (morale and self-esteem)

Smoking Cessation

Epidemiology
- smoking is the single most preventable cause of premature illness and death
- 70% of smokers see a physician each year
- 2008 Canadian data from the Canadian Tobacco Use Monitoring Survey (CTUMS) on population age 15 or older
  - 18% are current smokers (lowest since 1965)
  - highest prevalence in age group 20-24 (28%)
  - 15% of youth age 15-19 smoke (decreased from 25% in 2000): more males smoke than females; number of cigarettes consumed per day also decreasing

Management
- general approach
  - identify tobacco users; elicit smoking habits, previous quit attempts and results
  - every smoker should be offered treatment
  - make patient aware of withdrawal symptoms
    - low mood, insomnia, irritability, anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite
  - ≥4 counselling sessions >10 min each with 6-12 mo follow-up yields better results
  - 14% abstinent with counselling vs. 10% without counselling
  - approach depends on patient's stage of change (see Motivational Strategies for Behavioural Change, FM5)
  - willing to quit
    - follow the 5 As (see sidebar)
    - provision of social support, community resources
    - pregnant patients: advise to quit first without pharmacotherapy. Nicotine replacement therapy (NRT) should be made available to pregnant women who are unable to quit using non-pharmacologic methods; nicotine patches are strongly encouraged. Use bupropion (no evidence of fetal or reproductive harm) only if benefits > risks; consult Motherisk. Varenicline has not been studied in pregnancy and should not be used in pregnant women
  - pharmacologic therapy
    - 19.7% abstinent at 12 mo with NRT vs. 11.5% for placebo
    - no difference in achieving abstinence for different forms of NRT
    - reduces cravings and withdrawal symptoms without other harmful substances that are contained in cigarettes
    - use with caution: immediate post-MI, serious/worsening angina, serious arrhythmia

Physician Advice for Smoking Cessation
Cochrane DB Syst Rev 2008;2:CD000165
This systematic review of 17 trials compared brief advice by the physician versus no advice.
Reviewers' conclusions: Simple advice can increase cessation rates by 1-3%. More intensive advice and providing follow-up support may further increase the quit rates.

Assist Patient in Developing Quit Plan
STAR
- Set quit date
- Tell family and friends (for support)
- Anticipate challenges (e.g. withdrawal)
- Remove tobacco-related products (e.g. ashtrays/lighters)

The 5 As for Patients Willing to Quit
Ask if patient smokes
Advise patient to quit
Assess willingness to quit
Assist in quit attempt
Arrange follow-up
Table 9. Types of Nicotine Replacement Therapy

<table>
<thead>
<tr>
<th>Type</th>
<th>Dosage</th>
<th>Comment</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine Gum (OTC)</td>
<td>2 mg if &lt; 25 cig/d</td>
<td>Chew until “peppery” taste then “park” between gum and cheek to facilitate absorption Continue to chew-park intermittently for 30 min</td>
<td>Mouth soreness, Hiccups, Dysgeusia, Jaw ache, Most are transient</td>
</tr>
<tr>
<td></td>
<td>4 mg if &gt; 25 cig/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 piece q1-2h for 1-3 mo (max 24 pieces/d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine Patch (OTC)</td>
<td>Use for 8 wk</td>
<td>Start with lower dose if &lt; 10 cig/d Change patch q24h and alternate sides</td>
<td>Skin irritation, Insomnia, Palpitations, Anxiety</td>
</tr>
<tr>
<td></td>
<td>21 mg/d x 4 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 mg/d x 2 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 mg/d x 2 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine Inhaler (OTC)</td>
<td>6-16 cartridges/d for up to 12 wk</td>
<td>Nicotine inhaled through mouth, absorbed in mouth and throat not in lungs</td>
<td>Local irritation, Coughing</td>
</tr>
<tr>
<td>Nicotine Nasal Spray (Rx)</td>
<td>Newer form of NRT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 10. Bupropion as Treatment for Smoking Cessation

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Dosage</th>
<th>Prescribing*</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibits re-uptake of</td>
<td>1. 150 mg qAM x 3 d</td>
<td>1. Decide on a quit date 2. Continue to smoke for first 1-2 wk of treatment and then completely stop (therapeutic levels reached in 1 wk)</td>
<td>Seizure disorder, Eating disorder, MAOI use in past 14 d Simultaneous use of bupropion (Wellbutrin®) for depression</td>
</tr>
<tr>
<td>dopamine and/or</td>
<td>2. Then 150 mg bid x 7-12 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>norepinephrine</td>
<td>3. For maintenance consider 150 mg bid for up to 6 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Side effects:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>insomnia, dry mouth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine Gum (OTC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine Patch (OTC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine Inhaler (OTC)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 11. Varenicline as Treatment for Smoking Cessation

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Dosage</th>
<th>Prescribing*</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial nicotinic</td>
<td>1. 0.5 mg qAM x 3 d</td>
<td>1. Decide on a quit date 2. Continue to smoke for first wk of maintenance and then completely stop</td>
<td>Caution with pre-existing psychiatric condition</td>
</tr>
<tr>
<td>receptor agonist, and</td>
<td>2. Then 0.5 mg bid x 4 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>partial nicotinic</td>
<td>3. Continue 1 mg bid x 12 wk + additional 12 wk as maintenance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>receptor competitive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Side effects: nausea,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vomiting, constipation,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>headache, dream</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disorder, insomnia,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>increased risk of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>psychosis, depression,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>suicidal ideation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• unwilling to quit
  • motivational intervention (5 Rs) (see sidebar):
    1. Relevance to patient
      • relevant to patient’s disease status or risk, family or social situation (e.g. having children in the home), health concerns, age, gender
    2. Risks of smoking
      • short-term: SOB, asthma exacerbation, impotence, infertility, pregnancy complications, heartburn, URTI
      • long-term: MI, stroke, COPD, lung CA, other cancers
    3. Environmental: higher risk in spouse/children for lung CA, SIDS, asthma, respiratory infections
  3. Rewards: benefits
    • improved health, save money, food tastes better, good example to children
  4. Roadblocks: obstacles
    • fear of withdrawal, weight gain, failure, lack of support
  5. Repetition
    • reassure unsuccessful patients that most people try many times before successfully quitting (average number of attempts before success is 7)
• recent quitter
  ▪ highest relapse rate within 3 mo of quitting
  ▪ minimal practice: congratulate on success, encourage ongoing abstinence, review benefits and problems
  ▪ prescriptive interventions: address problem of weight gain, negative mood, withdrawal, lack of support

## Alcohol

• see Psychiatry, PS22

### Definition

• diagnostic categories occur along a continuum (see Figure 5)

### Epidemiology

• 10-15% of patients in family practice are problem drinkers
• 20-50% of hospital admissions, 10% of premature deaths, 30% of suicides, and 50% of fatal traffic accidents in Canada are alcohol-related
• more likely to miss diagnosis in women, elderly, patients with high socioeconomic status

### Assessment

• screen for alcohol dependence with CAGE questionnaire (see sidebar)
  ▪ if CAGE positive, explore with further questions for alcohol abuse/dependence
• assess drinking profile
  ▪ setting, time, place, occasion, with whom
  ▪ impact on: family, work, social
  ▪ quantity-frequency history
    ▪ how many drinks per day?
    ▪ how many days per week?
    ▪ maximum number of drinks on any one day in the past month?
• if identified positive for alcohol problem
  ▪ screen for other drug use
  ▪ identify medical/psychiatric complications
  ▪ ask about drinking and driving
  ▪ ask about past recovery attempts and current readiness for change

### Investigations

• GGT and MCV for baseline and follow-up monitoring
• AST, ALT (usually AST:ALT approaches 2:1 in an alcoholic)
• CBC (anemia, thrombocytopenia), INR (decreased clotting factor production by liver)

### Management

• intervention should be consistent with patient's motivation for change
• regular follow-up is crucial
• 10% of patients in alcohol withdrawal will have seizures or delirium tremens
• Alcoholics Anonymous/12-steps program
• outpatient/day programs for those with chronic, resistant problems
• family treatment (Al-Anon, Alateen, screen for spouse/child abuse)
• in-patient program if
  ▪ dangerous or highly unstable home environment
  ▪ severe medical/psychiatric problem
  ▪ addiction to drug that may require in-patient detoxification
  ▪ refractory to other treatment programs
• pharmacologic
  ▪ diazepam for withdrawal
  ▪ disulfiram (Antabuse™): impairs metabolism of alcohol by blocking conversion of acetaldehyde to acetic acid, leading to flushing, headache, nausea/vomiting, hypotension if alcohol is ingested (available in U.S., but no longer available in Canada)
  ▪ naltrexone: competitive opioid antagonist that reduces cravings and pleasurable effects of drinking
  ▪ may trigger withdrawal in opioid-dependent patients

### Prognosis

• relapse is common and should not be viewed as failure
• monitor regularly for signs of relapse
• 25-30% of abusers exhibit spontaneous improvement over 1 yr
• 60-70% of individuals with jobs and families have an improved quality of life 1 yr post-treatment

### Abstinence

#### Low Risk Drinking

<2 drinks/d
<9 drinks/wk for women
<14 drinks/wk for men

#### At Risk Drinking

Consumption above low-risk level but no alcohol-related physical or social problems

### Alcohol Abuse

Physical or social problems
Continued use despite consequences
Inability to fulfill life roles
Legal problems
No evidence of dependence

### Alcohol Dependence

#### Figure 5. Continuum of alcohol use

### Standard Drink Equivalents

- One standard drink = 14 g of pure alcohol
- Beer (5% alcohol) = 12 oz
- Wine (12-17% alcohol) = 5 oz
- Fortified wine = 3 oz
- Hard liquor (80 proof) = 1.5 oz

### CAGE Questionnaire

- C Have you ever felt the need to CUT down on your drinking?
- A Have you ever felt ANNOYED at criticism of your drinking?
- G Have you ever felt GUILTY about your drinking?
- E Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (EYE OPENER)

2 or more for men or ≥1 for women suggests possibility of problem drinking (sensitivity 85%, specificity 89%)

### Alcohol Metabolized per Hour

- Alcohol metabolism is constant (zero-order kinetics) regardless of blood alcohol level (BAL)
- Average metabolism ranges between 13.25 mg/dL blood/h or 100-200 mg/kg/h
- Equivalent to metabolizing 0.5-1 standard drink per hour or BAL decrease of 0.01% per hour
- Metabolism more rapid in chronic alcoholics

### Some Adverse Medical Consequences of Problem Drinking

- GI: gastritis, dyspepsia, pancreatitis, liver disease, bleeds, diarrhea, oral/esophageal cancer
- Cardiac: hypertension, alcoholic cardiomyopathy
- Neurologic: Wernicke-Korsakoff syndrome, peripheral neuropathy
- Hematologic: anemia, coagulopathies
- Other: trauma, insomnia, family violence, anxiety/depression, social/family dysfunction, sexual dysfunction, fetal damage
Common Presenting Problems

Abdominal Pain

- see Gastroenterology, G4 and General Surgery, GS4

Epidemiology
- 20% of individuals have experienced abdominal pain within the last 6-12 mo
- 90% resolve in 2-3 wk
- only 10% are referred to specialists, of those <10% admitted to hospital

Etiology
- most common diagnosis is “nonspecific abdominal pain,” which has no identifiable cause and is usually self-limited
- GI disorders (e.g. PUD, pancreatitis, IBD, appendicitis, gastroenteritis, IBS, diverticular disease, biliary tract disease)
- urinary tract disorders (e.g. UTI, renal calculi)
- gynecological disorders (e.g. PID, ectopic pregnancy, endometriosis)
- cardiovascular disorders (e.g. CAD, AAA, ischemic bowel)
- other: toxic ingestion, foreign body, psychogenic

Pathophysiology
- type of pain
  - somatic pain: sharp, localized pain
  - visceral pain: dull, generalized pain
- location of pain
  - epigastric (foregut): distal esophagus, stomach, proximal duodenum, biliary tree, pancreas, liver
  - periumbilical (midgut): distal duodenum to proximal 2/3 of transverse colon
  - hypogastric (hindgut): distal 1/3 of transverse colon to rectosigmoid region

Investigations
- guided by findings on history and physical
- possible bloodwork: CBC, electrolytes, BUN, Cr, amylase, lipase, AST, ALT, ALP, bilirubin, glucose, INR/PTT, tox screen, β-hCG
- imaging
  - CXR (for free air under the diaphragm) in setting of perforation in surgical abdomen
  - abdominal x-ray, KUB (consider: gas pattern, free air, kidney stones, constipation)
  - ultrasound (gallbladder disease, gynecological problems, liver disease, pancreatitis, diverticular disease, appendicitis)
  - CT scan (AAA, appendicitis)
- other tests
  - urinalysis
  - endoscopy (for peptic ulcers, gastritis, tumours, etc.)
  - H. pylori testing (urea breath test, serology, biopsy)

Allergic Rhinitis

- see Otolaryngology, OT23

Definition
- inflammation of the nasal mucosa that is triggered by an allergic reaction
- classification:
  - seasonal
    - symptoms during a specific time of the year
    - common allergens: trees, grass and weed pollens, airborne moulds
  - perennial
    - symptoms throughout the year with variation in severity
    - common allergens: dust mites, animal dander, moulds

Etiology
- increased IgE levels to certain allergens → excessive degranulation of mast cells → release of inflammatory mediators (e.g. histamine) and cytokines → local inflammatory reaction
Epidemiology
- affects approximately 40% of children and 20-30% of adults
- prevalence has increased in developed countries, particularly in the past two decades
- associated with asthma, sinusitis, and otitis media

Assessment
- identify allergens
- take an environmental/occupational history
- ask about related conditions (e.g. atopic dermatitis, asthma, sinusitis, and family history)

Management
- conservative
  - minimize exposure to allergens
  - most important aspect of management, often sufficient (may take months)
  - maintain hygiene, saline nasal rinses
- pharmacologic agents
  - oral antihistamines – first line therapy for mild symptoms
    - e.g. cetirizine (Reactine®), fexofenadine (Allegra®), loratadine (Claritin®)
  - intranasal corticosteroids for moderate/severe or persistent symptoms (>1 mo of consistent use to see results)
  - intranasal decongestants (use must be limited to <5 d to avoid rhinitis medicamentosa)
- allergy skin testing
  - for patients with chronic rhinitis
  - symptoms not controlled by allergen avoidance, pharmacological therapy
  - may identify allergens to include in immunotherapy treatment
- immunotherapy (allergy shots)
  - reserved for severe cases unresponsive to pharmacologic agents
  - consists of periodic (usually weekly) subcutaneous injections of custom prepared solutions of one or more antigens to which the patient is allergic

Amenorrhea
- see Gynecology, G12

Definition and Etiology
- classified as primary or secondary
  - primary
    - absence of menstruation by age 14 in women without secondary sexual characteristics or absence of menstruation by age 16 in women with secondary sexual characteristics
    - causes: Turner's syndrome, constitutional delay of growth and puberty, Kallmann syndrome, androgen insensitivity syndrome, Müllerian agenesis, imperforate hymen, transverse vaginal septum, + causes of secondary amenorrhea
  - secondary
    - absence of menstruation for 3 mo in women with previously normal menstruation, or absence of menstruation for 9 mo in women with previous oligomenorrhea
    - causes: pregnancy, hypothyroidism, hyperprolactinemia, medications, premature ovarian failure, anorexia or bulimia nervosa, CNS tumour, chronic illness, PCOS

Assessment
- history
  - menarche and menstrual history, sexual activity, exercise, weight loss, current or previous chronic illness, prescription/illicit drug use, previous CNS chemotherapy or radiation, previous pelvic radiation, psychosocial stressors
  - family history: of genetic defects, infertility, menarche and menstrual history, pubertal history
- physical
  - growth chart, BMI, Tanner staging, dysmorphic features (e.g. webbed neck, short stature), signs of Cushing's disease, thyroid exam, hirsutism or acne, pubic hair pattern, imperforate hymen, absent uterus

Investigations
- based on clinical picture
- consider β-hCG, prolactin, TSH, progesterone challenge test, FSH and LH levels, pelvic ultrasound, MRI brain, karyotype
Anxiety

- see Psychiatry, PS13

Epidemiology
- 25-30% of patients in primary care settings have psychiatric disorders
- many are undiagnosed or untreated; hence the need for good screening
- high rate of coexistence of anxiety disorders and depression

Screening
- screening questions:
  - Do you tend to be an anxious or nervous person?
  - Have you felt unusually worried about things recently?
  - Has this worrying affected your life? How?
- if positive response, follow up with symptom-specific questions (see Figure 6)

Assessment
- associated symptoms
- risk factors
  - family history of anxiety or depression, past history of anxiety, stressful life event, social isolation, female gender, co-morbid psychiatric diagnosis (e.g. depression)
- assess substance abuse, co-morbid depression, suicidal ideation/self-harm
- to differentiate anxiety disorders, consider symptoms and their duration (see Figure 6)

Differential Diagnosis of Anxiety Disorders (see Figure 6)
- Panic disorder
- GAD
- PTSD
- OCD
- Specific phobia
- Separation anxiety (children)
- Other: GMC, mood disorder, psychotic disorder

Management
- patient education: emphasize prevalence, good recovery rate of anxiety conditions
- lifestyle advice: decrease caffeine and alcohol intake, exercise, relaxation techniques, mindfulness strategies
- self-help materials, community resources (e.g. support groups)
- cognitive behavioural therapy: cognitive interventions, exposure therapy, etc.
- for pharmacotherapy, see Psychiatry, PS48

Symptoms of Anxiety
Are the symptoms predominantly...

In the form of panic with physical (autonomic) symptoms?
- Do the panic attacks come...
  - With a specific situation
  - “Out of the blue”
- Is patient avoiding situation?
  - Yes
  - No
- Patient afraid of another attack and its implications?
  - Yes
  - No

Secondary to a specific experienced trauma?
- Excessive worry and apprehension about common concerns?
- Are the thoughts intrusive, inappropriate and distressing?
- Are they accompanied by a repetitive behaviour meant to neutralize the anxiety?
- Excessive worry and apprehension about social situations?

ACUTE STRESS REACTION
- PTSD

ADJUSTMENT DISORDER
- GAD

PANIC DISORDER

SPECIFIC PHOobia

SOCIAL PHOobia

PANIC DISORDER WITH AGORAPHOBia

Figure 6. Differentiating anxiety disorders

Symptoms of GAD
AND I C REST
Anxious, nervous, or worried
- No control over the worry
- Duration >6 mo
- Irritability
- Concentration impairment
- Restlessness
- Energy decreased
- Sleep impairment
- Tension in muscles

Can Fam Physician 2005;51:1340-1342
Asthma/COPD

- see Respirology, R6

Definition
- asthma
  - chronic but reversible airway inflammation characterized by periodic attacks of wheezing, shortness of breath, chest tightness, and coughing
  - airways hyper-responsive to triggers/antigens leading to acute obstructive symptoms by bronchoconstriction, mucous plugs and increased inflammation
  - cannot be diagnosed at first presentation; called reactive airway disease until recurrent presentations
  - pulmonary function tests (PFTs) can be done from age 6 or when child able to follow instructions to do PFTs
  - peak flow meters are useful in the office and at home for monitoring
- chronic obstructive pulmonary disease (COPD)
  - a group of chronic, progressive, expiratory lung diseases characterized by limited airflow with variable degrees of air sac enlargement and lung tissue destruction
  - emphysema and chronic bronchitis are the most common forms of COPD

Table 12. Differentiating COPD from Asthma

<table>
<thead>
<tr>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of Onset</strong></td>
<td>Usually in 6th decade</td>
</tr>
<tr>
<td><strong>Role of Smoking</strong></td>
<td>&gt;10 pack yr</td>
</tr>
<tr>
<td><strong>Reversibility of Airflow Obstruction</strong></td>
<td>Airflow obstruction is chronic and persistent</td>
</tr>
<tr>
<td><strong>Evolution</strong></td>
<td>Slow, progressive worsening (with periodic exacerbations)</td>
</tr>
<tr>
<td><strong>History of Allergy</strong></td>
<td>Infrequent</td>
</tr>
<tr>
<td><strong>Precipitators</strong></td>
<td>Environmental irritants (air pollution), cigarette smoking, α-1 antitrypsin deficiency, viral infection, occupational exposure (firefighters, dusty jobs)</td>
</tr>
<tr>
<td><strong>Symptoms/Signs</strong></td>
<td>Chronic cough, sputum and/or dyspnea</td>
</tr>
<tr>
<td><strong>Diffusion Capacity</strong></td>
<td>Decreased (more so in pure emphysema)</td>
</tr>
<tr>
<td><strong>Hypoxemia</strong></td>
<td>Chronic in advanced stages</td>
</tr>
<tr>
<td><strong>Spirometry</strong></td>
<td>May have improvement with bronchodilators but not universally seen</td>
</tr>
<tr>
<td><strong>Chest X-ray</strong></td>
<td>Often normal</td>
</tr>
</tbody>
</table>
| **Management** | **Mild**
  - Step 1: SABA pm (salbutamol) or LAAC (i.e. tiotropium)
  - Step 2: SABA pm + LAAC (i.e. salbutamol) or LABA (e.g. salmeterol)
  - **Moderate**
  - Step 3: SABA pm + LAAC + low-dose combined ICS/LABA; consider inhaled vs. oral steroids
  - **Severe**
  - Step 4: ± theophylline | Ongoing patient education, and environmental control SABA taken pm as rescue medication + maintenance meds |
  | **Maintenance medications:** | **Step 1:** Low-dose ICS
  | | **Step 2:** Medium/high-dose ICS or low-dose ICS plus either LABA, LT modifier, or long-acting theophylline
  | | **Step 3:** Medium/high-dose ICS plus either LABA, LT modifier, or long-acting theophylline
  | | **Step 4:** As above plus immunotherapy ± oral glucocorticosteroids + pneumococcal vaccination, annual influenza immunization |

β₂-agonists
- Salbutamol – Ventolin® light blue/navy
- Salmeterol – Seretide® teal/light teal
- Terbutaline – Bricanyl® blue/white

ICS
- Fluticasone – Flonvert® orange/peach
- Budesonide – Pulmicort® white/brown

Combined long-acting β₂-agonist + ICS
- Fluticasone/Salmeterol – Advair® purple discus
- Budesonide/Formoterol – Symbicort® red/white
- Ipratropium/Albuterol – Combivent® clear/orange

Anticholinergics
- Ipratropium – Atrovent® clear/green
- Tiotropium – Spiriva® white/turquoise

More about Inhalers:
- Aerosols (puffers=MDIs, MDI + spacer)
- MDIs should be used with spacers to:
  - Reduce side effects
  - Improve amount inhaled
  - Increase efficiency of use
- Dry powder inhaler (discus, turbuhaler and diskhaler), they require deep and fast breathing (may not be ideal for children)
- Nebulizers can be used to convert liquid medications into a fine mist: recommended for use if contraindications to MDIs

Differential Diagnosis of Wheezing
- Allergies, anaphylaxis
- Asthma, reactive airway disease
- Gastroesophageal reflux disease
- Infections (bronchitis, pneumonia)
- Obstructive Sleep Apnea
- COPD
- Less common: congestive heart disease, foreign body, malignancy, cystic fibrosis, vocal cord dysfunction

When prescribing salbutamol, watch out for signs of hypokalemia: lethargy, irritability, paresthesias, myalgias, weakness, palpitations, nausea, vomiting, polyuria.
Benign Prostatic Hyperplasia (BPH)

- see Urology, U8

Definition
- hyperplasia of the stroma and epithelium in the periurethral transition zone

History and Physical
- include current/past health, surgeries, trauma, current and OTC meds
- specific urinary symptoms (see Table 13)
- physical exam must include DRE for size, symmetry, nodularity, and texture of prostate (prostate is symmetrically enlarged, smooth and rubbery in BPH)

Investigations
- urinalysis to exclude UTI and for microscopic hematuria (common sign)
- serum PSA: protein produced by prostatic tissue, see Urology, U25
  - values:
    - <4.0 ng/mL: normal, but must take into account patient’s age and velocity of PSA increase
    - 4-10 ng/mL: consider measuring free/total PSA
    - >10 ng/mL: high likelihood of prostate pathology
- PSA testing is inappropriate in men with a life expectancy less than 10 yr or patients with prostatitis, UTI
- increased PSA in a younger man is more often due to cancer than other causes
- abnormal DRE or PSA should trigger further assessment
- discuss test with men at increased risk of prostate cancer (FHx, African ancestry) or who are concerned about development of prostate cancer
- decision to test PSA in an asymptomatic man should involve discussion about the risks and possible benefits
- other tests:
  - Cr, BUN
  - post-void residual volume by ultrasound
  - urodynamic studies, renal ultrasound
  - patient voiding diary
- tests NOT recommended as part of routine initial evaluation include:
  - cystoscopy
  - cytology
  - prostate ultrasound or biopsy
  - IVP

Table 13. Symptoms and Complications of BPH

<table>
<thead>
<tr>
<th>Obstructive Symptoms</th>
<th>Irritative Symptoms</th>
<th>Late Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hesitancy (difficulty starting urine flow)</td>
<td>Urgency</td>
<td>Hydronephrosis</td>
</tr>
<tr>
<td>Diminution in size and force of urinary stream</td>
<td>Frequency</td>
<td>Loss of renal concentrating ability</td>
</tr>
<tr>
<td>Stream interruption (double voiding)</td>
<td>Nocturia</td>
<td>Systemic acidosis</td>
</tr>
<tr>
<td>Urinary retention (bladder does not feel completely empty)</td>
<td>Urge incontinence</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Post-void dribbling</td>
<td>Dysuria</td>
<td></td>
</tr>
<tr>
<td>Overflow incontinence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Management
- referral to urologist if moderate/severe symptoms
- conservative: for patients with mild symptoms or moderate/severe symptoms considered by the patient to be non-bothersome
  - fluid restriction (avoid alcohol and caffeine)
  - avoidance/monitoring of certain medications (e.g. antihistamines, diuretics, antidepressants, decongestants)
  - pelvic floor/Kegel exercises
  - bladder retraining (scheduled voiding)
- pharmacological: for moderate/severe symptoms
  - α-receptor antagonists [e.g. terazosin (Hytrin®), doxazosin (Cardura®), tamsulosin (Flomax®), alfuzosin (Xatral®)]
    - relaxation of smooth muscle around the prostate and bladder neck
  - 5α-reductase inhibitor [e.g. finasteride (Proscar®)]
    - only for patients with demonstrated prostatic enlargement due to BPH
    - inhibits enzyme responsible for conversion of testosterone into dihydrotestosterone (DHT) thus reducing growth of prostate

Differential Diagnosis
- Prostate cancer
- Urethral obstruction
- Bladder neck obstruction
- Neurogenic bladder
- Cystitis
- Prostatitis

Prostate-Cancer Mortality at 11 Years of Follow-up
- NEJM 2012;366:981-90
- Study: Updated “ERSPC” study – multicentre randomized trial of screening for prostate cancer using PSA.
- Patients: 162,388 men, age 55-69 from 8 different European countries.
- Intervention: PSA-based screening.
- Main Outcome: Mortality from prostate cancer.
- Results: In screening group, ARR = 21%, ARR = 1.07 deaths/1000 men, NNT = 1055 – therefore to prevent one death from prostate cancer, 1055 men would need to be screened.
phytotherapy (e.g. saw palmetto berry extract, *Pygeum africanum*)
- more studies required before this can be recommended as standard therapy
- considered safe
- surgical:
  - TURP (transurethral resection of the prostate), TUIP (transurethral incision of the prostate, for prostates <30 g)
  - absolute indications: failed medical therapy, intractable urinary retention, benign prostatic obstruction leading to renal insufficiency
  - complications: impotence, incontinence, ejaculatory difficulties (retrograde ejaculation), decreased libido

### Bronchitis (Acute)

**Definition**
- acute infection of the tracheobronchial tree causing inflammation leading to bronchial edema and mucus formation

**Epidemiology**
- 5th most common diagnosis in family medicine, most common is URTI

**Etiology**
- 80% viral: rhinovirus, coronavirus, adenovirus, influenza, parainfluenza, respiratory syncytial virus (RSV)
- 20% bacterial: *M. pneumoniae, C. pneumoniae, S. pneumoniae*

**Investigations**
- acute bronchitis is typically a clinical diagnosis
- sputum culture/Gram stain is not very informative
- CXR if suspect pneumonia (cough >3 wk, abnormal vital signs, localized chest findings) or CHF
- pulmonary function tests with methacholine challenge if suspect asthma

**Management**
- primary prevention: frequent hand washing, smoking cessation, avoid irritant exposure
- symptomatic relief: rest, fluids (3-4 L/d when febrile), humidity, analgesics and antitussives as required
- bronchodilators may offer improvement of symptoms (e.g. salbutamol)
- current literature does not support routine antibiotic treatment for the management of acute bronchitis because it is most likely to be caused by a viral infection
  - antibiotics may be useful if elderly, comorbidities, suspected pneumonia, or if the patient is toxic (refer to *Antimicrobial Quick Reference, FM53*)
  - antibiotics in children show no benefit

**Chest Pain**

- see *Cardiology and Cardiovascular Surgery, C4* and *Emergency Medicine, ER21*

**Differential Diagnosis**

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Pulmonary</th>
<th>GI</th>
<th>MSK/Neuro</th>
<th>Psychologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina*</td>
<td>Hemorrhax*</td>
<td>Cholecystitis</td>
<td>Arthritis</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Aortic dissection*</td>
<td>Lung CA</td>
<td>Esophageal spasm</td>
<td>Costochondritis</td>
<td>Depression</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>PE</td>
<td>GERD</td>
<td>Herpes zoster</td>
<td>Pan</td>
</tr>
<tr>
<td>MI</td>
<td>Pneumonia</td>
<td>Hepatitis</td>
<td>Intercostal strain</td>
<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Pneumothorax*</td>
<td>Perforated viscus*</td>
<td>Rib fractures</td>
<td></td>
</tr>
<tr>
<td>Pulmonary HTN</td>
<td>PUD</td>
<td>PUD</td>
<td>Trauma</td>
<td></td>
</tr>
</tbody>
</table>

*Emergent

**Investigations**
- ECG, CXR, and others if indicated (cardiac enzymes, D-dimers, liver function tests (LFTs), etc.)
- refer to ER if suspect serious etiology (e.g. aortic dissection, MI)

**Management of Common Causes of Chest Pain**
- angina/ischemic heart disease
  - nitroglycerin (NTG): wait 5 min between sprays and if no effect after 3 sprays, send to ER
- myocardial infarction
  - ASA (162-325 mg, chewed), clopidogrel (Plavix*), enoxaparin, morphine, oxygen, NTG
Reperfusion therapy with tissue plasminogen activator (tPA) or streptokinase (SK) if within 6 h (Note: can only use SK once in lifetime) or percutaneous intervention (cath lab)

- start β-blocker (e.g. metoprolol starting dose 12.5 mg PO OD and gradually increase dose, titrate to the HR rate goal of 60 bpm)

- endocarditis: antibiotic choice is based on whether patient has a native or prosthetic heart valve as well as culture and sensitivity results

- GERD: antacids, 

- costochondritis: NSAIDs

**Stable Ischemic Heart Disease**

- Life-style modification (address diet, alcohol, smoking, exercise)
- Manage concomitant disorders (e.g. hypertension, diabetes, hyperthyroidism, anemia)
- Anti-platelet therapy for all patients (ASA 81 mg PO OD unless contraindicated or failed)
- β-blocker for all post-MI patients or those with heart failure
- ACE inhibitor for patients age >55 or with any coincident indication
- Statin therapy for patients with coronary disease

- If symptoms persist
  - Start a β-blocker (if not already using it)/switch to β-1 selective blocker
  - Sublingual nitrate for prophylaxis and acute symptom relief

- If symptoms persist
  - Add long-acting (oral or transdermal) nitrate ± calcium channel blocker

- If symptoms persist
  - Assess suitability for coronary artery revascularization

**Common Cold (Acute Rhinitis)**

**Definition**
- viral URTI with inflammation

**Epidemiology**
- most common diagnosis in family medicine, peaks in winter months
- incidence: adults = 2-4/yr, children = 6-10/yr
- organisms
  - mainly rhinoviruses (30-35% of all colds)
  - others: coronavirus, adenovirus, RSV, influenza, parainfluenza, coxsackie virus
- incubation: 1-5 d
- transmission: person-person contact via secretions on skin/objects and by aerosol droplets

**Risk Factors**
- psychological stress, excessive fatigue, allergic nasopharyngeal disorders, smoking, sick contacts

**Clinical Features**
- symptoms
  - local: nasal congestion, clear to mucopurulent secretions, sneezing, sore throat, conjunctivitis, cough
  - general: malaise, headache, myalgias, mild fever
- signs
  - boggy and erythematous nasal/oropharyngeal mucosa, enlarged lymph nodes
  - normal chest exam
- complications
  - secondary bacterial infection: otitis media, sinusitis, bronchitis, pneumonia
  - asthma/COPD exacerbation

**Differential Diagnosis**
- allergic rhinitis, pharyngitis, influenza, laryngitis, croup, sinusitis, bacterial infections

**High-Risk Symptoms and Signs of Chest Pain include:**
- Severe pain
- Pain for <20 min
- New onset pain at rest
- Severe SOB
- Loss of consciousness
- Hypotension
- Tachycardia
- Bradycardia
- Cyanosis

**Common Cold Etiology**

<table>
<thead>
<tr>
<th>PRIMA</th>
<th>Paramyxoviruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinoviruses</td>
<td>Influenza viruses</td>
</tr>
<tr>
<td>Myxoviruses</td>
<td>Adenoviruses</td>
</tr>
</tbody>
</table>

**Influenza vs. Colds: A Guide to Symptoms**

<table>
<thead>
<tr>
<th>Features</th>
<th>Flu</th>
<th>Cold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of illness</td>
<td>Sudden</td>
<td>Slow</td>
</tr>
<tr>
<td>Fever</td>
<td>High fever</td>
<td>None</td>
</tr>
<tr>
<td>Exhaustion level</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Cough</td>
<td>Dry, severe or hacking</td>
<td></td>
</tr>
<tr>
<td>Throat</td>
<td>Fine</td>
<td>Sore</td>
</tr>
<tr>
<td>Nose</td>
<td>Dry and clear</td>
<td>Runny</td>
</tr>
<tr>
<td>Head</td>
<td>Achy</td>
<td>Headache-free</td>
</tr>
<tr>
<td>Appetite</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Muscles</td>
<td>Achy</td>
<td>Fine</td>
</tr>
<tr>
<td>Chills</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**Zinc for the Treatment of the Common Cold: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**

- Study: Meta-analysis of 17 randomized control trials with a total of 2127 participants.
- Patients: All populations.
- Intervention: Oral zinc vs. placebo or no treatment.
- Results: Patients receiving zinc had a shorter duration of cold symptoms compared with those given placebo (mean difference -1.85 d). Zinc shortened the duration of symptoms in adults but no significant difference was seen in children. Adverse event such as nausea were more common in the zinc group (RR 1.64).
Management

- patient education
  - symptoms peak at 1-3 d and usually subside within 1 wk
  - cough may persist for days to weeks after other symptoms disappear
  - no antibiotics indicated because of viral etiology
  - secondary bacterial infection can present within 3-10 d after onset of cold symptoms
- prevention
  - frequent hand washing, avoidance of hand to mucus membrane contact, use of surface disinfectant
- symptomatic relief
  - rest, hydration, gargling warm salt water, steam, nasal irrigation (spray/pot)
  - analgesics and antipyretics: acetaminophen, ASA (not in children because risk of Reye's syndrome)
  - cough suppression: dextromethorphan or codeine if necessary (children under 6 yr of age should not use any cough/cold medications)
  - decongestants, antihistamines
  - zinc lozenge use may help to reduced the duration of cold symptoms
- patients with reactive airway disease will require increased use of bronchodilators and inhaled steroids

Contraception

- see Gynecology, GY19

<table>
<thead>
<tr>
<th>Method of Contraception</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined OCP</td>
<td>99.9% effective with perfect use, 97-99% with typical use, cycle control, ↓ dysmenorrhea, ↓ menstrual flow, ↓ ovarian cancer, ↓ endometrial cancer, ↓ risk of fibroids, ↓ acne, ↓ hirsutism</td>
<td>Irregular bleeding, systemic hormonal side effects (breast tenderness, nausea, mood changes), no STI protection, slightly increased risk of venous thromboembolism (VTE), MI, stroke, decreased quantity of breast milk postpartum</td>
</tr>
<tr>
<td>Progesterin Only Pill</td>
<td>At least 95% effective with perfect use, no increased risk of VTE, MI or stroke, suitable for postpartum</td>
<td>Hormonal side effects (see Combined OCP)</td>
</tr>
<tr>
<td>Transdermal Patch</td>
<td>Same as OCP, easy to use, changed weekly, 99% effective with correct use</td>
<td>Same as OCP skin irritation</td>
</tr>
<tr>
<td>NuvaRing®</td>
<td>Same as OCP, easy to use (in for 3 wk, out for 1 wk), less systemic hormonal side effects, 99% effective with correct use</td>
<td>Same as OCP vaginitis, some women may be uncomfortable with self-insertion</td>
</tr>
<tr>
<td>IM progesterone injection q12wk</td>
<td>99.7% effective against pregnancy, infrequent dosing, ↓ menstrual flow or amenorrhea, ↓ risk of endometrial cancer</td>
<td>Irregular bleeding, delayed return of fertility, no STI protection, systemic hormonal side effects (most common is headache), weight gain, ↓ bone mineral density (check after 5 yr)</td>
</tr>
<tr>
<td>Male Condom</td>
<td>97% effective against pregnancy and STIs when used properly. When used properly WITH spermicide they are close to 99.9% effective, no Rx required</td>
<td>Latex allergy, irritation, only effective before the expiry date, must be applied properly, can only be used once</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>92-96% effective with perfect use, non-hormonal, female-controlled method of contraception, ↓ risk of cervical cancer</td>
<td>Must be left in for 6 h after intercourse, must be used with spermicide, incomplete STI protection, latex allergy, must be fitted by health care worker, ↑ risk of UTI, risk of toxic shock syndrome</td>
</tr>
<tr>
<td>Sponge</td>
<td>One-size-fits-all barrier method, does not require fitting by MD, available in pharmacies, 90% effective without a condom, 99% effective with a condom</td>
<td>Relatively expensive, only ~60% effective in parous women, incomplete STI protection, risk of toxic shock syndrome</td>
</tr>
<tr>
<td>Intrauterine Device (IUD)</td>
<td>99% effective against pregnancy, effective for 5 yr, no daily regimen required, can be easily removed, ideal in post-partum women</td>
<td>No STI protection, ↑ relative risk of PID in first month, must be inserted by MD, risk of post-insertion vaso-vagal response, risk of uterine rupture is 0.6-1.6 per 1000, 2-10% expulsion rate</td>
</tr>
<tr>
<td>Levonorgestrel (e.g. Mirena®)</td>
<td>Spotting, less systemic hormonal side effects than OCP</td>
<td>Hormonal side effects are possible, but less than OCP (see combined OCP), expensive (~$400)</td>
</tr>
<tr>
<td>Copper IUD (e.g. Nova T®)</td>
<td>↓ risk of endometrial cancer, less expensive than Mirena® (~$170)</td>
<td>Irregular bleeding or ↑ menstrual flow, 6-20% women discontinue use in first 5 yr because of pain or ↑ bleeding</td>
</tr>
<tr>
<td>Fertility Awareness/ Natural Family Planning (e.g. symptothermal method)</td>
<td>Effectiveness: 95-96% with perfect use, 75-98% with typical use, increased awareness of gynecological health, reasonable for couples for whom an unplanned pregnancy would be acceptable</td>
<td>High probability of failure if not used consistently and correctly, no STI protection</td>
</tr>
<tr>
<td>Lactational Amenorrhea</td>
<td>Can be effective in breastfeeding women if menses not returned, fully or nearly fully breastfeeding baby and baby is under 6 mo old</td>
<td>Not effective if infant receives any food supplementary to breastfeeding</td>
</tr>
</tbody>
</table>

Common Presenting Problems

- Management
  - patient education
  - symptomatic relief
  - prophylactic measures

- Contraception
  - see Gynecology, GY19

Echinacea for Preventing and Treating the Common Cold

Cochrane DB Syst Rev 2006;1:CD000530

This systematic review of 16 trials assessed the effect of Echinacea in preventing and treating common colds. Trials compared preparations containing Echinacea with placebo, no treatment, or an alternative common cold treatment. Variations in preparations and quality of Echinacea made meta-analysis difficult, but in general, results suggested some preparations of Echinacea may be better than placebo.

Conclusions: Echinacea preparations vary widely. Some preparations with E. purpurea may be effective but results are inconsistent.
**EMERGENCY CONTRACEPTION (EC)**
- hormonal EC ('Yuzpe' or Plan B®, usually 2 doses taken 12 h apart) or post-coital IUD insertion
- hormonal EC is effective if taken within 72 h of unprotected intercourse (reduces chance of pregnancy by 75-85%), most effective if taken within 24 h, does not affect an established pregnancy
- post-coital IUDs inserted within 5 d of unprotected intercourse are significantly more effective than hormonal EC (reduces chance of pregnancy by ~99%)
- pregnancy test should be performed if no menstrual bleeding within 21 d of either treatment
- advance provision of hormonal EC increases the use of EC without decreasing the use of regular contraception
- pharmacists across Canada can dispense Plan B® OTC

**Cough**

**History and Physical**
- duration (chronic >3 mo), onset, frequency, quality (dry vs. productive), sputum characteristics, provoking/relieving factors, recent changes
- associated symptoms: fever, dyspnea, hemoptyis, wheezing, chest pain, orthopnea, PND, rhinitis
- constitutional symptoms: fever, chills, fatigue, night sweats
- risk factors: smoking, occupation, exposure, family history of lung CA or other CA, TB status, recent travel
- medications (e.g. ACE inhibitors), allergies
- PMH: lung (asthma, COPD, CF), heart (CHF, MI, arrhythmias), chronic illness, GI (reflux)
- vitals including O₂ saturation, respiratory exam, HEENT and precordial exam

**Investigations**
- guided by findings on history and physical
  - consider throat swab, CXR, PFTs, upper GI series, sputum culture test for acid-fast bacilli (if TB is suspected)

**Dementia**

- see Psychiatry, PS20

**Epidemiology**
- 10% in patients over the age of 65, 25% in patients over the age of 85, 50% in patients over the age of 90
- prevalence increases with age. Down syndrome and head trauma
differential diagnosis: Alzheimer’s dementia, vascular dementia, Lewy-Body dementia, frontotemporal dementia

**Investigations**
- history, physical, MMSE, MOCA (best screening test), dementia quick screen (see sidebar)
- investigations are completed to exclude reversible causes of dementia and should be selected based on the clinical circumstances
- CBC, liver enzymes, TSH, renal function tests, serum electrolytes, serum calcium, serum glucose, vitamin B₁₂, folate, VDRL, HIV, single photon emission computed tomography, head CT, EEG

**Management**
- treat and prevent reversible causes
- provide orientation cues (e.g. calendars, clocks) and optimize vision and hearing
- family education, counselling and support (respite programs, group homes)
- pharmacologic therapy: NMDA receptor antagonists and cholinesterase inhibitors slow rate of cognitive decline; low-dose neuroleptics and antidepressants can be used to treat behavioral and emotional symptoms
- 20% of patients develop clinical depression, most commonly seen in vascular dementia

**Depression**

- see Psychiatry, PS9

**Etiology**
- often presents as non-specific complaints (e.g. sleep disturbance, chronic fatigue, pain)
depression is a clinical diagnosis and tests are done in order to rule out other causes of symptoms
- 2/3 of depressed persons may not receive appropriate treatment for their depression
- identification and early treatment improve outcomes

**Absolute Contraindications to Estrogen Containing Contraception (Combined OCP/Transdermal Patch/ Nuvaring)**
- Known/suspected pregnancy
- Undiagnosed abnormal vaginal bleeding
- Thromboembolic disorders (e.g. previous DVT, PE)
- Coronary cardiovascular or coronary artery disease
- Estrogen dependent tumours (breast, uterus)
- Impaired liver function with acute liver disease
- Congenital hyperthriglyceridemia
- Smoker age >35
- Migraines with focal neurological symptoms
- Uncontrolled hypertension

**Differential Diagnosis**

**Common Causes**
- Upper airway cough syndrome (postnasal drip)
- Asthma/COPD
- GERD
- Non-asthmatic eosinophilic bronchitis

**Other Causes**
- ACE inhibitors
- Aspiration
- Bronchectasis
- Cystic fibrosis
- Chronic interstitial lung disease
- CHF
- Lung/laryngeal cancer
- Pertussis
- Psychogenic
- Restrictive lung disease
- TB, atypical mycobacterium, and other chronic lung infections

**Dementia Quick Screen**
- 3 simple tests, takes about 2 min
- Use when suspect mild cognitive impairment or when patient is at high risk
- Screen involves:
  1. 3 word recall (normal = recalls 2-3 words)
  2. Naming animals in 1 min (normal = >12 in one min)
  3. Clock Drawing – including numbers and hands so time shows 10 min past 11 (normal = correct number/hand placing, or only minor spacing problems)

**INTERPRETATION:** If all 3 results within normal range, cognitive impairment unlikely.
If any results abnormal, possible cognitive impairment, further evaluation necessary.

**Must Ask About/Rule Out**
- Bipolar/manic/hypomanic episodes
- Psychosis
- Anxiety
- Bereavement
- Substance use/abuse/withdrawal
- Suicidal/homicidal ideation
- Organic cause
Screening Questions
• Are you depressed? (high specificity and sensitivity)
• Have you lost interest or pleasure in the things you usually like to do? (anhedonia)
• Do you have problems sleeping?
• For geriatric population, use the Geriatric Depression Scale (GDS) short form for screening

Assessment
• risk factors: see Psychiatry, PS11
• personal or family history of depression
• medications and potential substance abuse problems
• high risk suicidality/homicidality
  • fill out Form 1 (in Ontario): application by physician to hospitalize a patient against his/her will for psychiatric assessment (up to 72 h)
  • functional impairment (e.g. work, relationships)
  • at least 5 out of 9 criteria including anhedonia or depressed mood ≥2 wk for actual diagnosis to be met (see sidebar)
• validated depression rating scales: Beck's depression inventory, Zung's self-rating depression scale, Children's depression inventory, Geriatric Depression Scale, Personal Health Questionnaire Depression Scale (PHQ-9)
  • routine medical workup (physical examination, CBC, TSH, electrolytes, urinalysis, glucose, etc.)

Treatment
• goal: full remission of symptoms and return to baseline psychosocial function
• phases of treatment
  • acute phase (8-12 wk): relieve symptoms and improve quality of life
  • maintenance phase (6-12 mo after symptom resolution): prevent relapse/recurrence, must stress importance of continuing medication treatment for full duration to patients
• treatment can consist of pharmacotherapy alone or psychotherapy alone
• combination of antidepressant drug therapy and psychotherapy results in synergistic effects

Table 16. Common Medications

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Action</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>paroxetine (Paxil®)</td>
<td>Block serotonin reuptake</td>
<td>Sexual dysfunction (impotence, decreased libido, delayed ejaculation, anorgasmia), headache, GI upset, weight loss, tremors, insomnia, fatigue, increase QT interval (baseline ECG is suggested)</td>
<td>First line therapy for teens is fluoxetine; paroxetine is not recommended for teens (controversial)</td>
</tr>
<tr>
<td></td>
<td>fluoxetine (Prozac®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>sertraline (Zoloft®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>citalopram (Celexa®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>fluvoxamine (Luxor®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>escitalopram (Cipralex®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNRI</td>
<td>venlafaxine (Effexor®)</td>
<td>Block serotonin and NE reuptake</td>
<td>Insomnia, tremors, tachycardia, sweating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>duloxetine (Cymbalta®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDRI</td>
<td>bupropion (Wellbutrin®)</td>
<td>Block dopamine and NE reuptake</td>
<td>Headache, insomnia, nightmares, seizures, less sexual dysfunction than SSRIs</td>
<td>Often chosen for lack of sexual side effects, can be used for augmentation of anti-depressant effects with other classes of medication</td>
</tr>
<tr>
<td>TCA</td>
<td>amitriptyline (Elavil®)</td>
<td>Block serotonin and NE reuptake</td>
<td>Sexual dysfunction, weight gain, tremors, tachycardia, sweating</td>
<td>Narrow therapeutic window, lethal in overdose</td>
</tr>
</tbody>
</table>

Prognosis
• up to 40% resolve spontaneously within 6-12 mo
• risks of recurrence: 50% after 1 episode; 70% after 2 episodes; 90% after 3 episodes

Diabetes Mellitus (DM)

• see Endocrinology, E6

Epidemiology
• major health concern, affecting up to 10% of Canadians
• type 1 diabetes mellitus (DM1): 10-15% of DM, peak incidence age 10-15
• type 2 diabetes mellitus (DM2): 85-90% of DM, peak incidence age 50-55, up to 60,000 new cases in Canada per year
• gestational diabetes mellitus (GDM): 2-4% of all pregnancies
• incidence of type DM2 is rising dramatically as a result of an aging population, rising rates of obesity, and sedentary lifestyles
• leading cause of new-onset blindness and renal dysfunction
• Canadian adults with diabetes are twice as likely to die prematurely, compared to persons without diabetes
Risk Factors
• DM1
  • personal or family history of autoimmune disease
• DM2
  • first degree relative with DM
  • age ≥40 yr
  • obesity (especially abdominal), hypertension, hyperlipidemia, coronary artery disease, vascular disease
  • prior GDM, macrosomic baby (>4 kg)
  • PCOS
  • history of impaired glucose tolerance or impaired fasting glucose
  • presence of complications associated with diabetes
  • presence of associated diseases: PCOS, acanthosis nigricans, psychiatric disorders, HIV
  • medications: glucocorticoids, atypical antipsychotics, HAART
• both
  • member of a high risk population (e.g. Aboriginal, Hispanic, Asian or African descent)

Diagnosis
• persistent hyperglycemia is the hallmark of all forms of diabetes

Table 17. Diagnosis of Insulin Associated Disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>One of the following on 2 occasions:</td>
</tr>
<tr>
<td></td>
<td>• Random BG ≥11.1 mmol/L (200 mg/dL) with symptoms of DM (fatigue, polyuria, polydipsia, unexplained weight loss) OR</td>
</tr>
<tr>
<td></td>
<td>• Fasting BG ≥7.0 mmol/L (126 mg/dL) OR</td>
</tr>
<tr>
<td></td>
<td>• BG 2 h post 75 g OGTT ≥11.1 mmol/L (200 mg/dL) OR HbA1c ≥6.5% (in adults)</td>
</tr>
<tr>
<td>Impaired Fasting Glucose</td>
<td>Fasting BG = 6.1-6.9 mmol/L (110-124 mg/dL)</td>
</tr>
<tr>
<td>(IFG)</td>
<td></td>
</tr>
<tr>
<td>Impaired Glucose Tolerance</td>
<td>BG 2 h post 75 g OGTT = 7.8-11.0 mmol/L (141-198 mg/dL)</td>
</tr>
</tbody>
</table>

Screening
• DM2
  • FBG in everyone ≥40 q3yr , or at high risk using the CANRISK calculator
  • more frequent and/or earlier testing if presence of ≥1 risk factor (see above)
• GDM (see Obstetrics, OB14)
  • all pregnant women between 24-28 wk gestation
  • non-fasting 1 h 50 g OGCT ≥10.3 mmol/L (186 mg/dL) is diagnostic
  • if between 7.8-10.2 mmol/L (141-184 mg/dL), do confirmatory fasting 2 h 75 g OGTT
  • if develop GDM, have a 50% chance of developing DM2 over 20 yr

Goals of Therapy

Table 18. Goals of Therapy in DM

| General                           | Avoid complications (e.g. ketoacidosis, hyperglycemia, infection)                     |
|                                  | Prevent long-term complications (microvascular and macrovascular)                   |
|                                  | Minimize negative sequelae associated with therapies (e.g. hypoglycemia, weight gain) |
| Fasting or Preprandial BG        | Ideal: 4-7 mmol/L (72-126 mg/dL); action may be required                              |
|                                  | Suboptimal: 7.1-10 mmol/L (128-180 mg/dL); action required                           |
|                                  | Inadequate: >10.0 mmol/L (180 mg/dL); action required                               |
| HbA1c                             | ≤7% or ≤6.5% in some DM2 patients at risk for nephropathy                             |
|                                  | Suboptimal: 7-8.4%                                                                  |
|                                  | Inadequate: >8.4%                                                                  |
| 2 h Postprandial BG              | 5-10 mmol/L (90-180 mg/dL) if HbA1c target met                                      |
|                                  | 5-8 mmol/L (90-144 mg/dL) if HbA1c target not met                                   |
| Blood Pressure                   | <130/80 in adults (DM and HTN guidelines)                                           |
| Lipids                           | LDL <2.0 mmol/L (38 mg/dL)                                                         |
|                                  | Triglycerides <1.5 mmol/L (27 mg/dL)                                               |
|                                  | Total cholesterol/HDL ratio <4.0 mmol/L (72 mg/dL)                                  |
Assessment and Monitoring

### Table 19. Assessment and Monitoring

<table>
<thead>
<tr>
<th>Initial Assessment</th>
<th>q2-4months</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Symptoms of hyperglycemia, ketoacidosis, hypoglycemia</td>
<td>• Diabetes-directed history</td>
<td>• Diabetes-directed history</td>
</tr>
<tr>
<td>• Past medical history</td>
<td>• Screen for awareness and frequency of hypoglycemia and DKA</td>
<td>• Screen for awareness and frequency of hypoglycemia and DKA</td>
</tr>
<tr>
<td>• Functional inquiry</td>
<td>• Glucose monitoring</td>
<td>• Glucose monitoring</td>
</tr>
<tr>
<td>• Family history</td>
<td>• Use of insulin and oral agents</td>
<td>• Use of insulin and oral agents</td>
</tr>
<tr>
<td>• Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sexual function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lifestyle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Diabetes-directed history</td>
<td>• Foot exam for sensation (using a 10 g monofilament), ulcers, or infection</td>
<td>• Complete neuro exam for peripheral neuropathy</td>
</tr>
<tr>
<td>• Screen for awareness and frequency of hypoglycemia and DKA</td>
<td></td>
<td>• Remainder of exam as per PHE</td>
</tr>
<tr>
<td>• Glucose monitoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• General: Ht, Wt, BMI, BP, WC</td>
<td>• Wt, BP, BMI, WC</td>
<td>• HbA1c q3mo</td>
</tr>
<tr>
<td>• Head and neck: fundoscopy, thyroid exam</td>
<td>• Foot exam for sensation (using a 10 g monofilament), ulcers, or infection</td>
<td>• FBG as needed</td>
</tr>
<tr>
<td>• Cardiovascular exam: signs of PVD, pulses, bruits</td>
<td></td>
<td>• Fasting lipid profile</td>
</tr>
<tr>
<td>• Abdominal exam (e.g. for organomegaly)</td>
<td></td>
<td>• Resting or exercise ECG if age &gt;35</td>
</tr>
<tr>
<td>• Hand/foot/skin exam</td>
<td></td>
<td>• Dipstick analysis for gross proteinuria; if negative: annual microalbuminuria screening with random albumin:creatinine ratio for DM2 and DM1 (5 yr post puberty)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If positive: 24-h urine for endogenous creatinine clearance rate and microalbuminuria q6-12mo</td>
</tr>
<tr>
<td>• Neurological exam</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fasting lipids, microalbumin:creatinine ratio</td>
<td>• HbA1c q3mo</td>
<td>• Fasting lipid profile</td>
</tr>
<tr>
<td>• ECG</td>
<td>• FBG as needed</td>
<td>• Resting or exercise ECG if age &gt;35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dipstick analysis for gross proteinuria; if negative: annual microalbuminuria screening with random albumin:creatinine ratio for DM2 and DM1 (5 yr post puberty)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If positive: 24-h urine for endogenous creatinine clearance rate and microalbuminuria q6-12mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Nutritional and physical education</td>
<td>• Assess progress towards long-term complications</td>
<td>• Calibrate home glucose monitor</td>
</tr>
<tr>
<td>• Consider referral to diabetes education program if available</td>
<td>• Adjust treatment plan if necessary</td>
<td>• Arrange ophthalmology follow-up annually for DM1 and q2yr for DM2</td>
</tr>
<tr>
<td>• Monitoring BG: explain methods and frequency</td>
<td></td>
<td>• Influenza vaccination annually</td>
</tr>
<tr>
<td>• Medication counselling: oral hypoglycemics and/or insulin, method of administration, dosage adjustments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pneumococcal vaccination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• DM1 within 5 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• DM2 at diagnosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Nonpharmacologic Management

- **diet**
  - all diabetics should see a registered dietitian
  - can reduce HbA1c by 1-2%
  - strive to attain healthy body weight
  - decrease combined saturated fats and trans-fatty acids to <10% of calories
  - avoid simple sugars, encourage complex carbohydrates, choose low glycemic-index foods
- **physical activity and exercise**
  - at least 150 min of aerobic exercise per wk, plus 2 sessions per wk of resistance exercise is recommended
  - encourage 30-45 min of moderate exercise 4-7 d/wk
  - promote cardiovascular fitness: increases insulin sensitivity, lowers BP and improves lipid profile
  - if insulin treated, may require alterations of diet, insulin regimen, injection sites and self-monitoring

### Self-Monitoring of Blood Glucose

- DM1: 3 or more self-tests/d is associated with a 1% reduction in HbA1c
- DM2: at least once per day, if once daily insulin regime
- if FBG >14 mmol/L, perform ketone testing to rule out DKA
- if bedtime level is <7 mmol/L, have bedtime snack to reduce risk of nocturnal hypoglycemia
Calculate Total Insulin Required:

- DM1: 0.5-0.7 units/kg/d
- DM2: 0.3 units/kg/d

Clinical Assessment

- **Lifestyle intervention (initiation of nutrition therapy and physical activity)**

  - **HbA1c < 9.0%**
    - Initiate **metformin**

  - **HbA1c ≥ 9.0%**
    - Initiate **pharmacotherapy** immediately without waiting for effect from lifestyle interventions:
      - Consider initiating **metformin** concurrently with another agent from a different class; or initiate insulin

- **Symptomatic hyperglycemia with metabolic decompensation**

  - Initiate **insulin ± metformin**

  - If not at target
    - Add an agent best suited to the individual based on the advantages/disadvantages listed below

<table>
<thead>
<tr>
<th>Class</th>
<th>HbA1c</th>
<th>Hypoglycemia</th>
<th>Other Advantages</th>
<th>Other Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-glucosidase inhibitor</td>
<td>↓</td>
<td>Rare</td>
<td>Improved postprandial control</td>
<td>GI side effects</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>↓ to ↓</td>
<td>Rare</td>
<td>Improved postprandial control</td>
<td>New agent (unknown long-term safety)</td>
</tr>
<tr>
<td>Insulin</td>
<td>↓ ↓</td>
<td>Yes</td>
<td>No dose ceiling Many types, flexible regimens</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Insulin secretagogue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meglitinide</td>
<td>↓ to ↓</td>
<td>Yes*</td>
<td>Improved postprandial control</td>
<td>Requires tid to qid dosing Weight gain</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>↓</td>
<td>Yes</td>
<td>Newer sulfonylureas (gliacide, gimepiride) are associated with less hypoglycemia than glyburide</td>
<td></td>
</tr>
<tr>
<td>TZD</td>
<td>↓</td>
<td>Rare</td>
<td>Requires 6-12 wk for maximal effect</td>
<td>Weight gain Edema, rare CHF, rare fractures in females</td>
</tr>
<tr>
<td>Weight loss agent</td>
<td>↓</td>
<td>None</td>
<td>Weight loss</td>
<td>GI side effects (orlistat) Increased heart rate/BP (sibutramine)</td>
</tr>
</tbody>
</table>

- If not at target
  - Add another drug from a different class; or
  - Add bedtime basal insulin to other agent(s); or
  - Intensify insulin regimen

<table>
<thead>
<tr>
<th>HbA1c – glycated hemoglobin</th>
<th>DPP-4 – dipeptidyl peptidase-4</th>
<th>↓ – &lt;1.0% decrease in A1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP – blood pressure</td>
<td>GI – gastrointestinal</td>
<td>↓ ↓ – 1.0-2.0% decrease in A1c</td>
</tr>
<tr>
<td>CHF – congestive heart failure</td>
<td>TZD – thiazolidinedione</td>
<td>↓ ↓ ↓ – &gt;2.0% decrease in A1c</td>
</tr>
</tbody>
</table>

*Gaps hypoglycemia in the context of missed meals

**Note:** Physicians should refer to the most recent edition of the Compendium of Pharmaceuticals and Specialties (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and for detailed prescribing information

Figure 9. Types of insulin preparation

Figure 10. Management of hyperglycemia in type 2 diabetes

Hypoglycemic Agents (DM2)
- oral
  - biguanide: metformin (Glucophage®)
  - thiazolidinedione: troglitazone (Rezulin®), rosiglitazone (Avandia®)
  - α-glucosidase inhibitor: acarbose (Precose®)
  - nonsulfonylureas: nateglinide (Starlix®), repaglinide (Gluconorm®)
  - sulfonylureas: glyburide (DiaBeta®), gliclazide (Diamicron®)
- injectable
  - GLP-1 analogue: liraglutide (Victoza®)

Other Medications Used in DM
- ACE inhibitors for:
  - all hypertensive diabetics
  - elevated microalbuminuria (30-300 mg albumin in urine in 24 h)
  - overt nephropathy (>300 mg albumin in urine in 24 h)
  - ARBs are second line for these conditions
- ASA 81 mg once a day for:
  - all diabetics, unless contraindicated
- statins
  - as required to attain target lipid profile

Diarrhea
- see Gastroenterology, G15

Definition
- passage of 3 or more loose or liquid stools in a day or more frequently than is normal for the individual (WHO definition)
- can be acute (<14 d duration) or chronic (>14 d duration)

Etiology and Clinical Features
- acute diarrhea:
  - majority of cases are self-limiting
  - most commonly caused by viral infection (e.g. rotavirus, norovirus)
  - fever and bloody stools increase probability of bacterial infection
  - consider C. difficile infection if recent hospitalization, recent antibiotic use (e.g. broad spectrum antibiotics, fluoroquinolones, clindamycin), chronic use of PPIs, age >65, immunosuppression
- chronic diarrhea:
  - most commonly of non-infectious etiology
  - common causes include drugs (e.g. laxatives, antibiotics), infection (e.g. bacteria, parasites), inflammation (e.g. IBD, diverticulitis), neoplasia (e.g. colon cancer), malabsorption (e.g. celiac disease), maldigestion (e.g. lactose intolerance), and idiopathic

Treatment
- acute diarrhea: ensure adequate hydration, treat underlying cause (e.g. antibiotics for bacterial infection)
- chronic diarrhea: nonspecific treatment often required before workup is complete
  - oral rehydration solution (if needed): offset electrolyte imbalances
  - lifestyle modification (dietary changes, exercise)
  - fibre (e.g. psyllium): commonly used as adjunctive treatment
  - antidiarrheal opiates (e.g. loperamide): most effective nonspecific treatment
    - should be used on a scheduled basis before meals rather than prn

Dizziness
- see Otolaryngology, OT5

Epidemiology
- 70% see general practitioners initially; 4% referred to specialists
- frequency proportional to age; commonest complaint of ambulatory patients age >75
Differential Diagnosis

**Dizziness**

- **Vertigo (vestibular)**
  - Objective (external world seems to revolve around individual) or subjective (individual revolves in space)
  - **Central (15%)**
    - Brainstem
    - Cerebellar
  - **Peripheral (85%)**
    - Inner ear (vestibular nerve)
    - Vestibular nerve
    - Idiopathic Meniere’s
    - BPPV
    - Acoustic neuroma
    - Trauma
    - Drugs
    - Labyrinthitis

- **Nonvertiginous (nonvestibular)**
  - Feeling “light-headed,” “giddy,” “dazed,” “mentally confused,” or “disoriented”
  - **Vascular**
    - Basilar migraine
    - TIA
    - Orthostatic hypotension
    - Stokes-Adams syndrome
    - Arhythmia
    - CHF
    - Aortic stenosis
    - Vasovagal episodes
    - Metabolic causes
  - **Ocular**
    - Decreased visual acuity

**Figure 11. Differential diagnosis of dizziness**

**History**
- clarify type of dizziness: vertigo, pre-syncpe, disequilibrium, light-headedness
- onset, precipitating/alleviating factors, preceding infections and activities, associated symptoms, previous experiences of dizziness
- duration (seconds, minutes, hours, days, weeks, or persistent)
- exacerbations
  - worse with head movement or eye closure (vestibular)
  - no change with head movement and eye closure (nonvestibular)
  - worse with exercise (cardiac/pulmonary causes)
- associated symptoms
  - neurologic (central)
    - transient diplopia, dysphagia, dysarthria, ataxia (TIA, VBI, migraine)
    - persistent headache, alterations in level of consciousness, sensory and/or motor deficits (CNS)
  - audiologic (peripheral)
    - hearing loss, tinnitus, otalgia, aural fullness
  - others
    - nausea, vomiting (peripheral vestibular disorders)
    - SOB, palpitations (hyperventilation, cardiac problem)
- general medical history
  - HTN, diabetes, heart disease, fainting spells, seizures, cerebrovascular disease, migraines
  - ototoxic drugs: aminoglycosides (gentamicin, streptomycin, tobramycin), erythromycin, ASA, antimalarials
  - hypotension (secondary to diuresis): furosemide, caffeine, alcohol

**Physical Exam/Investigations**
- syncopal
  - cardiac (orthostatic changes in vitals), peripheral vascular, and neurologic exams
  - bloodwork, ECG, 24-h Holter, treadmill stress test, loop ECG, tilt table testing, carotid and vertebral doppler, EEG
- vertiginous
  - ENT and neurologic exams
  - Dix-Hallpike (see sidebar), consider audiometry and MRI if indicated
- non-syncopal, non-vertiginous
  - cardiac and neurologic exams
  - 3-min hyperventilation trial (patient is coached to hyperventilate until patient becomes dizzy to identify if symptoms are reproducible and confirm that hyperventilation is the etiology of the symptoms), ECG, EEG

**Treatment**
- guided by history, physical and investigations
- include education, lifestyle modification, physical maneuvers (e.g. Epley for BPPV), symptomatic management (e.g. antiemetics), pharmacotherapy and surgery
- refer when significant central disease is suspected, when vertigo of peripheral origin is persistent (lasting >2-4 wk), or atypical presentation
Domestic Violence/Elder Abuse

INTIMATE PARTNER VIOLENCE

Definition
- includes physical, sexual, emotional, psychological and financial abuse
  (see Emergency Medicine, ER29)

Epidemiology
- lifetime prevalence of intimate partner violence against women is between 25-30%
- women who experience abuse have increased rates of injury, death and health consequences
  including 50-70% increase in gynecological, central nervous system, stress-related problems
- occurs in all socioeconomic, educational and cultural groups with increased incidence in
  pregnancy, disabled women, and 18-24 age group
- 25-50% chance of child abuse or neglect in families where partner abuse occurs
- physician recognition rates as low as 5%

Presentation
- multiple visits with vague, ill-defined complaints such as: headaches, gastrointestinal symptoms,
  insomnia, chronic pain, hyperventilation
- may also present with injuries inconsistent with history

Management
- screen ALL patients
  - always have a high index of suspicion
  - physician is often first person to get disclosure
  - health care visits are an important opportunity for physicians to address intimate partner violence
  - asking about abuse is the strongest predictor of disclosure
  - several screening tools (see sidebar) exist to identify victims of partner violence
  - make sure to determine the victim's level of immediate and long term danger and ask if there
    are weapons in the house
  - ensure patient safety
    - victim most at risk for homicide when attempting to leave home or following separation
    - involve social workers or domestic violence advocates
  - provide community resources
    - safety planning includes ensuring that there is access to an exit in the home, establishing a
      safe place to go and having money, clothes, keys, medications, important documents and
      other emergency items prepared should the patient need to leave quickly
    - shelter or helpline number with legal advocacy and counselling services
    - marital counselling inappropriate until safety is established and violence under control
    - appointment for follow-up to assess whether condition is better or worse
    - reassure patient she/he is not to blame and that the assault is a crime
  - goal is to convey the message that “As your doctor, I am concerned for your safety” and
    “Your partner has a problem that he/she needs help with” and “I want to help you”
  - reporting suspected or known child abuse is mandatory (see Emergency Medicine, ER59)
  - spousal abuse is a criminal act, but not reportable without the woman’s/man’s permission
  - DOCUMENT all evidence of abuse-related visits for medico-legal purposes (see sidebar)

ELDER ABUSE

Definition
- mistreatment of elderly by those in a position of trust, power, or responsibility for their care
- types of abuse:
  - psychological (e.g. threatening, intimidating, insulting, demeaning, withholding information
    that may be important to them, ignoring)
  - financial (e.g. stealing, pressuring to sell or share home, misusing power of attorney)
  - physical (e.g. hitting, burning, locking in room, inappropriate use of physical restraints,
    withholding or misusing medication)
  - sexual
  - neglect

Epidemiology
- 7% of adults in Canada age >65 reported experiences of emotional or financial abuse
- older adults who live with someone are more likely to be abused than those who live alone
- 31% of reported violent abuse cases involved family members (Statistics Canada, 2009):
  - most often at the hands of adult children (32%) followed by spouses (28%)
  - older females are more likely to be abused than older males
  - men are more likely than women to be victimized by an adult child (34% vs. 31%)
- women are more likely than men to experience violence at the hands of a spouse (32% vs. 22%)
- reasons for under-reporting: fear, shame, cognitive impairment, language/cultural barriers, and
  social and geographic isolation

How to Document Abuse
- always have a high index of suspicion
- safety planning includes ensuring that there is access to an exit in the home, establishing a
  safe place to go and having money, clothes, keys, medications, important documents and
  other emergency items prepared should the patient need to leave quickly
- shelter or helpline number with legal advocacy and counselling services
- marital counselling inappropriate until safety is established and violence under control
- appointment for follow-up to assess whether condition is better or worse
- reassure patient she/he is not to blame and that the assault is a crime
- goal is to convey the message that “As your doctor, I am concerned for your safety” and
  “Your partner has a problem that he/she needs help with” and “I want to help you”
- reporting suspected or known child abuse is mandatory (see Emergency Medicine, ER59)
- spousal abuse is a criminal act, but not reportable without the woman’s/man’s permission
- DOCUMENT all evidence of abuse-related visits for medico-legal purposes (see sidebar)

Screening Instruments for Domestic Violence
A) Woman Abuse Screening Tool (WAST)-SHORT
1. In general how would you describe your relationship?
   a. A lot of tension
   b. Some tension
   c. No tension
2. Do you and your partner work out arguments with . . .?
   a. Great difficulty
   b. Some difficulty
   c. No difficulty
Endorsing either question 1 ("a lot of tension") or question 2 ("great difficulty") makes intimate partner
violence exposure likely

B) HITS
How often does your partner:
1. Physically hurt you?
2. Insult you?
3. Threaten you with harm?
4. Scream or curse at you?
Each question on HITS to be answered on a 5 point scale ranging from 1
(= never) to 5 (= frequently)
A total score of 10.5 is significant
Screening
- insufficient evidence to include or exclude as part of the periodic health examination, but recommended that physicians be alert for indicators of abuse and institute measures to prevent further abuse
- general questions such as “Do you feel safe at home?” and move into more specific questions about different kinds of abuse

Presentation
- signs that an older adult is being abused may include:
  - depression, fear, anxiety, passivity, unexplained injuries, dehydration, malnutrition, poor hygiene, rashes, pressure sores, and over-sedation/inappropriate medication use

Management
- gather information from all sources (e.g. family members, health care providers, neighbours)
- perform a thorough physical examination
- ensure immediate safety and devise a plan for follow-up
- additional steps depend on whether the patient accepts intervention and whether they are capable of making decisions about their care
- interventions may include use of protective and legal services, senior resource nurses, elder abuse intervention teams and senior support groups

Dyspepsia

Definition and Clinical Features
- defined as epigastric pain or discomfort
- can be associated with fullness, belching, bloating, heartburn, food intolerance, nausea or vomiting

Epidemiology
- annual incidence 1-2%, prevalence 20-40%

Etiology
- common: functional, peptic ulcer disease, gastroesophageal reflux disease (GERD), gastritis
- others: cholelithiasis, irritable bowel syndrome, esophageal or gastric cancer, pancreatitis, pancreatic cancer, Zollinger-Ellison syndrome, and abdominal angina

History
- symptoms may not be useful in finding cause
- association with food, anorexia, nausea, vomiting, NSAID use

Investigations and Management
- lifestyle modifications: dietary changes, decreased EtOH consumption, smoking cessation
- empiric therapy: H₂ receptor blockers, proton pump inhibitors (PPIs) for short periods of time (8 wk with taper)
- testing for H. pylori: serology, urea breath test
- upper endoscopy (preferred), upper GI series

Dyspnea

Definition and Clinical Features
- see Gastroenterology, G10

History and Physical
- history:
  - cough, sputum, hemoptysis, wheezing, chest pain, palpitations, dizziness, edema
  - asthma, allergy, eczema, ASA/NSAID sensitivity, nasal polyps
  - constitutional symptoms
  - smoking, recreational drugs, medications
  - occupational exposure, environmental exposure (e.g. pets, allergens, smoke)
  - travel and birth place
  - FHx of atopy
  - previous CXR or PFTs
- physical exam: vitals, respiratory, precordial, HEENT, signs of anemia/liver failure/heart failure

Investigations
- CXR, ECG
- PFTs, ABG acutely if indicated

Management
- ABCs: send to ER if in severe respiratory distress
- depends on cause

DDx of Dyspepsia
Pulmonary
- COPD
- Asthma
- Restrictive lung disease
- Pneumothorax
- Congenital lung disease

Cardiac
- CHF
- CAD
- MI (recent or past)
- Cardiomyopathy
- Valve dysfunction
- Pericarditis
- Arrhythmia
- Hypertrophy

Mixed/Other
- Deconditioning
- Trauma
- Pain
- Neuromuscular
- Metabolic condition
- Functional: anxiety, panic attack, hyperventilation
Dysuria

- see Urology, U5

Definition

- the sensation of pain, burning or discomfort on urination

Epidemiology

- in adulthood, more common in women than men
- approximately 25% of women report one episode of acute dysuria per year
- most common in women age 25-54 and in those who are sexually active
- in men, dysuria becomes more prevalent with increasing age

Etiology

- infectious
  - most common cause
  - presents as cystitis, urethritis, pyelonephritis, vaginitis or prostatitis
- non-infectious
  - hormonal conditions (hypoestrogenism), obstruction (BPH, urethral strictures), allergic reactions, chemicals, foreign bodies, trauma, neoplasm, kidney stones

Table 20. Etiology, Signs and Symptoms of Dysuria

<table>
<thead>
<tr>
<th>Infection</th>
<th>Etiology</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI/Cystitis</td>
<td>KEPES bacteria (Klebsiella, E. coli, Enterobacter, Proteus mirabilis, Pseudomonas, S. saprophyticus)</td>
<td>Internal dysuria throughout micturition, frequency, urgency, incontinence, hematuria, nocturia, back pain, suprapubic discomfort, low grade fever (rare)</td>
</tr>
<tr>
<td>Urethritis</td>
<td>C. trachomatis, N. gonorrhoeae, Trichomonas, Candida, herpes</td>
<td>Initial dysuria, urethral/vaginal discharge, history of STI</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>Candida, Gardnerella, Trichomonas, C. trachomatis, atrophic, herpes, lichen sclerosis</td>
<td>External dysuria/pain, vaginal discharge, irritation, dyspareunia, abnormal vaginal bleeding</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>E. coli, C. trachomatis, S. saprophyticus, Proteus mirabilis, Enterobacter, Klebsiella, Pseudomonas</td>
<td>Dysuria, fever, chills, urgency, frequency, tender prostate, rectal pain</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>E. coli, S. saprophyticus, Proteus mirabilis, Enterobacter, Klebsiella, Pseudomonas</td>
<td>Internal dysuria, fever, chills, flank pain radiating to groin, CVA tenderness, nausea or vomiting</td>
</tr>
</tbody>
</table>

Investigations

- no investigations necessary when history and physical consistent with uncomplicated UTI – treat empirically (urinalysis can be performed when indicated by dipstick or microscopy)
- urinalysis/dipstick: positive for nitrites and leukocytes
- urine R&M: pyuria, bacteruria, hematuria
- urine C&S
- if vaginal/urethral discharge present: wet mount, Gram stain, KOH test, vaginal pH, culture for yeast and trichomons, endocervical/urethral swab or urine PCR for N. gonorrhoeae and C. trachomatis
- radiologic studies and other diagnostic tests if atypical presentation
- see Pediatrics, P65 for UTI in children

Management

- see Antimicrobial Quick Reference, FM55 for treatment
- UTI/cystitis
  - pregnant women with bacteriuria (2-7%) must be treated even if asymptomatic, due to risk of preterm labour; need to follow with monthly urine cultures and retreat if still infected
  - patients with recurrent UTIs (>3/yr) should be considered for prophylactic antibiotics
  - if complicated UTI, patients require longer courses of broader spectrum antibiotics
  - urethritis
    - when swab or PCR is positive for chlamydia or gonorrhea must report to Public Health
    - all patients should return 4-7 d after completion of therapy for clinical evaluation

UTI Clinical Decision Aid

- Dysuria
  - + Leukocytes
  - + Nitrites

If 2 or more criteria MET, then treat without culture, otherwise culture required prior to treatment.
Arch Intern Med 2007;67:2201-2206

Risk Factors for Complicated UTI

- Male sex
- Pregnancy
- Recent urinary tract instrumentation
- Functional or anatomic abnormality of the urinary tract
- Chronic renal disease
- Diabetes
- Immunosuppression
- Indwelling catheter

Prevention of UTIs

- Maintain good hydration (especially with cranberry juice)
- Wipe urethra from front to back to avoid contamination of the urethra with feces from the rectum
- Avoid feminine hygiene sprays and scented douches
- Empty bladder immediately before and after intercourse

Cranberries for Preventing Urinary Tract Infections

Cochrane DB Syst Rev 2008;1:CD001321
Study: Meta-analysis of 10 RCTs, n = 1049.
Patients: All populations.
Intervention: Cranberry juice vs. placebo, juice or water was evaluated in seven studies, and cranberry tablets vs. placebo in four studies.
Main Outcome: UTIs – symptomatic and asymptomatic.
Results: Cranberry products significantly reduced the incidence of UTIs at 12 mo (RR 0.65, 95% CI 0.46 to 0.90) compared with placebo/control.
Conclusion: There is some evidence that cranberry products may decrease the number of symptomatic UTIs over a 12 mo period, particularly for women with recurrent UTIs.

Investigations

- no investigations necessary when history and physical consistent with uncomplicated UTI – treat empirically (urinalysis can be performed when indicated by dipstick or microscopy)
- urinalysis/dipstick: positive for nitrites and leukocytes
- urine R&M: pyuria, bacteruria, hematuria
- urine C&S
- if vaginal/urethral discharge present: wet mount, Gram stain, KOH test, vaginal pH, culture for yeast and trichomons, endocervical/urethral swab or urine PCR for N. gonorrhoeae and C. trachomatis
- radiologic studies and other diagnostic tests if atypical presentation
- see Pediatrics, P65 for UTI in children

Management

- see Antimicrobial Quick Reference, FM55 for treatment
- UTI/cystitis
  - pregnant women with bacteriuria (2-7%) must be treated even if asymptomatic, due to risk of preterm labour; need to follow with monthly urine cultures and retreat if still infected
  - patients with recurrent UTIs (>3/yr) should be considered for prophylactic antibiotics
  - if complicated UTI, patients require longer courses of broader spectrum antibiotics
  - urethritis
    - when swab or PCR is positive for chlamydia or gonorrhea must report to Public Health
    - all patients should return 4-7 d after completion of therapy for clinical evaluation
### Epistaxis

- see Otolaryngology, OT26

#### Table 21. Characteristics of Anterior vs. Posterior Bleeds

<table>
<thead>
<tr>
<th></th>
<th>Anterior (90%)</th>
<th>Posterior (10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location/ Origin</strong></td>
<td>Little’s area/Kiesselbach’s plexus</td>
<td>Woodruff’s plexus/sphenopalatine artery</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>2-10, 50-80</td>
<td>Usually &gt;50</td>
</tr>
<tr>
<td><strong>Common Cause</strong></td>
<td>Trauma (digital, fracture, foreign body), dry air, cool climate, post URTI, nasal dryness, chemical (nasal sprays, cocaine), tumour</td>
<td>Systemic: hepatic disease, primary/secondary bleeding disorder, medications (ASA, NSAIDs, warfarin), HTN, atherosclerosis</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Bloodwork (CBC, INR/PTT, cross and type, LFTs)</td>
<td>Same as for anterior bleeds</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Conservative:</td>
<td>Emergency: ENT/ER consult for posterior packing with an intranasal balloon/foley catheter embolization/surgery</td>
</tr>
<tr>
<td></td>
<td>• Position: upright leaning forward with direct digital pressure over soft part of nostril for &gt;10 min (“pinch” up to cartilage)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Humidifier in bedroom, nasal saline sprays, bacitracin or Vaseline® application to Little’s area</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Silver nitrate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Gelfoam/haemostat</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Nasal packing with Vaseline® gauze, nasal catheter or sponge</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cotton soaked in vasoconstrictor (oxymetazoline 0.5%) and topical anesthetic (4% lidocaine) placed in anterior nasal cavity with direct pressure for &gt;10 min</td>
<td></td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Usually stops with &gt;10 min of pressure to nose</td>
<td>Copious bleed, often swallowed and vomited May lead to hypovolemic shock if not treated promptly</td>
</tr>
</tbody>
</table>

### Erectile Dysfunction (ED)

- see Urology, U30

#### Definition
- consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual performance of ≥3 mo duration

#### Epidemiology
- ~20% of men aged 40; ~50% of men aged 70

#### Etiology
- organic: vascular (90%) (arterial insufficiency, atherosclerosis), endocrine (low testosterone, diabetes), anatomic (structural abnormality, e.g. Peyronie’s), neurologic (post-op, diabetes), medications (clonidine, antihypertensives, psychotropics)
- psychogenic (10%)

#### Table 22. Differentiation Between Organic and Psychogenic ED

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Organic</th>
<th>Psychogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Gradual</td>
<td>Acute</td>
</tr>
<tr>
<td>Circumstances</td>
<td>Global</td>
<td>Situational</td>
</tr>
<tr>
<td>Course</td>
<td>Constant</td>
<td>Varying</td>
</tr>
<tr>
<td>Non-coital erection</td>
<td>Poor</td>
<td>Rigid</td>
</tr>
<tr>
<td>Morning erection</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Psychosexual problem</td>
<td>Secondary</td>
<td>Long history</td>
</tr>
<tr>
<td>Partner problem</td>
<td>Secondary</td>
<td>At onset</td>
</tr>
<tr>
<td>Anxiety and fear</td>
<td>Secondary</td>
<td>Primary</td>
</tr>
</tbody>
</table>

*Walsh: Campbell’s Urology, 8th ed. Table 46-4*

#### History
- comprehensive sexual, medical and psychosocial history
- time course
  - last satisfactory erection
  - gradual or sudden onset
  - attempts at sexual activity
quantify (see Table 22, FM31)
- presence of morning or night time erections
- stiffness (scale of 1-10)
- ability to initiate and maintain an erection with sexual stimulation
- erection stiffness during sex (scale of 1-10)

qualify
- partner or situation specific
- loss of erection before penetration or climax
- degree of concentration required to maintain an erection
- percentage of sexual attempts satisfactory to patient and/or his partner
- significant bends in penis or pain with erection
- difficulty with specific positions
- impact on quality of life and relationship

Investigations
- hypothalamic-pituitary-gonadal axis evaluation: testosterone (free + total), prolactin, LH
- risk factor evaluation: fasting glucose, HbA1c, lipid profile
- others: TSH, CBC, urinalysis
- specialized testing
  - psychological and/or psychiatric consultation
  - in-depth psychosexual and relationship evaluation
  - nocturnal penile tumescence and rigidity (NPTR) assessment
  - vascular diagnostics (e.g. doppler studies, angiography)

Management

<table>
<thead>
<tr>
<th>Table 23. Management of Erectile Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpharmacologic</td>
</tr>
<tr>
<td>Lifestyle changes (alcohol, smoking, exercise)</td>
</tr>
<tr>
<td>Relationship/sexual counselling</td>
</tr>
<tr>
<td>Vacuum devices</td>
</tr>
</tbody>
</table>

- pharmacologic treatment
  - phosphodiesterase type 5 inhibitors (see Table 24)
  - α-adrenergic blockers (e.g. yohimbine)
  - serotonin antagonist and reuptake inhibitor (e.g. trazodone)
  - testosterone – currently only indicated in patients presenting with hypogonadism and testosterone deficiency (note: breast/prostate cancer are absolute contraindications)

<table>
<thead>
<tr>
<th>Table 24. Phosphodiesterase Type 5 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examples</td>
</tr>
<tr>
<td>sildenafil (Viagra®)</td>
</tr>
<tr>
<td>tadalafil (Cialis®)</td>
</tr>
<tr>
<td>vardenafil (Levitra®)</td>
</tr>
</tbody>
</table>

Eye Complaints
- see Ophthalmology, OP3, for Vision Loss and Red Eye

Falls in the Elderly
- see Geriatric Medicine, GM5

Fatigue

Epidemiology
- 25% of office visits to family physicians
- peaks in ages 20-40
- women 3-4x > men
- 50% have associated psychological complaints/problems, especially if <6 mo duration
Differential Diagnosis

Table 25. Differential Diagnosis of Fatigue: PS VINDICATE

| P | Psychogenic | Depression, sleep disorder, life stresses, anxiety disorder, chronic fatigue syndrome, fibromyalgia |
| S | Sedentary   | Unhealthy/sedentary lifestyle, obstructive sleep apnea |
| V | Vascular    | Stroke |
| I | Infectious  | Any malignancy |
| N | Neoplastic  | Anemia (Fe deficiency, B12 deficiency) |
| D | Drugs       | β-blockers, antihistamines, anticholinergics, benzodiazepines, antiepileptics |
| I | Idiopathic  | Substance abuse (e.g. alcohol), heavy metal |
| C | Chronic Illnesses | CHF, lung diseases (e.g. COPD, sarcoidosis), renal failure, chronic liver disease |
| A | Autoimmune  | SLE, RA, mixed connective tissue disease, polyarthritis rheumatica |
| T | Toxin       | Hypothyroidism, diabetes, Cushing’s syndrome, adrenal insufficiency, pregnancy |
| E | Endocrine   | Any malignancy |

Common causes are in **bold**

Investigations
- Psychosocial causes are common, so usually minimal investigation is warranted
- Physical causes of fatigue usually have associated symptoms/signs that can be elicited from a focused history and physical examination
- Investigations should be guided by history and physical and may include:
  - CBC and differential, electrolytes, BUN, Cr, ESR, glucose, TSH, ferritin, vit B12, serum protein electrophoresis, Bence-Jones, albumin, AST, ALT, ALP, bilirubin, calcium, phosphate, ANA, β-hCG
  - Urinalysis, CXR, ECG
  - Additional tests: serologies (Lyme disease, hepatitis B and C screen, HIV, ANA) and Mantoux skin tests

Treatment
- Treat underlying cause
- If etiology cannot be identified (1/3 of patients)
  - Reassurance and follow-up, especially with fatigue of psychogenic etiology
  - Quick follow-up for reassurance
  - Supportive counselling, behavioural, or group therapy
  - Encourage patient to stay physically active to maximize function
  - Review all medications, OTC, and herbal remedies for drug-drug interactions and side effects
  - Prognosis: after 1 yr, 40% are no longer fatigued

CHRONIC FATIGUE SYNDROME (CFS)

**Definition (CDC 2006)** - must meet both criteria
1. new or definite onset of unexplained, clinically evaluated, persistent or relapsing chronic fatigue, not relieved by rest, which results in occupational, educational, social, or personal dysfunction
2. Concurrent presence of at least 4 of the following symptoms for a minimum of 6 mo:
   - Impairment of short-term memory or concentration, severe enough to cause significant decline in function
   - Sore throat
   - Tender cervical or axillary lymph nodes
   - Muscle pain
   - Multi-joint pain with no swelling or redness
   - New headache
   - Unrefreshing sleep
   - Post-exertion malaise lasting >24 h
- Exclusion criteria: medical conditions that may explain the fatigue, certain psychiatric disorders (depression with psychotic or melancholic features, schizophrenia, eating disorders), substance abuse, severe obesity (BMI >45)

**Epidemiology**
- F>>>M, Caucasians > other groups, majority in their 30s
- Found in <5% of patients presenting with fatigue

**Etiology**
- Unknown, likely multifactorial
- May include infectious agents, immunological factors, neurohormonal factors, and/or nutritional deficiency

**Exercise Therapy for Chronic Fatigue**
Cochrane Depression, Anxiety, and Neurosis Group Cochrane Database of Systematic Reviews 2004, Issue 4

**Purpose:** To determine the effectiveness of exercise therapy for Chronic Fatigue Syndrome (CFS).

**Methods:** Systematic review of 5 RCTs with 336 patients of all ages with a clinical diagnosis of CFS.

**Intervention:** Exercise therapy alone was compared with treatment as usual (or relaxation and flexibility), pharmacotherapy (fluoxetine), or exercise therapy combined with either pharmacotherapy or patient education.

**Results:** At 12 wk, patients undergoing exercise therapy were less fatigued than controls (SMD -0.77; 95% CI, -1.26 to -0.28). Physical functioning was also significantly improved, but there were more dropouts with exercise therapy. Compared with fluoxetine, patients receiving exercise therapy were less fatigued (WMD -1.24; 95% CI, -5.31 to 2.83). Patients receiving combination therapy with exercise therapy and either fluoxetine or patient education, did better than those on monotherapy.

**Conclusions:** Patients may benefit from exercise therapy. Combination therapy with either fluoxetine or education may offer additional benefit. Further high quality trials are needed.
**Investigations**
- no specific diagnostic laboratory tests

**Treatment**
- promote sleep hygiene
- provide support and reassurance that most patients improve over time
- non-pharmacological
  - regular physical activity, optimal diet, psychotherapy (e.g. CBT), family therapy, support groups
- pharmacological
  - to relieve symptoms: e.g. antidepressants, anxiolytics, NSAIDs, antimicrobials, antiallergy therapy, antihypotensive therapy

---

**Fever**

- see *Pediatrics*, P54, for fever in pediatric population

**Definition**
- oral temperature >37.2°C (AM), 37.7°C (PM)
- fever in children under 2 must be a rectal temperature for accuracy
- TM not accurate for measurement until child is over the age of 5

**Table 26. Differential Diagnosis of Fever**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Cancer</th>
<th>Medications</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>Leukemia</td>
<td>Allopurinol</td>
<td>Nifedipine</td>
</tr>
<tr>
<td>Viral</td>
<td>Lymphoma</td>
<td>Captopril</td>
<td>Phenytion</td>
</tr>
<tr>
<td>TB</td>
<td>Other Malignancies</td>
<td>Cimetidine</td>
<td>Diuretics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heparin</td>
<td>Barbiturates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INH</td>
<td>Antihistamines</td>
</tr>
</tbody>
</table>

**History**
- fever
  - peak temperature, thermometer, route, duration
  - time of day
  - response to antipyretics
- systemic symptoms
  - weight loss, fatigue, rash, arthralgia, night sweats
- symptoms of possible source
  - UTI/pyelonephritis: dysuria, foul-smelling urine, incontinence, frequency, hematuria, flank pain
  - pneumonia: cough, pleuritic chest pain
  - URTI: cough, coryza, ear pain
  - meningitis: headache, confusion, stiff neck, rash
  - osteomyelitis: bone pain
  - skin: purulent discharge
  - PID: discharge, dyspareunia, lower abdominal pain
  - gastroenteritis: abdominal pain, diarrhea, blood per rectum, vomit
  - medications
  - PE/DVT: swollen legs, pain in calf, shortness of breath, pleuritic chest pain
  - history of cancer/family history of cancer
- infectious contacts
  - travel history, camping, day care, contact with TB, foodborne, animals

**Investigations**
- CBC and differential, blood culture, urine culture, urinalysis
- stool O&P, Gram stain, culture
- CXR, Mantoux skin test, sputum culture
- LP

**Management**
- increase fluid intake
- general: sponge bath, light clothing
- acetaminophen/ibuprofen as needed
- treat underlying cause

---

**Mean Body Temperature**
- Oral = 36.8°C
- Tympanic Membrane = 36.4°C
- Rectal = 37.2°C
- Diurnal Variation = 0.5°C higher at 4 pm vs. 6 am
- See *Pediatrics*, P54 for normal temperature in children
Joint Pain

- see Rheumatology, RH3

Table 27. Differential Diagnosis of Joint Pain

<table>
<thead>
<tr>
<th>Non-Articular</th>
<th>Generalized</th>
<th>Inflammatory</th>
<th>Articular</th>
<th>Degenerative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td></td>
<td>Seropositive</td>
<td>Primary</td>
<td></td>
</tr>
<tr>
<td>Bursitis</td>
<td>Fibromyalgia</td>
<td>Rheumatoid arthritis</td>
<td>Familial Heberden’s node</td>
<td></td>
</tr>
<tr>
<td>Tendonitis</td>
<td>Polymyalgia rheumatica</td>
<td>Systemic lupus erythematosus</td>
<td>Osteoarthritis</td>
<td></td>
</tr>
<tr>
<td>Capsulitis</td>
<td></td>
<td>Scleroderma</td>
<td>Regional hip or knee</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polymyositis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sjogren’s syndrome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Articular</th>
<th>Degenerative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seronegative</td>
<td></td>
<td>Secondary</td>
</tr>
<tr>
<td></td>
<td>Anklylosing spondylitis</td>
<td>Metabolic</td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease</td>
<td>Hemophilic</td>
</tr>
<tr>
<td></td>
<td>Psoriatic arthritis</td>
<td>Neuropathic</td>
</tr>
<tr>
<td></td>
<td>Reactive arthritis</td>
<td>Traumatic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Crystal</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gout</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudogout</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milwaukee shoulder, calcific periarthritis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

History
- number of joints involved: monoarticular, oligoarticular, polyarticular
- pattern of joints involved: symmetrical vs. asymmetrical, large vs. small joints, axial skeleton
- onset: acute vs. chronic (>6 wk)
- trauma, infection, medications (steroids, diuretics)
- FHx of arthritis
- co-morbidities: diabetes mellitus (carpal tunnel syndrome), renal insufficiency (gout), psoriasis (psoriatic arthritis), myeloma (low back pain), osteoporosis (fracture), obesity (OA)
- constitutional symptoms (neoplasm)

Physical Exam
- vitals
- specific joint exams
- systemic features (skin, nails, eyes, hands)

Investigations
- CBC and differential, ESR, CRP, RF, ANA, HLA-B27, serum uric acid, calcium
- urinalysis
- tissue cultures
- x-ray
- joint aspirate for cell count + differential, culture, Gram stain, microscopy

Treatment
- patient education including lifestyle modifications
- physiotherapy, occupational therapy
- manage pain (acetaminophen, NSAIDs)
- treat specific causes (antibiotics, DMARDs)
Headache

Primary Headaches

Table 28. Primary Headaches

<table>
<thead>
<tr>
<th>Migraine</th>
<th>Tension-type</th>
<th>Cluster</th>
<th>Caffeine Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>12% of adults</td>
<td>38% of adults, can be episodic or chronic</td>
<td>&lt;0.1% of adults, M&gt;&gt;F</td>
</tr>
<tr>
<td>Duration</td>
<td>5-72 h</td>
<td>May occur as isolated incident or daily, duration is variable</td>
<td>&lt;3 h at same time of day</td>
</tr>
<tr>
<td>Pain</td>
<td>Classically unilateral and pulsatile, but 40% are bilateral, moderate-severe intensity, nausea/vomiting, photo-/phonophobia</td>
<td>Mild to moderate pain, bilateral, fronto-occipital or generalized pain, band-like pain, ± contracted neck/scalp muscles, associated with little disability</td>
<td>Sudden, unilateral, severe, usually centered around eye, frequently awakens patient</td>
</tr>
<tr>
<td>Triggers</td>
<td>Numerous (e.g., food, sleep disturbance, stress, hormonal, fatigue, weather, high altitude) Aggravated by physical activity</td>
<td>Stressful events, NOT aggravated by physical activity</td>
<td>Often alcohol</td>
</tr>
<tr>
<td>Treatment of Acute Headache</td>
<td>1st line: acetaminophen, ASA ± caffeine</td>
<td>Rest and relaxation</td>
<td>Sumatriptan</td>
</tr>
<tr>
<td></td>
<td>2nd line: NSAIDs</td>
<td></td>
<td>Dihydroergotamine</td>
</tr>
<tr>
<td></td>
<td>3rd line: 5HT agonists ± antiemetic</td>
<td></td>
<td>High-flow O2</td>
</tr>
<tr>
<td>Prophylactic Therapy</td>
<td>1st line: β-blockers</td>
<td>Rest and relaxation</td>
<td>Lithium carbonate, prednisone, methysergide</td>
</tr>
<tr>
<td></td>
<td>2nd line: TCAs</td>
<td>physical activity, biofeedback</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3rd line: anticonvulsants</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Secondary Headaches

- caused by underlying organic disease
- account for <10% of all headaches, may be life-threatening
- etiology
  - aneurysm
  - space-occupying lesion
  - systemic infection (meningitis, encephalitis)
  - stroke
  - subarachnoid hemorrhage
  - systemic disorders (thyroid disease, hypertension, pheochromocytoma, etc.)
  - temporal arteritis
  - traumatic head injuries
  - TMJ or C-spine pathology
  - serious ophthalmological and otolaryngological causes of headache
- treatment
  - based on underlying disorder
  - analgesics may provide symptomatic relief

Investigations

- indicated only when red flags are present and may include:
  - CBC for suspected systemic or intracranial infection
  - ESR for suspected temporal arteritis
  - neuroimaging (CT or MRI) to rule out intracranial pathology
  - CSF analysis for suspected intracranial hemorrhage, infection
Hearing Impairment

- see Otolaryngology, OT9

**Definition**
- hearing impairment: a raised hearing threshold measured as decibels of hearing loss relative to the normal population at specific frequencies
- hearing disability: hearing impairment that interferes with performing daily tasks

**Epidemiology**
- 10% of the population is hard of hearing or deaf
- 90% of age-related hearing loss (presbycusis) is sensorineural
- hearing loss detectable by audiology is present in greater than 1/3 of people over 65
- associated with significant physical, functional and mental health consequences

**Classification**
- conductive (sound does not reach cochlea)
- sensorineural (sound is not converted or transmitted via neural signals)
- mixed

**Assessment**
- infants
  - universal newborn hearing screening program
- elderly
  - whispered-voice test
    - whisper six test words 6 inches to 2 feet away from the patient’s ear out of the visual field, ask patient to repeat the words (with non-test ear distraction)
  - tuning fork test
  - Rinne and Weber (not for general screening)
  - audioscope
    - delivers pure tone frequencies to obtain thresholds for frequencies of 250-8000 Hz

**Management**
- counsel about noise control and hearing protection programs (grade A evidence)
- refer patients with hearing loss for a complete audiological examination
- hearing amplification (e.g. hearing aids), assistive listening devices, and cochlear implants can dramatically improve quality of life

Hypertension

**Hypertension Guidelines are reviewed and updated annually.**
*For up to date recommendations, please see www.hypertension.ca/chep*

**Epidemiology**
- 20-25% of Canadian adults have HTN (up to 50% undiagnosed)
- 16% of those diagnosed are well controlled
- approximately 50% of adult Canadians are hypertensive by age 60
- 3rd leading risk factor associated with death

**Definition**
- hypertension
  - BP ≥140/90 mmHg, unless DM (≥130/80 mmHg), or age ≥80 yr (≥150/90 mmHg)
- isolated systolic hypertension
  - sBP ≥140 and dBP <90
  - associated with progressive reduction in vascular compliance
  - usually begins in 5th decade
- accelerated hypertension
  - significant recent increase in BP over previous hypertensive levels associated with evidence of vascular damage on fundoscopy but without papilledema
- malignant hypertension
  - sufficient elevation in BP to cause papilledema and other manifestations of vascular damage (retinal hemorrhages, bulging discs, mental status changes, increasing creatinine)
- not defined by absolute level of BP, but often requires BP of >200/140
- hypertensive urgency
  - sBP >210 or dBP >120 with minimal or no target-organ damage
- hypertensive emergency
  - high BP + acute target-organ damage

Symptoms of hypertension are usually NOT PRESENT (this is why it is called the “silent killer”).
May have occipital headache upon awakening or organ specific complaints if advanced disease.
Etiology
• essential (primary) hypertension (>90%)
  ▪ undetermined cause
• secondary hypertension (10%), see Table 29
• watch for labile, “white coat” hypertension (office-induced elevated BP)

Predisposing Factors
• family history
• obesity (especially abdominal)
• alcohol consumption
• stress
• sedentary lifestyle
• smoking
• male gender
• age >30
• excessive salt intake/fatty diet
• African American ancestry
• dyslipidemia

Table 29. Causes of Secondary Hypertension

<table>
<thead>
<tr>
<th>Common Cause</th>
<th>Renal</th>
<th>Endocrine</th>
<th>Vascular</th>
<th>Drug-induced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Renovascular HTN</td>
<td>1º hyperaldosteronism</td>
<td>Coarctation of the aorta</td>
<td>Estrogens</td>
</tr>
<tr>
<td></td>
<td>Renal parenchymal disease, glomerulonephritis, pyelonephritis, polycystic kidney</td>
<td>Pheochromocytoma</td>
<td>Renal artery stenosis</td>
<td>MADI's</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cushing’s syndrome</td>
<td></td>
<td>Cocaine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperthyroidism/hyperparathyroidism</td>
<td></td>
<td>Amphetamines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypercalcemia of any cause</td>
<td></td>
<td>Alcohol</td>
</tr>
</tbody>
</table>

Investigations
• for all patients with hypertension
  ▪ CBC, electrolytes, Cr, fasting glucose and lipid profile, 12-lead ECG, urinalysis
• for specific patient subgroups
  ▪ DM OR renal disease: urinary protein excretion
  ▪ increasing Cr OR history of renal disease OR proteinuria OR HTN resistant to 3 meds OR presence of abdominal bruit: renal ultrasound, captopril renal scan, MRA/CTA
  ▪ if suspected endocrine cause: plasma aldosterone, plasma renin
  ▪ if suspected pheochromocytoma: 24 h urine for metanephrines and catecholamines
  ▪ ECG for left ventricular dysfunction assessment if indicated

Hypertensive Emergencies
• Malignant HTN
• Cerebrovascular:
  ▪ Hypertensive encephalopathy
  ▪ CVA with severe hypertension
  ▪ Intracerebral hemorrhage
  ▪ SAH
• Cardiac:
  ▪ Acute aortic dissection
  ▪ Acute refractory LV failure
  ▪ Acute MI with persistent ischemic pain after CABG
• Renal:
  ▪ Acute glomerulonephritis
  ▪ Renal crises from collagen vascular diseases
  ▪ Severe hypertension following renal transplantation
• Excessive circulating catecholamines:
  ▪ Pheochromocytoma
  ▪ Tyramine containing foods or drug interactions with MAOIs
  ▪ Sympathomimetic drug use (e.g. cocaine)
  ▪ Rebound HTN after cessation of anti-hypertensive drugs (e.g. clonidine)
• Eclampsia
• Surgical:
  ▪ Severe HTN prior to emergent surgery
  ▪ Severe post-op HTN
  ▪ Post-op bleeding from vascular suture lines
• HTN following severe burns
• Severe epistaxis

Causes of Secondary Hypertension
ABCDE
Apnea, Aldosteronism
Bruits, Bad kidneys
Coarctation, Cushing’s, Catecholamines,
Calcemia
Drugs
Endocrine disease
Diagnosis

The Expedited Assessment and Diagnosis of Patients with Hypertension
Focus on Validated Technologies for Blood Pressure Assessment

- Elevated Out-of-the-Office BP Measurement
  - Hypertension Visit 1
    - BP measurement
    - History and physical Examination
    - Diagnostic tests ordering at visit 1 or 2
  - Hypertension Visit 2 within 1 month
    - BP ≥160/110 mmHg
    - OR
    - BP 140-179/90-109 mmHg with target organ damage or diabetes
  - No
  - BP 140-179/90-109 mmHg
  - Elevated Random Office BP Measurement
    - Hypertensive Urgency/Emergency
    - dBP > 120 mmHg or signs of end-organ damage

- Office BPM (OBPM)
  - Hypertension Visit 3
    - ≥160 mmHg sBP or ≥100 mmHg dBP
  - <160 mmHg
    - or
  - <160 mmHg
    - ABPM or HBPM if available
    - Diagnosis of HTN
  - <140 mmHg sBP or ≥90 mmHg dBP
    - Home BPM (HBPM) (if available)
    - Hypertension Visit 4-5
      - ≥140 mmHg sBP or ≥90 mmHg dBP
    - Continue to follow-up
  - <140/90 mmHg
    - Continue to follow-up

- Ambulatory BPM (ABPM) (if available)
  - Awake BP ≥135 mmHg sBP or ≥85 mmHg dBP
    - and
  - ≥24 hour <130/80 mmHg
    - Continue to follow-up
  - <135/85 mmHg
  - Repeat HBPM
  - ≥135 mmHg sBP
  - ≥85 mmHg dBP
    - Diagnosis of HTN

- Diagnosis of HTN

Figure 12. Approach to hypertension
Adapted from: CHEP 2013 Guidelines

Treatment
- target BP is <140/90 mmHg, <130/80 mmHg if DM
- lifestyle modification (in all HTN patients)
  - may be sufficient in patients with stage 1 HTN (140-159/90-99)
  - diet
    - follow Canada’s Guide to Healthy Eating (see Nutrition, FM5) and Dietary Approaches to Stop Hypertension (DASH) (reduced cholesterol and saturated fats)
    - limit daily sodium intake to 65-100 mmol (1.5-2.3 g)
    - potassium/magnesium/calcium supplementations are NOT recommended for HTN
  - moderate intensity dynamic exercise: 30-60 min, 4-7 x/wk; higher intensity exercise is no more effective
  - smoking cessation
  - stress management
  - low-risk alcohol consumption (see Alcohol, FM12)
    - achieve and maintain a healthy BMI and waist circumference; BP will decrease by 4.0/2.8 mmHg for each 4.4 kg of weight loss; use multidisciplinary approach to weight loss
    - individualized cognitive behavioural interventions for stress management
- pharmacological
  - indications regardless of age (caution with elderly patients)
    - dBP ≥90 mmHg with target organ damage or independent cardiovascular risk factors
    - dBP ≥100 mmHg or sBP ≥160 mmHg without target organ damage or cardiovascular risk factors
    - sBP ≥140 with target organ damage

The Effects of Lifestyle Modification on Diet, Weight, Physical Fitness and Blood Pressure Control. 18-month Follow-up Results from the PREMIER Collaborative Research Group
Ann Intern Med 2006;144:485-495

Study: Multicentre, randomized trial.

Patients: 810 adults with prehypertension or stage 1 hypertension (sBP 120-159, dBP 80-95).

Interventions: Multicomponent behavioural intervention using established recommendations (“established”) arm, established recommendations plus the Dietary Approaches to Stop Hypertension (DASH) diet (“established + DASH”) arm, and advice only arm.

Main outcomes: Lifestyle status and blood pressure.

Results: At 18 mo, absolute blood pressures were reduced for both intervention arms compared to advice only but differences were non-significant. The odds for HTN at 18 mo were reduced for both treatment arms compared to advice only. Statistically significant weight loss, fat intake and sodium intake were noted for both treatment arms.

Dieting to Reduce Body Weight for Controlling Hypertension in Adults
Cochrane DB Syst Rev 2008;4:CD000484

A systematic review of 18 trials showed that weight-reducing diets in overweight hypertensive persons can affect modest weight loss in the range of 3-9% of body weight and are probably associated with modest blood pressure decreases of roughly 3 mmHg systolic and diastolic. Weight-reducing diets may decrease dosage requirements of persons taking antihypertensive medications.
• first line antihypertensives: thiazide, ACEI, ARB, CCB, β-blocker (if age <60)
• if partial response to standard dose monotherapy, add another first-line drug
• caution with combination of non-DHP CCB and β-blocker
• combination of ACEI and ARB is not recommended
• if still not controlled or adverse effects, can add other classes of anti-hypertensives

Table 30. Pharmacologic Treatment of Hypertension in Patients with Unique Conditions

<table>
<thead>
<tr>
<th>Condition or Risk Factor</th>
<th>Recommended Drugs</th>
<th>Alternative Drugs</th>
<th>Not Recommended/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated Diastolic HTN</td>
<td>Thiazide diuretic, β-blocker, ACEI, ARB, or long-acting CCB (consider ASA and statin in select patients)</td>
<td>Combinations of first-line drugs</td>
<td>β-blocker monotherapy (age &gt;60) or combination of ACEI with an ARB</td>
</tr>
<tr>
<td>Isolated Systolic HTN</td>
<td>Thiazide diuretic, ARB or long acting dihydropyridine CCB</td>
<td>Combinations of first-line drugs</td>
<td>Same as above</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>ACEI or ARB; β-blocker for patients with stable angina</td>
<td>Long acting CCB, when combination therapy for high risk patients, ACEI/DHP CCB is preferred</td>
<td>Short-acting CCB (nifedipine) or ACEI + ARB is not recommended</td>
</tr>
<tr>
<td>Prior MI</td>
<td>β-blocker + ACEI (ARB if can’t tolerate ACEI)</td>
<td>Long-acting CCB</td>
<td>ACEI + ARB combination is not recommended</td>
</tr>
<tr>
<td>Left Ventricular Hypertrophy</td>
<td>ACEI, ARB, thiazide, or long-acting CCB</td>
<td>Combination of additional agents</td>
<td>Hydralazine and minoxidil can increase LVH, thus not recommended</td>
</tr>
<tr>
<td>Cerebrovascular Disease (stroke/TIA)</td>
<td>ACEI + diuretic</td>
<td>Combination of additional agents</td>
<td>ACEI + ARB combination after a stroke is not recommended</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>ACEI (ARB if ACEI intolerant) and β-blocker</td>
<td>ARB in addition to ACEI. Hydralazine/orosorbide dinitrate combination if ARB or ACEI not tolerated/contraindicated</td>
<td>Non-DHP CCB not recommended. Carefully monitor for side effects if using ACEI + ARB</td>
</tr>
<tr>
<td>Dyslipidemias</td>
<td>Does not affect initial treatment recommendations</td>
<td>Combination of additional agents</td>
<td>ACEI + ARB combination after a stroke is not recommended</td>
</tr>
<tr>
<td>Diabetes Mellitus with Albuminuria (ACR &gt;2.0 mg/mmol in men and &gt;2.8 mg/mmol in women)</td>
<td>ACEI or ARB</td>
<td>Add thiazide diuretic, cardioselective β-blocker, long acting CCB</td>
<td>If serum Cr &gt;150 μmol/L, a loop diuretic should be considered instead of low-dose thiazide diuretic</td>
</tr>
<tr>
<td>Diabetes Mellitus without Albuminuria (criteria listed above)</td>
<td>ACEI, ARB, DHP CCB, or thiazide diuretic</td>
<td>Combination of first-line drugs or, first-line agents not tolerated, cardioselective β-blocker or non-DHP CCB</td>
<td>ACEI + ARB combination not recommended</td>
</tr>
<tr>
<td>Non-diabetic Chronic Kidney Disease with Proteinuria (urinary protein &gt;500 mg/24 h or ACR &gt;30 mg/mmol)</td>
<td>ACEI (ARB if ACEI intolerant), diuretic as additive therapy</td>
<td>Thiazide for additive antihypertensive therapy, loop diuretic for volume overload</td>
<td>ACEI + ARB combination is not recommended</td>
</tr>
<tr>
<td>Renovascular Disease</td>
<td>Same as HTN without other indications</td>
<td></td>
<td>Caution in using ACEI or ARB – monitor for AKI</td>
</tr>
<tr>
<td>Asthma</td>
<td>K+- sparing + thiazide diuretic for patients on salbutamol</td>
<td></td>
<td>β-blocker, unless specific indications like angina or post-MI</td>
</tr>
<tr>
<td>Gout</td>
<td>Thiazide, but asymptomatic hyperuricemia is not a contraindication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Low dose thiazide</td>
<td></td>
<td>β-blocker</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Methyldopa</td>
<td>Hydralazine</td>
<td>Labetolol, nifedipine</td>
</tr>
<tr>
<td>Elderly (≥60)</td>
<td>As for uncomplicated diastolic HTN, except for use of β-blocker</td>
<td></td>
<td>β-blocker not recommended as first line treatment</td>
</tr>
<tr>
<td>Emergency</td>
<td>BP &gt;169/90 = labetolol, nifedipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If ≥3 cardiovascular risk factors or established atherosclerotic disease</td>
<td>Statin, ASA</td>
<td></td>
<td>Caution with use of ASA in patients with uncontrolled BP</td>
</tr>
</tbody>
</table>

Follow-Up
- assess and encourage adherence to pharmacological and non-pharmacological therapy at every visit
- lifestyle modification → q3-6mo
- pharmacological
  - q1-2mo until BP under target for 2 consecutive visits
  - more often for symptomatic HTN, severe HTN, antihypertensive drug intolerance, target
    organ damage
  - q3-6mo once at target BP
- referral is indicated for cases of refractory hypertension, suspected secondary cause or
  worsening renal failure
- hospitalization is indicated for malignant hypertension

Low Back Pain
- see Orthopedics, OR22
- see www.bigbackpain.com for more information

Definition
- acute: <6 wk
- subacute: 6-12 wk
- chronic: >12 wk

Epidemiology
- 5th most common reason for visiting a physician
- lifetime prevalence: 90%
- peak prevalence: age 45-60
- largest WSIB category
- most common cause of chronic disability for individuals <45 yr old
- 90% resolve in 6 wk, <5% become chronic

Etiology
- source of pain can be local, radicular, referred, or related to a psychiatric illness
- 98% are mechanical causes
  - pain is worse with movement, better with rest
  - sprain (ligament), strain (muscle), facet joint degeneration, disc degeneration/herniation,
    spinal stenosis (e.g. spondylolisthesis), compression fracture, pregnancy
- 2% are non-mechanical causes
  - most concerning when pain is worse at rest and does not change with position
  - surgical emergencies:
    - cauda equina syndrome (areflexia, lower extremity weakness, decreased anal tone, saddle
      anesthesia, fecal incontinence, urinary retention), AAA (pulsatile abdominal mass)
  - medical conditions:
    - neoplastic (primary, metastatic, multiple myeloma)
    - infectious (osteomyelitis, TB)
    - metabolic (osteoporosis, osteomalacia, Paget's disease)
    - rheumatologic (ankylosing spondylitis, polymyalgia rheumatica)
    - referred pain (perforated ulcer, pancreatitis, pyelonephritis, ectopic pregnancy, herpes
      zoster)

Physical Exam
- neurologic exam for L4/L5/S1 helps determine level of spinal involvement (power, reflexes,
  sensation)
- posture, gait, ROM and peripheral pulses
- percussion of spine to illicit fracture or infection
- special tests
  - straight leg raise (positive if pain at <70 degrees and aggravated by ankle dorsiflexion),
    positive test is indicative of sciatica
  - crossed straight leg raise (raising of uninvolved leg elicits pain in leg with sciatica), more
    specific than straight leg raise
  - femoral stretch test (patient prone, knee flexed, examiner extends hip) to diagnose L4
    radiculopathy

Investigations
- plain films not recommended in initial evaluation
- if infection/cancer suspected: CBC, ESR
- if neurologic deficits worsening or infection/cancer suspected: consider CT or MRI

Red Flags for Back Pain
- Bowel or bladder dysfunction
- Anesthesia (saddle)
- Constitutional symptoms/malignancy
- Paresthesias
- Age >50 and mild trauma
- IV drug use/infection
- Neurologic deficits

Yellow Flags for Back Pain
- Psychosocial barriers to recovery that may indicate the risk of long-term disability and work loss
  - Belief that pain and activity are harmful
  - Negative or low mood, social withdrawal
  - Problems with claim and compensation
  - History of back pain, time off, and/or other claims
  - Poor job satisfaction
  - Overprotective family or lack of support
  - Persistent pain for 4-6 wk with little to no improvement in symptoms

Indications for Lumbar Spine X-ray
- No improvement after 6 wk
- Fever >38°C
- Unexplained weight loss
- Prolonged corticosteroid use
- Significant trauma
- Progressive neurological deficit
- Suspicion of ankylosing spondylitis
- History of cancer (rule out metastases)
- Alcohol/drug abuse (increased risk of osteomyelitis, trauma, fracture)
Menopause/Hormone Replacement Therapy (HRT)

- see Gynecology, GY32

Epidemiology

- mean age of menopause = 51.4 yr
- a woman will spend over 1/3 of her life in menopause

Clinical Features

- associated with estrogen deprivation
- urogenital tract: atrophy, vaginal dryness/itching, urinary frequency/urgency/incontinence, bleeding
- blood vessels and heart: vasomotor instability (e.g., hot flashes), increased risk of heart disease
- bones: bone loss, joint/muscle/back pain, fractures, loss of height
- brain: depression, irritability, mood swings, memory loss
Management
- encourage physical exercise, smoking cessation, and a balanced diet with adequate intake/supplementation of calcium (1200-1500 mg/d) and vitamin D (800-2000 IU/d)
- hormone replacement therapy (HRT)
  - prescribe for moderate to severe symptoms for no longer than 5 yr; routine use is not recommended
  - regimens: cyclic estrogen-progestin, continuous estrogen-progestin, estrogen only (if no uterus), estrogen patch/gel/cream/ring/vaginal tablet
- decreases risk of osteoporotic fractures, colorectal cancer
- increases risk of breast cancer, coronary heart disease, stroke, DVT, and PE
- initiation of HRT requires a thorough discussion of short- and long-term benefits and risks
- consider venlafaxine, SSRIs, or gabapentin to ease vasomotor instability

Osteoarthritis

- see Rheumatology, RH5

Epidemiology
- most common form of arthritis seen in primary care
- prevalence is 10-12% and increases with age
- results in long-term disability in 2-3% of patients with OA
- almost everyone over the age of 65 shows signs of OA on x-ray, but only 33% of these individuals will be symptomatic

Clinical Features
- joint pain with activity, improved with rest, morning stiffness or gelling <30 min
- deformity, bony enlargement, crepitus, limitation of movement, peri-articular muscle atrophy
- usually affects distal joints of hands, spine, hips, and knees

Investigations
- no laboratory tests for the diagnosis of OA
- hallmark radiographic features: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes

Management
- goals: relieve pain, preserve joint motion and function, prevent further injury
  - conservative
    - patient education, weight loss, low-impact exercise (OT/PT), assistive devices (e.g. canes, orthotics, raised toilet seats)
  - pharmacological
    - consider comorbidities such as PUD, HTN, IHD, hepatic disease, and renal disease
    - medications do not alter natural course of OA
    - 1st line: acetaminophen up to 4 g/d (OA is not an inflammatory disorder)
    - 2nd line: NSAIDs in the lowest effective dose for the shortest duration of time, along with gastroprotection; COX-2 selective inhibitors (celecoxib/Celebrex®, Meloxicam/Mobicox®) are recommended if long-term treatment or if high risk for serious GI problems
    - combination analgesics (e.g. acetaminophen and codeine)
    - intra-articular corticosteroid injections (no more than 3-4x/yr) may be helpful in acute flares (benefits last 4-6 wk, can be up to 6 mo)
    - topical NSAID (diclofenac/Pennsaid®)
    - capsaicin cream (Zostrix®)
    - oral glucosamine
  - surgery
    - consider if persistent significant pain and functional impairment despite optimal pharmacotherapy (e.g. debridement, osteotomy, total joint arthroplasty)

Osteoporosis

- see Endocrinology, E42

for current guidelines see www.osteoporosis.ca
- age-related disease characterized by decreased bone mass and increased susceptibility to fractures
- affects 1 in 4 Canadian women and 1 in 8 Canadian men
Encourage basic bone health for all individuals over age 50, including regular active weight-bearing exercise, calcium (diet and supplements) 1200 mg daily, vitamin D 800-2000 IU (20-50 µg) daily and fall-prevention strategies

Table 32. First-line Therapies with Evidence for Fracture Prevention in Postmenopausal Women

<table>
<thead>
<tr>
<th>Type of Fracture</th>
<th>Antiresorptive Therapy</th>
<th>Bone Formation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bisphosphonates</td>
<td>Denosumab</td>
</tr>
<tr>
<td>Vertebral</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hip</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Non-vertebral</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Adapted from CMAJ 2010;182:1864-1873

Disorders Strongly Associated with Osteoporosis include:
- Primary hyperparathyroidism, DM1, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (≤45 yr).
- Cushing’s disease, chronic malnutrition or malabsorption, chronic liver disease, COPD and chronic inflammatory conditions (e.g. IBD)

10-yr Fracture Risk Assessment
FRAX (WHO Fracture Risk Assessment Tool) and CAROC (Canadian Association of Radiologists and Osteoporosis Canada) have been validated in the Canadian Population

How much Calcium do we Need?
- 4-8 1000 mg
- 9-18 1300 mg
- 19-50 1200 mg
- >50 1200 mg
- Pregnant and lactating women 1000 mg

Calcium Content of Common Foods
- 1 cup milk = 300 mg
- ¼ cup yogurt = 332 mg
- ⅓ can salmon with bones = 240 mg
- ½ cup cooked broccoli = 33 mg
- 1 medium orange = 50 mg

Vitamin D Content of Common Foods
- Milk fortified with vitamin D3 contains 100 IU/s per 250 mL glass.
- Foods such as margarine, eggs, chicken livers, salmon, sardines, herring, mackerel, swordfish and fish oils (halibut and cod liver oils) all contain small amounts.
- Supplementation is necessary to obtain adequate levels as dietary intake has minimal impact.
- Most multivitamins provide 400 IU of vitamin D3

Figure 14. 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada (integrated management model). Adapted from CMAJ 2010;182:1864-1873

Management
- Falls prevention: home safety assessment, optimize vision (e.g. cataract removal), consider hip protectors in older adults living in long-term care facilities
- Exercise: weight-bearing, balance, and strengthening exercises as appropriate for the patient’s age and functional capacity
- Habits: smoking cessation, decrease alcohol intake
- Diet: calcium 1200 mg/d through diet and supplements; vitamin D 400-1000 IU/d if healthy and at low risk of deficiency, 800-2000 IU/d if >50 yr and moderate risk of deficiency
- Pharmacological
  - Vertebral, hip, and non-vertebral fractures: bisphosphonates (alendronate, risedronate, zoledronate), monoclonal Ab (denosumab), estrogen (first line in women with menopausal symptoms)
  - Vertebral fractures only: SERM (raloxifene)
• for postmenopausal women, ✓ indicates first-line therapies (grade A)
• for men, alendronate, risedronate, and zoledronate can be used as first-line therapies for prevention of fractures (grade D)
• non-vertebral fractures: hip, femur, pelvis, tibia, humerus, radius, clavicle
• estrogen can be used as first-line therapy in women with menopausal symptoms but the risks may outweigh the benefits (see Gynecology, GY33)
• reflux, esophagitis, and esophageal ulcers are the major side effects of oral bisphosphonates

Rash
• see Dermatology, D5

**ATOPIC DERMATITIS**
• clinical features
  - affects all ages but is more common in children
  - pruritus is the most common symptom; scratching worsens the rash, creating a vicious cycle
• treatment
  - goals: limit itching, repair skin
  - moisturizers, emollients, topical corticosteroids; oral corticosteroids and topical calcineurin inhibitors may be used

**SEBORRHEIC DERMATITIS**
• clinical features
  - affects all ages but is most common in infants within the first 3 months of life (e.g. pityriasis capitis or "cradle cap") and adults age 30-60 yr
  - affects the scalp, central face, and anterior chest; often presents as scalp scaling (dandruff) in adolescents and adults
  - may cause mild to marked erythema of the nasolabial fold, often with greasy scaling
• treatment
  - topical antifungals, topical low-potency steroids; topical calcineurin inhibitors may be used

**ROSACEA**
• clinical features
  - stages: (1) facial flushing, (2) erythema and/or edema and ocular symptoms, (3) papules and pustules, (4) rhinophyma
• treatment
  - topical or oral antibiotics, oral retinoids
  - laser treatment may be an option for progressive telangiectasis or rhinophyma
  - referral may be required to manage rhinophyma, ocular complications, or severe disease

**ACNE VULGARIS**
• clinical features
  - types: (I) comedonal, (II) papular, (III) pustular, (IV) nodulocystic
  - predilection for the face, neck, upper chest, and back
• treatment
  - mild acne: topical treatments (antibiotics, benzoyl peroxide, retinoids)
  - moderate acne: after topical treatments have failed, add oral antibiotics and consider hormonal therapy
  - severe acne: consider systemic retinoids

**ONYCHOMYCOSIS (TINEA UNGUIUM)**
• definition: fungal infection of the nail bed, matrix, or plate
• clinical features
  - occurs primarily in adults, most commonly after age 60 yr
  - crumbling, distally dystrophic nails; yellowish, opaque with subungual hyperkeratotic debris; toenails are affected more often than fingernails
• investigations
  - microscopy of subungual scrapings under KOH preparation, culture
• treatment
  - oral antifungals (terbinafine/Lamisil®, itraconazole/Sporanox®), topical antifungals (ciclopirox/Loprox®)
## Rhinorrhea

- see [Otolaryngology, OT22](#)

### Differential Diagnosis
- common cold, sinusitis, influenza, strep pharyngitis, ear infection, vasomotor rhinitis
- allergies, contact with substances, tearing
- foreign body
- opioid withdrawal
- basilar skull fracture

### Investigations
- CBC, throat swab, nasopharyngeal swab, x-ray if injury, allergy testing

### Management
- nasal saline rinse
- consider medications: antihistamines, decongestants, corticosteroid nasal spray

---

## Sexually Transmitted Infections (STIs)

- see [Gynecology, GY26](#)

### Definition
- diverse group of infections caused by multiple microbial pathogens
- transmitted by either secretions or fluids from mucosal surfaces

### Epidemiology
- high incidence rates worldwide
- Canadian prevalence in clinical practice
  - common: chlamydia (most common), gonorrhea (2nd most common), HPV, genital herpes (increasing incidence of chlamydia and gonorrhea)
  - less common: hepatitis B, HIV and syphilis (both increasing in incidence), trichomoniasis
  - rare: chancroid, granuloma inguinale, lymphogranuloma venereum
- non-sexually transmitted genital tract infections: vulvovaginal candidiasis (VVC), bacterial vaginosis (BV)
- three most common infections associated with vaginal discharge in adult women are BV, VVC, and trichomoniasis

### History
- sexual history
  - age of first intercourse, sexual orientation, sexual activity (oral, anal, and/or vaginal intercourse), sexual activity during travel
  - total number of partners in the past year/month/week and duration of involvement with each
- STI history
  - STI awareness, contraception, previous STIs and testing (including pap tests), partner communication regarding STIs
  - local symptoms such as burning, itching, discharge, sores, vesicles, testicular pain, dysuria, abdominal pain
  - systemic symptoms such as fever, lymphadenopathy, arthralgia

### Investigations/Screening
- individuals at increased risk, even those who are asymptomatic, should be screened for chlamydia, gonorrhea, hepatitis B, HIV, and syphilis
- Pap test if none performed in the preceding 12 mo

### Management
- primary prevention is vastly more effective than treating STIs and their sequelae
- offer hepatitis B vaccine if not immune, offer Gardasil® to women under age 26
- discuss STI risk factors (e.g. decreasing the number of sexual partners)
- direct advice to ALWAYS use condoms or to abstain from intercourse
- condoms are not 100% effective against HPV or HSV
- an STI patient is not considered treated until the management of his/her partner(s) is ensured
- patients should abstain from sexual activity until treatment completion and for 1 mo afterwards or until test of cure completed
- mandatory reporting: chlamydia, gonorrhea, hepatitis B, HIV, syphilis

---

**Prophylactic Vaccination Against Human Papillomavirus Infection and Disease in Women: A Systematic Review of Randomized Controlled Trials**

*CMAJ 2007;177:469-479*

**Purpose:** To evaluate prophylactic HPV vaccination in preventing high- and low-grade cervical lesions, persistent HPV infection, external genital lesions, adverse events, and death using meta-analysis.

**Studies:** 9 reports from 6 different trials with 40,323 patients were included and all studies were of high methodologic quality. Three studies used the quadrivalent vaccine, two used the bivalent, and one used a monovalent. The longest mean duration of follow-up was 48 mo.

**Results:** Prophylactic HPV vaccination decreased the frequency of high-grade cervical lesions caused by vaccine-type HPV strains compared to the control group (OR 0.14 (95% CI 0.09-0.21)). Vaccinations also prevented persistent HPV infection, low-grade lesions and genital warts and the reported adverse events were mostly minor. Compared to placebo, there was no difference in serious adverse events or death.

**Conclusion:** Prophylactic HPV vaccination is highly efficacious in preventing infection and precancerous cervical disease in women aged 15-25 who have not previously been infected with vaccine-type HPV strains.
Management of Acute Sinusitis

- may provide symptom relief: oral analgesics (acetaminophen, NSAIDs), nasal saline rinse, short-term use of topical or oral decongestants
- do not prescribe antihistamines
- intra-nasal corticosteroids if diagnosed with mild to moderate acute bacterial sinusitis
- antibiotics and intra-nasal corticosteroids if diagnosed with severe acute bacterial sinusitis
- ENT referral if: anatomic defect (e.g. deviated septum, polyp, adenoid hypertrophy), failure of second-line therapy, ≥4 episodes/yr, development of complications (e.g. mucocele, orbital extension, meningitis, intra-cranial abscess, venous sinus thrombosis)


don't prescribe antihistamines
intra-nasal corticosteroids if diagnosed with mild to moderate acute bacterial sinusitis
antibiotics and intra-nasal corticosteroids if diagnosed with severe acute bacterial sinusitis
ENT referral if: anatomic defect (e.g. deviated septum, polyp, adenoid hypertrophy), failure of second-line therapy, ≥4 episodes/yr, development of complications (e.g. mucocele, orbital extension, meningitis, intra-cranial abscess, venous sinus thrombosis)
Figure 15. Diagnosis and management of sinusitis
ABRS = acute bacterial rhinosinusitis

Sleep Disorders

- see Respirology, R31 and Neurology, N41

Definition
- most often characterized by one of three complaints:
  - insomnia
    - difficulty falling asleep, difficulty maintaining sleep, early-morning wakening, non-refreshing sleep
  - parasomnias
    - night terrors, nightmares, restless leg syndrome, somnambulism (performing complex behaviour during sleep with eyes open but without memory of event)
  - excessive daytime sleepiness

Epidemiology
- 1/3 of patients in primary care setting have occasional sleep problems, 10% have chronic sleep problems
Etiology
- primary sleep disorders
  - primary insomnia, narcolepsy, obstructive sleep apnea, restless leg syndrome, periodic limb movements of sleep
- secondary causes
  - medical: COPD, asthma, CHF, hyperthyroidism, chronic pain, BPH, menopause, GERD, PUD
  - drugs: alcohol, caffeine, nicotine, nicotine replacement therapy, β-agonists, antidepressants, steroids
  - psychiatric: especially mood and anxiety disorders
  - lifestyle factors: shift work

Investigations
- complete sleep diary every morning for 1-2 wk
  - record bedtime, sleep latency, total sleep time, awakenings, quality of sleep
- rule out specific medical problems (e.g. CBC and differential, TSH)
- refer for sleep study, nocturnal polysomnogram, or daytime multiple sleep latency test if suspicion of sleep apnea or periodic leg movements of sleep

Treatment
- treat any suspected medical or psychiatric cause
- psychologic treatment
  - sleep hygiene: avoid alcohol, caffeine, nicotine; comfortable sleep environment; regular sleep schedule; no napping
  - exercise regularly, avoid heavy exercise within 3 h of bedtime
  - relaxation therapy: deep breathing, meditation, biofeedback
  - stimulus control therapy: re-association of bed/bedroom with sleep, re-establishment of a consistent sleep-wake schedule, reduce activities that cue staying awake
  - sleep restriction therapy: total time in bed should closely match the total sleep time of the patient (improves sleep efficacy)
  - CBT: address inappropriate beliefs and attitudes that perpetuate dysfunctional sleep
- pharmacologic treatment
  - short-acting benzodiazepines (e.g. lorazepam, oxazepam, temazepam) at the lowest effective dose should be used <7 consecutive nights to break cycle of chronic insomnia or to manage an exacerbation of previously controlled primary insomnia
  - non-benzodiazepines: zopiczone (Imovane®)
  - F/U every 2-4 wk initially (to reinforce behavioural interventions and renew/consider pharmacotherapy) then every 3 mo; if no progress or limited improvement, consider referral to sleep medicine program

Specific Problems
- primary insomnia
  - majority of cases
  - person reacts to insomnia with fear or anxiety around bedtime or with a change in sleep hygiene, which can progress to a chronic disorder (psychophysiological insomnia)
- snoring
  - results from soft tissue vibration at the back of the nose and throat due to turbulent airflow through narrowed air passages
  - physical exam: obesity, nasal polyps, septal deviation, hypertrophy of the nasal turbinates, enlarged uvula and tonsils
  - investigations (only if severely symptomatic): nocturnal polysomnography and airway assessment (CT/MRI)
  - treatment
    - sleep on side (position therapy), weight loss
    - nasal dilators (noninvasive external dilator made with elastic adhesive backing applied over nasal bridge), tongue-retaining devices, mandibular advancement devices
    - at risk of developing obstructive sleep apnea
- obstructive sleep apnea (OSA)
  - apnea (no breathing for ≥10 s) resulting from upper airway obstruction due to collapse of the base of the tongue, soft palate with uvula, and epiglottis; respiratory effort is present; leads to a distinctive snorting, choking, awakening type pattern as the body rouses itself to open the airway (resuscitative breath)
  - apneic episodes can last from 20 s to 3 min and occur 100-600 episodes/night
  - diagnosis is based on nocturnal polysomnography: >15 apneic/hypopneic episodes per hour of sleep with arousal recorded
  - consequences
    - daytime somnolence, non-restorative sleep
    - poor social and work performance

Risk Factors for Insomnia
- Older age
- Female
- Unemployed or less educated
- Separated or divorced
- Medical comorbidities
- Depression
- Anxiety
- Substance abuse

Risk Factors for Snoring
- Male
- Obesity
- Alcohol consumption
- Smoking
- Use of tranquilizers or muscle relaxants

Risk Factors for Obstructive Sleep Apnea
- 2% of women, 4% of men between ages 30-60
- Obesity (due to upper airway narrowing), BMI ≥28 kg/m² present in 60-90% of cases
- Children (commonly due to large tonsils and adenoids)
- Aging (due to decreased muscle tone)
- Persistent URI's, allergies, nasal tumours, hypothryoidism (due to macroglottis), neuromuscular disease
- Family history
• mood changes: anxiety, irritability, depression
• sexual dysfunction: poor libido, impotence
• morning headache (due to hypercapnia)
• HTN (2x increased risk), CAD (3x increased risk), stroke (4x increased risk), arrhythmias
• pulmonary HTN, right ventricular dysfunction, cor pulmonale (due to chronic hypoxemia)
• memory loss, decreased concentration, confusion

• investigations
  • evaluate BP, inspect nose and oropharynx (enlarged adenoids or tonsils)
  • blood gas not helpful, TSH if clinically indicated
  • nocturnal polysomnography

• treatment
  • modifiable factors: avoid sleeping supine; weight loss; avoid alcohol, sedatives, opioids; inhaled steroids if nasal swelling present; dental appliances to modify mandibular position
  • primary treatment of OSA is CPAP: maintains patent airway in 95% of OSA cases
  • surgery: somnoplasty, uvulopalatopharyngoplasty (UPPP), tonsillectomy and adenoidectomy (in children)
  • report patient to Ministry of Transportation if OSA is not controlled by CPAP

• central sleep apnea
  • definition
    • brain fails to send appropriate signals to the breathing muscles to initiate respirations
    • defining feature is absent respiratory effort
  • often secondary to CNS diseases: brainstem infarction, infection, neuromuscular disease
  • investigations: PFTs, nocturnal polysomnography, MRI
  • treatment: CPAP or mechanical ventilation (if brainstem origin)
  • prognosis: poor

---

Sore Throat (Pharyngitis)

**Definition**
- inflammation of the oropharynx
- may be caused by a wide range of infectious organisms, most of which produce a self-limited infection with no significant sequelae

**Etiology**
- viral: adenovirus, rhinovirus, influenza virus, RSV, EBV, coxsackie virus, herpes simplex virus, CMV, HIV
- bacterial: group A β-hemolytic Streptococcus (GABHS), group C and G β-hemolytic Streptococcus, Neisseria gonorrhoeae, Chlamydia pneumoniae, Mycoplasma pneumoniae, Corynebacterium diphtheriae

**Epidemiology**
- viral
  - most common cause, occurs year round
- bacterial
  - GABHS
    - most common bacterial cause
    - occurs most often in winter months
    - 5-15% of adult cases and up to 50% of all pediatric cases of acute pharyngitis
    - most prevalent between 5-17 yr old

**Clinical Features**
- viral
  - pharyngitis, conjunctivitis, rhinorrhea, hoarseness, cough
  - nonspecific flu-like symptoms such as fever, malaise, and myalgia
  - often mimics bacterial infection
  - EBV (infectious mononucleosis)
    - pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash
  - coxsackie virus (hand, foot and mouth disease)
    - primarily late summer, early fall
    - sudden onset of fever, pharyngitis, headache, abdominal pain and vomiting
    - appearance of small vesicles that rupture and ulcerate on soft palate, tonsils, pharynx
    - ulcers are pale grey and several mm in diameter, have surrounding erythema, and may appear on hands and feet
  - herpes simplex virus
    - like coxsackie virus but ulcers are fewer and larger
    - pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash

---

Red Flags in Patients with “Sore Throat”
- Persistence of symptoms longer than 1 wk without improvement
- Respiratory difficulty (particularly stridor, croup, etc.)
- Difficulty in handling secretions (peritonsillar abscess)
- Difficulty in swallowing (Ludwig’s angina)
- Severe pain in the absence of erythema (supraglottitis/epiglottitis)
- Palpable mass (neoplasm)
- Blood in the pharynx or ear (trauma)
• bacterial
  ▪ symptoms: pharyngitis, fever, malaise, headache, abdominal pain, absence of cough
  ▪ signs: fever, tonsillar or pharyngeal erythema/exudate, swollen/tender anterior cervical nodes, halitosis
  ▪ complications: rheumatic fever, glomerulonephritis, suppurative complications (abscess, sinusitis, otitis media, cervical adenitis, pneumonia), meningitis, impetigo

Investigations
• suspected GABHS
  ▪ see Table 34 for approach to diagnosis and management of GABHS
  ▪ gold standard for diagnosis is throat culture
  ▪ rapid test for streptococcal antigen: high specificity (95%) but low sensitivity (50-90%)
  ▪ suspected EBV (infectious mononucleosis)
    ▪ peripheral blood smear, heterophile antibody test (i.e. the latex agglutination assay or "monospot")

Table 34. Modified Centor Score: Approach to Diagnosis and Management of GABHS

<table>
<thead>
<tr>
<th>POINTS</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chance patient has strep</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough absent?</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of fever &gt;38ºC?</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonsillar exudate?</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swollen, tender anterior nodes?</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 3-14 yr?</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 15-44 yr?</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;45 yr?</td>
<td>–1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In communities with moderate levels of strep infection (10-20% of sore throats):

<table>
<thead>
<tr>
<th>Score</th>
<th>0-1-2.5%</th>
<th>5-10%</th>
<th>11-17%</th>
<th>28-35%</th>
<th>51-53%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested action</td>
<td>NO culture or antibiotic</td>
<td>Culture all, treat with antibiotics only if culture is positive</td>
<td>Culture all, treat with antibiotics on clinical grounds 1, discontinue antibiotics if culture comes back negative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1Clinical grounds include a high fever or other indicators that the patient is clinically unwell and is presenting early in the course of the illness
Limitations: 1) This score is not applicable to patients less than 3 yr of age
2) If an outbreak or epidemic of illness caused by GABHS is occurring in any community, the score is invalid and should not be used

Management
• viral pharyngitis
  ▪ antibiotics not indicated
  ▪ symptomatic therapy: acetaminophen/NSAIDs for fever and muscle aches, decongestants
• GABHS (see Table 34)
  ▪ antibiotic treatment decreases severity and duration of symptoms, risk of transmission (after 24 h of treatment), and risk of rheumatic fever and suppurative complications
  ▪ incidence of glomerulonephritis is not decreased with antibiotic treatment
  ▪ no increased incidence of rheumatic fever with 48 h delay in antibiotic treatment; if possible, delay antibiotic treatment until culture confirms diagnosis
  ▪ routine F/U and/or post-treatment throat cultures are not required for most patients
  ▪ F/U throat culture only recommended for: patients with history of rheumatic fever, patients of family member(s) with history of acute rheumatic fever, suspected streptococcal carrier
• infectious mononucleosis (EBV)
  ▪ self-limiting course; antibiotics are not indicated
  ▪ symptomatic treatment: acetaminophen/NSAIDs for fever, pharyngitis, malaise
  ▪ avoid heavy physical activity and contact sports for at least one month or until splenomegaly resolves because of risk of splenic rupture
  ▪ if acute airway obstruction, give corticosteroids and consult ENT
Epidemiology
- 50-75% of Canadians report some use of CAM over their lifetime, and only half will disclose this use to their physician
- use is highest in Western provinces and lowest in Atlantic provinces
- more likely to be used by younger patients and those with higher education and income
- examples: chiropractic, acupuncture, massage, naturopathy, homeopathy, traditional Chinese medicine, craniosacral therapy, osteopathy

Herbal Products
- over 50% of Canadians use natural health products (NHPs)
- most commonly used include echinacea, ginseng, ginkgo, garlic, St. John’s Wort, and soy
- relatively few herbal products have been shown to be effective in clinical trials
- many patients believe herbal products are inherently safe and are unaware of potential side effects and interactions with conventional medicines
- all NHPs must be regulated under The Natural Health Products Regulations as of January 1, 2004, including herbal remedies, homeopathic medicines, vitamins, minerals, traditional medicines, probiotics, amino acids, and essential fatty acids (e.g. omega-3)
- always ask patients whether they are taking any herbal product, herbal supplement, or other natural remedy. Further questions may include:
  - are you taking any prescription or non-prescription medications for the same purpose as the herbal product?
  - are you allergic to any plant products?
  - are you pregnant or breastfeeding?
- information resources: National Center for CAM (www.nccam.nih.gov), Health Canada website

Table 35. Common Herbal Products

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Reported Uses</th>
<th>Possible Adverse Effects</th>
<th>Possible Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black cohosh</td>
<td>Menopausal symptoms, PMS, labour induction, arthritis</td>
<td>Hepatitis, liver failure, headaches, GI discomfort, heaviness in legs, weight problems</td>
<td>None reported</td>
</tr>
<tr>
<td>Chamomile</td>
<td>Mild sedative, anxiolytic, GI complaints, common cold</td>
<td>Allergic/contact dermatitis, anaphylaxis</td>
<td>Anxiolytics, sedatives</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Common cold, flu, wound treatment, urinary tract infections, cancer</td>
<td>Hypersensitivity, hepatotoxicity with prolonged use, avoid use if immunosuppressed</td>
<td>Potentiates warfarin</td>
</tr>
<tr>
<td>Evening primrose</td>
<td>Dysmenorrhoea, menopausal sx, inflammation, allergies, eczema, arthritis, MS</td>
<td>Headache, restlessness, nausea, diarrhea, may decrease seizure threshold</td>
<td>Anticoagulants, antiplatelets</td>
</tr>
<tr>
<td>Feverfew</td>
<td>Migraine prevention, rheumatoid arthritis, anti-inflammatory</td>
<td>Anxiety, upset stomach, skin rash, miscarriage</td>
<td>Anticoagulants, antiplatelets</td>
</tr>
<tr>
<td>Flaxseed oil</td>
<td>Laxative, menopausal sx, source of omega-3 fatty acids</td>
<td>Diarrhea</td>
<td>Do not take with other medications as fibre content can bind drugs</td>
</tr>
<tr>
<td>Garlic</td>
<td>Elevated lipids, hypertension, hyperglycaemia, antimicrobial</td>
<td>GI irritation, contact dermatitis, may increase post-op bleeding</td>
<td>Anticoagulants, potentiates antihypertensives</td>
</tr>
<tr>
<td>Ginger</td>
<td>Nausea, motion sickness, dyspepsia, anti-inflammatory</td>
<td>Heartburn, not to be used for morning sickness</td>
<td>None known</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Increases peripheral circulation (AD, dementia, intermittent claudication), premensual syndrome, vertigo</td>
<td>Headache, cramping, bleeding, mild digestive problems; reports of intracranial hemorrhage</td>
<td>Anticoagulants, thiazide diuretics, MAO inhibitors</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Energy enhancer, decreases stress, adjunct support for chemotherapy/radiation</td>
<td>Hypertension, nervousness, insomnia, breakthrough bleeding, palpitations</td>
<td>Stimulant medications, antihypertensives, hormonal therapies</td>
</tr>
<tr>
<td>Glucosamine (Chondroitin)</td>
<td>Osteoarthritis</td>
<td>GI distress, headache, drowsiness, palpitations</td>
<td>Caution if shellfish allergy</td>
</tr>
<tr>
<td>Saw palmetto</td>
<td>BPH, adjunct to finasteride</td>
<td>Mild GI distress</td>
<td>C-β-adrenegics, finasteride</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>Mild to moderate depression</td>
<td>Phototensitivity, increased liver enzymes, drowsiness, diziness, nausea, headaches</td>
<td>CNS depressants, C/I with indinavir</td>
</tr>
<tr>
<td>Valerian root</td>
<td>Sedative, anxiolytic, muscle relaxant, PMS</td>
<td>Drowsiness, headache, digestive problems, paradoxical insomnia</td>
<td>CNS depressants, antihistamines</td>
</tr>
</tbody>
</table>


St. John’s Wort for Depression
Cochrane DB Syst Rev 2006;2:CD000840
A meta-analysis of 37 trials, including 26 which compared St. John’s Wort with placebo and 14 which compared St. John’s Wort with standard antidepressants. The main outcome measure was the ratio of responders to non-responders, and the main outcome measure for adverse effects was the number of patients dropping out due to adverse experiences. Significant heterogeneity was noted among placebo-controlled trials, but trials were statistically homogeneous for trials comparing St. John’s Wort with antidepressants. For major depression, compared with placebo, the OR for 6 larger trials was 1.15 (95% CI 1.02-1.29) and 5 smaller trials, 2.06 (95% CI 1.65-2.58). Compared with SSRIs and biclycines, the response rates were 0.90 (95% CI 0.85-1.01) and 0.80 (95% CI 0.70-0.88), respectively. Fewer patients on St John’s Wort dropped out due to adverse effects compared to those taking bicallycines (OR 0.25; 95% CI 0.14-0.45), and a similar but non-significant trend was seen when compared with SSRIs (OR 0.60; 95% CI 0.31-1.15). Drawing solid conclusions is difficult given the degree of study heterogeneity and number of conflicting studies.
### Primary Care Models

**Table 36. Primary Care Models**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Comprehensive Care Model</th>
<th>Family Health Team</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• FP/GPs in solo practice with limited after-hours availability</td>
<td>• Groups of health care professionals (e.g. FP, GPs, RNs, NPs, dieticians, social workers)</td>
</tr>
<tr>
<td></td>
<td>• Payment model: fee-for-service</td>
<td>• Wider range of services (e.g. rehabilitation, palliative care), with increased after-hours availability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Receives provincial funding for allied health</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Payment model: paid annually per patient rostered depending on demographic category</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Group of ≥3 FP, with some after-hours availability as well as on-call to telephone health advisory services</td>
<td>• Payment model: fee-for-service plus premiums</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Group of ≥3 FP, can utilize nurse practitioners, with telephone health advisory services to provide around the clock primary care coverage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Payment model: salary-based</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Same as FHT but usually larger in scale in terms of personnel</td>
<td></td>
</tr>
</tbody>
</table>

### Antimicrobial Quick Reference

<table>
<thead>
<tr>
<th>Condition</th>
<th>Microorganisms</th>
<th>Antimicrobial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RESPIRATORY/ENT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Rhinitis (common cold)</td>
<td>Rhinovirus, Coronavirus, Influenza, RSV, Parainfluenza, Adenovirus</td>
<td>None</td>
</tr>
<tr>
<td>Pharyngitis (sore throat)</td>
<td>Rhinovirus, Adenovirus, Influenza, Parainfluenza, Coxsackievirus, Coronavirus</td>
<td>None</td>
</tr>
<tr>
<td>Strep Pharyngitis</td>
<td>Group A β-Hemolytic Strep</td>
<td>Children:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st line: penicillin V 40 mg/kg/d PO div bid-tid (max 750 mg/d) x 10 d (use adult dose if &gt;27 kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: erythromycin estolate 40 mg/kg/d PO div bid-tid x 10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd line: cefalexin-AX 30-40 mg/kg/d PO div bid x 10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st line: penicillin V 300 mg PO tid or 600 mg bid x 10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: erythromycin 250 mg PO qid x 10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd line: cefprozil 15 mg/kg/d PO div bid x 10 d</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>S. pneumoniae, H. influenzae, M. catarrhalis, S. aureus</td>
<td>Children:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st line: amoxicillin 80 mg/kg/d PO div bid-tid x 5-10 d (max 3 g/d) x 10-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: amoxicillin/clavulanate 40-80 mg/kg/d div bid (max 3 g/d) x 10-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd line: cefuroxime-AX 30-40 mg/kg/d PO div bid x 10-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st line: amoxicillin 500 mg PO tid x 10-10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: amoxicillin/clavulin 500 or 875 mg PO bid x 5-10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd line: levofloxacin 500 mg PO OD x 5-10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>maxifloxacin 400 mg PO OD x 5-10 d</td>
</tr>
<tr>
<td>Acute Otitis Media</td>
<td>S. pneumoniae, H. influenzae, M. catarrhalis, Group A Strep, S. aureus</td>
<td>Children:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treat if under age 6 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If age 6-24 mo, watchful waiting appropriate if parents can observe child for 48-72 h with appropriate medical follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If age &gt; 24 mo, treat if worsens after 48-72 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 d course if age &lt; 24 mo, 5 d course if age &gt; 24 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st line: amoxicillin 80 mg/kg/d PO div bid-tid (max 3 g/d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: amoxicillin/clavulanate 40-80 mg/kg/d div bid (max 3 g/d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cefprozil 30 mg/kg/d PO div bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd line: cefuroxime-AX 30-40 mg/kg/d PO div bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clarithromycin 15 mg/kg/d PO div bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops bid x 5 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st line: amoxicillin 500 mg PO tid x 7-10d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: amoxicillin/clavulanate 500 mg PO tid or 875 mg PO bid x 7-10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cefprozil 250-500 mg PO bid x 7-10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops bid</td>
</tr>
<tr>
<td>Condition</td>
<td>Microorganisms</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>----------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>RESPIRATORY/ENT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otis Externa</td>
<td><em>P. aeruginosa</em></td>
<td>1st line: Buro-sol® otic solution 2-3 drops tid or qid</td>
</tr>
<tr>
<td></td>
<td><em>Coliforms</em></td>
<td>2nd line: Cortisporin® otic solution 4 drops tid or qid (3 drops tid or qid for children)</td>
</tr>
<tr>
<td></td>
<td><em>S. aureus</em></td>
<td>TM defect: Ciprol® otic suspension 4 drops bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Necrotizing (i.e. bone involvement): ciprofloxacin 750 mg PO bid x 4-8 wk</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>Influenza, parainfluenza, coronavirus, rhinovirus, RSV</td>
<td>None</td>
</tr>
<tr>
<td><strong>Community Acquired Pneumonia: Outpatient without Comorbidity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>S. pneumoniae</em></td>
<td>1st line: amoxicillin 1 g PO tid x 7-14 d</td>
</tr>
<tr>
<td></td>
<td><em>M. pneumoniae</em></td>
<td>(for patients over age 50 yr where mycoplasma infection is less likely)</td>
</tr>
<tr>
<td></td>
<td><em>C. pneumoniae</em></td>
<td>erythromycin 500 mg PO qid x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clarithromycin 500 mg PO bid or 1000 mg (ER) PO OD x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>azithromycin 500 mg PO on 1st d then 250 mg PO OD x 4 d or 500 mg PO OD x 3 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: doxycycline 100 mg PO on 1st d then 100 mg PO OD x 7-14 d</td>
</tr>
<tr>
<td><strong>Community Acquired Pneumonia: Outpatient with Comorbidity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>S. pneumoniae</em></td>
<td>ANY ONE of the β-lactam agents below:</td>
</tr>
<tr>
<td></td>
<td><em>M. pneumoniae</em></td>
<td>amoxicillin 1000 mg PO tid x 7-14 d</td>
</tr>
<tr>
<td></td>
<td><em>C. pneumoniae</em></td>
<td>amoxicillin/clavulinate 500 mg PO tid or 875 mg PO bid x 7-14 d</td>
</tr>
<tr>
<td></td>
<td><em>H. influenza</em></td>
<td>cefuroxime-AX 500 mg PO bid x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PLUS ONE of the following:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clarithromycin 500 mg PO bid or 1000 mg (ER) PO OD x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>azithromycin 500 mg PO OD on 1st d then 250 mg PO OD x 4d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>doxycycline 100 mg PO on 1st d then 100 mg PO OD x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR ANY ONE of the following:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>levofloxacin 750 mg PO OD x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>moxifloxacin 400 mg PO OD x 7-14 d</td>
</tr>
<tr>
<td><strong>Dental Infections/Periapical and Periodontal Abscesses</strong></td>
<td>Oral Flora</td>
<td>penicillin V potassium 500 mg PO qid x 7-10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clindamycin 300 mg PO qid or 600 mg bid x 7-10 d</td>
</tr>
<tr>
<td><strong>GASTROENTEROLOGY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea – Enteritis</td>
<td>Enteroxytigenic <em>E. coli</em> (ETEC)</td>
<td>Mild to moderate (i.e. &lt; 3 BM/d, no blood, no fever): OTC loperamide 4 mg PO STAT then 2 mg PO after each loose stool (max 8 doses/d)</td>
</tr>
<tr>
<td></td>
<td>Campylobacter</td>
<td>OTC bismuth subsalicylate (Pepto Bismol®) 2 tabs or 30 mL repeat q30min pm (max 8 doses/d) (prevention: 2 tabs or 30 mL qid with meals and in the evening)</td>
</tr>
<tr>
<td></td>
<td>Salmonella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shigella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Viruses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Protozoa</td>
<td></td>
</tr>
<tr>
<td>Diarrhea – post abx</td>
<td><em>C. difficile</em></td>
<td>Mild to moderate (WBC &lt;5 x 10⁹/L and Cr &lt;1.5 x baseline): metronidazole 500 mg PO tid or 250 mg PO qid x 10 d (children: 15-30 mg/kg/d PO div tid-qid max 4 g/d)</td>
</tr>
<tr>
<td>(common with clindamycin)</td>
<td></td>
<td>Severe (WBC ≥15 x 10⁹/L and Cr ≥1.5 x baseline): vancomycin 125 mg PO qid x 10-14d (children: 40 mg/kg/d PO div tid-qid x 10-14d max 2 g/d)</td>
</tr>
<tr>
<td>Peptic Ulcer Disease</td>
<td><em>H. pylori</em></td>
<td>PPI: 1st line: Lansoprazole 30 mg or omeprazole 20 mg or pantoprazole 40 mg or rabeprazole 20 mg</td>
</tr>
<tr>
<td>(non-NSAID related)</td>
<td></td>
<td>1st line: [PPI PO bid + amoxicillin 1000 mg PO bid + clarithromycin 500 mg PO bid x 7 d (e.g. HP-PAC: Lansoprazole 30 mg PO bid + amoxicillin 1000 mg PO bid + clarithromycin 500 mg PO bid x 7 d)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[PPI PO bid + metronidazole 500 mg PO bid + clarithromycin 500 mg or 250 mg PO bid x 7 d]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: [PPI PO bid + metronidazole 500 mg PO bid + amoxicillin 1000 mg PO bid x 7 d]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[PPI PO bid + bismuth subsalicylate 2 tabs or 30 mL qid + metronidazole 250 mg PO qid + tetracycline 500 mg PO qid x 7-14 d]</td>
</tr>
<tr>
<td>Condition</td>
<td>Microorganisms</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>GENITOURINARY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UTI/Cystitis</td>
<td>Klebsiella</td>
<td>1st line: TMP/SMX 2 tabs bid or 1 DS tab bid x 3 d</td>
</tr>
<tr>
<td></td>
<td><em>E. coli</em></td>
<td>trimethoprim 100 mg PO bid or 200 mg PO OD x 3 d</td>
</tr>
<tr>
<td></td>
<td>Enterobacter</td>
<td>nitrofurantoin 50-100 mg PO qid or Macrobid® 100 mg bid x 5 d</td>
</tr>
<tr>
<td></td>
<td><em>Enterococci</em></td>
<td>2nd line: amoxicillin 500 mg PO tid x 7 d</td>
</tr>
<tr>
<td></td>
<td><em>Proteus</em></td>
<td>norfloxacin 400 mg PO bid x 3 d</td>
</tr>
<tr>
<td></td>
<td><em>S. saprophyticus</em></td>
<td>ciprofloxacin 250 mg PO bid or 500 mg (ER) OD x 3 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NB: High-rate of amoxicillin resistance in community <em>E. coli</em>; use only after lab susceptibility obtained</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd line: cephalexin 250-500 mg PO qid x 7 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>levofloxacin 250 mg PO OD x 3 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy: cephalxin 250-500 mg PO qid x 7 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nitrofurantoin 50-100 mg PO bid x 5 d amoxicillin 500 mg PO tid x 7 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NB: Nitrofurantoin is contraindicated in pregnancy after 36 wk</td>
</tr>
<tr>
<td>Head and Pubic Lice (crabs)</td>
<td>Pediculosis humanus capitis</td>
<td>permethrin cream 1%; apply as liquid onto washed hair for 10 min, then rinse; repeat in 1 wk</td>
</tr>
<tr>
<td></td>
<td>Phthirus pubis</td>
<td></td>
</tr>
<tr>
<td>Vulvovaginal Candidiasis</td>
<td><em>Candida</em></td>
<td>Treat only if patient is symptomatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fluconazole 150 mg PO single dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>miconazole 2% cream (Monistat 7®): one applicator (5 g) intravaginally qhs x 7 d</td>
</tr>
<tr>
<td>Bacterial Vaginosis</td>
<td>Overgrowth of:</td>
<td>If patient is asymptomatic, treatment is unnecessary unless high-risk pregnancy, prior IUD insertion, gynecologic surgery, induced abortion, or upper tract instrumentation.</td>
</tr>
<tr>
<td></td>
<td><em>G. vaginalis</em></td>
<td>1st line: metronidazole 500 mg PO bid x 7 d</td>
</tr>
<tr>
<td></td>
<td><em>M. hominis</em></td>
<td>metronidazole 0.75% gel: one applicator (5 g) intravaginally qhs x 5 d</td>
</tr>
<tr>
<td></td>
<td>Anaerobes</td>
<td>clindamycin 2% cream: one applicator (5 g) intravaginally qhs x 7 d</td>
</tr>
<tr>
<td>Herpes</td>
<td>Herpes simplex virus</td>
<td>1° episode: acyclovir 400 mg PO tid x 5-7 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>famciclovir 250 mg PO tid x 5-7 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>valacyclovir 500-1000 mg PO bid x 5-7 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent Episode: acyclovir 400 mg PO tid x 5 d or 800 mg PO bid x 5 d or 800 mg PO tid x 2 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>famciclovir 125 mg PO bid x 5 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>valacyclovir 500 mg PO bid x 3 d or 1000 mg PO OD x 3 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy: acyclovir 200 mg PO 5xd x 5-10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior infection within previous yr: acyclovir 200 mg PO qid at 36 wk</td>
</tr>
<tr>
<td>Gonorrhea/Chlamydia</td>
<td><em>N. gonorrhoeae</em></td>
<td>ceftriaxone 250 mg IM x 1 dose + azithromycin 1 g PO</td>
</tr>
<tr>
<td></td>
<td><em>C. trachomatis</em></td>
<td>single dose or doxycycline 100 mg PO bid x 7 d</td>
</tr>
<tr>
<td><strong>DERMATOLOGIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastitis</td>
<td><em>S. aureus</em></td>
<td>cloxacillin 500 mg PO qid x 7 d</td>
</tr>
<tr>
<td></td>
<td><em>S. pyogenes</em></td>
<td>cephalxin 500 mg PO qid x 7 d</td>
</tr>
<tr>
<td>Tinea Cruris/Pedis (jock itch/athlete’s foot)</td>
<td>Trichophyton</td>
<td>clotrimazole 1% cream bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ketoconazole 2% cream bid</td>
</tr>
<tr>
<td>Uncomplicated Cellulitis</td>
<td><em>S. aureus</em></td>
<td>Children:</td>
</tr>
<tr>
<td></td>
<td>Group A Strep</td>
<td>1st line: cephalxin 50-100 mg/kg/d div qid x 10-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: cloxacillin 50 mg/kg/d div qid x 10-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clindamycin 25 mg/kg/d x 10-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adults:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st line: cephalxin 500 mg PO qid x 10-14d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: cloxacillin 500 mg PO qid x 10-14d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clindamycin 300 mg PO x 10-14 d</td>
</tr>
</tbody>
</table>
### References

**Abuse**


**Diabetes**


**Diet and Obesity**


**Dyslipidemia, Hypertension and Heart Disease**


**Viral Conjunctivitis**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Microorganisms</th>
<th>Antimicrobial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Conjunctivitis</td>
<td>Adenovirus, Coxsackievirus, ECHO virus</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NB: very contagious</td>
</tr>
</tbody>
</table>

| Bacterial Conjunctivitis | S. aureus, S. pneumoniae, H. influenzae, M. catarrhalis | Duration is 5-7 d unless otherwise specified |
| | | All doses should be administered while awake |
| | | OTC for adults and children age > 1 yr: |
| | | gramicidin-polymyxin drops (Polysporin® or Optimyxin®): 1 drop q4h |
| | | bacitracin-polymyxin ointment (Polysporin® or Optimyxin®): 1/2 inch qid |
| | | Prescription for adults and children age > 1 yr: |
| | | erythromycin 0.5% ointment: 1/2-1 inch qid |
| | | fusidin 1% drops (children age > 2 yr): 1 drop bid |
| | | sulfacetamide sodium 10% drops: 1-2 drops q2-3h then taper to bid |
| | | Fluoroquinolones preferred for more serious cases, especially suspected Pseudomonas (e.g. contact lens wearers), corneal involvement, or treatment failure: |
| | | ciprofloxacin 0.3% drops: 1-2 drops q2h x 2 d then q4h x 5 d |
| | | ciprofloxacin 0.3% ointment: 1/4 inch bid-tid |
| | | gatifloxacin 0.3% drops: 1-2 drops q2h x 2 d then qid x 5 d |

| Bacterial Conjunctivitis | S. aureus, S. epidermidis, P. acnes, Corynabacteria | Lid hygiene: Mainstay of treatment and works best OD or bid |
| | | Abx ointment: Helpful in short-term of acute phase but resistance rapidly ensues if treatment is prolonged |
| | | 1st line: bacitracin-polymyxin ointment (Polysporin® or Optimyxin®): 1/2 inch qhs |
| | | erythromycin 0.5% ointment: 1/2 inch qhs |
| | | 2nd line: gentamicin 0.3% ointment: 1/2 inch qhs |
| | | tobramycin 0.3% ointment: 1/2 inch qhs |

*All doses are adult doses unless otherwise specified

*This chart is not all-encompassing and is non-inclusive of special exceptions (i.e. pregnancy, poor renal clearance, etc.)

**References**

- Canadian Hypertension Education Program. 2010 Canadian hypertension education program recommendations for the management of hypertension. Can J Cardiol 2010;26:241-258.
-롤토노트 2014

# Gastroenterology

Ian Brasg and Ahmad Zaheen, chapter editors  
Grace Lam and Hamed Nazzari, associate editors  
Gautam Goel, EBM editor  
Dr. Gabor Kandel, Dr. Piero Tartaro, and Dr. Elaine Yong, staff editors

---

## Acronyms

- Gastroesophageal Reflux Disease (GERD)
- Barrett’s Esophagus
- Eosinophilic Esophagitis
- Dysphagia
- Peptic Stricture (from Esophagitis)
- Esophageal Carcinoma
- Gastrostomy
- Mallory-Weiss Tear
- Upper Gastrointestinal Bleeding
- Approach to Iron Deficiency Anemia
- Esophageal Varices
- Mallory-Weiss Tear
- Lower Gastrointestinal Bleeding
- COLORECTAL CARCINOMA (CRC)
- Colorectal Polyps
- Familial Colon Cancer Syndromes
- Benign Anorectal Disease

## Anatomy Review

Overview of Gastrointestinal Tract

## Visualizing the GI Tract

### Differential Diagnosis of Common Presenting Complaints

- Nausea/Vomiting
- Dysphagia
- Odynophagia
- Abdominal Distention
- Acute Abdominal Pain
- Chronic/Recurrent Abdominal Pain
- Acute Diarrhea
- Chronic Diarrhea
- Constipation
- Dyspepsia
- Upper GI Bleed
- Lower GI Bleed
- Jaundice

## Esophagus

- Gastroesophageal Reflux Disease (GERD)
- Barrett’s Esophagus
- Eosinophilic Esophagitis
- Dysphagia
- Esophageal Motor Disorders
- Esophageal Diverticula
- Peptic Stricture (from Esophagitis)
- Esophageal Carcinoma
- Webs and Rings
- Infectious Esophagitis

## Stomach and Duodenum

- Dyspepsia
- Gastric Acid Secretion
- Gastritis
- Peptic Ulcer Disease (PUD)
- *H. pylori*-Induced Peptic Ulceration
- NSAID-Induced Ulceration
- Stress-Induced Ulceration
- Gastric Carcinoma

## Small and Large Bowel

- Classification of Diarrhea
- Acute Diarrhea
- Traveller’s Diarrhea
  - (see Infectious Diseases, ID14)
- Chronic Diarrhea
- Malabsorption and Malabsorption
- Celiac Disease (Gluten Enteropathy/Sprue)
- Inflammatory Bowel Disease (IBD)
- Crohn’s Disease
- Ulcerative Colitis (UC)
- Irritable Bowel Syndrome (IBS)
- Constipation

## Liver

- Investigations of Hepatobiliary Disease
- Acute Viral Hepatitis (General)
- Hepatitis A Virus (HAV)
- Hepatitis B Virus (HBV)
- Hepatitis C Virus (HCV)
- Autoimmune Chronic Active Hepatitis
- Drug-Induced Liver Disease
- Wilson’s Disease
- Hemochromatosis
- Alcoholic Liver Disease
- Non-Alcoholic Fatty Liver Disease (NAFLD)
- Acute Liver Failure (ALF; Formerly Fulminant Hepatic Failure)
- Cirrhosis
- Hepatocellular Carcinoma (HCC)
- Jaundice
- Gilbert’s Syndrome
- Sclerosing Cholangitis
- Primary Biliary Cirrhosis (PBC)
- Secondary Biliary Cirrhosis
- Biliary Colic, Cholecystitis
- Ascending Cholangitis

## Pancreas

- Pancreatic Enzyme Abnormalities
- Acute Pancreatitis
- Chronic Pancreatitis
- Autoimmune Pancreatitis

## Clinical Nutrition

- Determination of Nutritional Status
- Enteral Nutrition (EN)
- Parenteral Nutrition (PN)

## Common Medications

- Landmark Gastroenterology Trials

## References
The gastrointestinal tract runs from mouth to anus ("gum to bum").

**Table 1. Summary of Gastrointestinal Tract Structure and Function**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Function</th>
<th>Blood Supply</th>
<th>Innervation</th>
<th>Histology and Structural Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>• Muscular tube approximately 25 cm long with a diameter of 2 cm</td>
<td>• Arterial: left gastric artery and left inferior phrenic artery &lt;br&gt; • Venous: &lt;br&gt; - Left gastric vein → portal venous system &lt;br&gt; - Esophageal veins → azygos vein → IVC (systemic)</td>
<td>• Parasympathetic innervation via anterior and posterior gastric nerves (vagal trunks) &lt;br&gt; • Sympathetic innervation via thoracic trunks of the greater splanchnic nerves</td>
<td>• Mucosa: stratified squamous epithelium &lt;br&gt; • Submucosa: connective tissue, lymphocytes, plasma cells, nerve cells &lt;br&gt; • Muscularis propria (muscularis externa): inner circular, outer longitudinal muscle &lt;br&gt; - Upper 1/3: striated muscle &lt;br&gt; - Middle 1/3: transition zone &lt;br&gt; - Lower 1/3: smooth muscle</td>
</tr>
<tr>
<td>Stomach</td>
<td>• Delivers food to intestine for digestion and absorption &lt;br&gt; • Secretes acid, probably to reduce enteric infections/pneumonia; facilitate digestion of protein/iron/B₁₂ &lt;br&gt; • Secretes intrinsic factor to facilitate B₁₂ absorption &lt;br&gt; • Minor contribution to initial protein digestion via pepsin</td>
<td>• Lesser curvature: &lt;br&gt; - Right and left gastric arteries (from celiac trunk) &lt;br&gt; - Greater curvature: &lt;br&gt; - Right and left gastroental (gastronephric) arteries (from gastroduodenal and splenic a. respectively) &lt;br&gt; • Fundus: short and posterior gastric arteries (from the splenic artery)</td>
<td>• Parasympathetic innervation via vagus nerve &lt;br&gt; • Sympathetic innervation via celiac plexus (from T₅-T₉)</td>
<td>5 parts: &lt;br&gt; - Cardia &lt;br&gt; - Fundus &lt;br&gt; - Body &lt;br&gt; - Antrum &lt;br&gt; - Pylorus</td>
</tr>
<tr>
<td>Duodenum</td>
<td>• Modulates enteral pH via secretin → decreased gastric acid secretion, increased bicarbonate secretion &lt;br&gt; • Secretes cholecystokinin (CCK) to stimulate bile secretion &lt;br&gt; • Site of iron absorption</td>
<td>• Branches of celiac artery and superior mesenteric artery (SMA)</td>
<td>• Parasympathetic innervation via vagus nerve &lt;br&gt; • Sympathetic innervation via greater and lesser splanchnic nerves</td>
<td>4 parts &lt;br&gt; - Superior (5 cm) &lt;br&gt; - Descending (7-10 cm) &lt;br&gt; - Horizontal (6-8 cm) &lt;br&gt; - Ascending (5 cm) &lt;br&gt; • 1st part is intraperitoneal; rest is retroperitoneal</td>
</tr>
</tbody>
</table>
### Table 1. Summary of Gastrointestinal Tract Structure and Function (continued)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Function</th>
<th>Blood Supply</th>
<th>Innervation</th>
<th>Histology and Structural Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jejunum</td>
<td>Absorption of salt, water and nutrients (protein, carbohydrates, fat, folic acid, and vit A, B, C, D, E, K)</td>
<td>Superior mesenteric artery</td>
<td>Parasympathetic innervation via fibers of the posterior vagal trunk</td>
<td>Deep red colour&lt;br&gt;2.4 cm in thickness&lt;br&gt;Has a thick and heavy wall&lt;br&gt;Plicae circulars are large, tall and closely packed&lt;br&gt;Has long vasa recta&lt;br&gt;Scant fat in mesentery&lt;br&gt;Scant Peyer’s patches</td>
</tr>
<tr>
<td>Ileum</td>
<td>Absorption of salt, water, nutrients, soluble vitamins (only site of vit B₁₂ absorption) and bile salt (entero-hepatic circulation)</td>
<td>Superior mesenteric artery</td>
<td>Same as jejunum&lt;br&gt;When compared to jejunum: Paler pink colour&lt;br&gt;2.3 cm in thickness&lt;br&gt;Has a thin and light wall&lt;br&gt;Plicae circulars are small and sparse&lt;br&gt;Contains more fat in mesentery than jejunum&lt;br&gt;Has many Peyer’s patches</td>
<td></td>
</tr>
<tr>
<td>Large Bowel</td>
<td>Absorption of water (5-10% of total water)</td>
<td>Branches of superior and inferior mesenteric arteries&lt;br&gt;Rectal blood supply: sigmoid, right pudendal and rectal arteries</td>
<td>Parasympathetic innervation via fibers of the anterior and posterior vagal trunks</td>
<td>Consists of cecum, colon (ascending, transverse, descending, and sigmoid), rectum and anal canal&lt;br&gt;Features include teniae coli, haustra, and omental appendices</td>
</tr>
<tr>
<td>Liver</td>
<td>Glucose homeostasis&lt;br&gt;Plasma protein synthesis&lt;br&gt;Lipid and lipoprotein synthesis&lt;br&gt;Bile acid synthesis and secretion&lt;br&gt;Vitamin A, D, E, K, B₁₂, storage&lt;br&gt;Biotransformation, detoxification&lt;br&gt;Excretion of compounds</td>
<td>2 sources&lt;br&gt;Portal vein (75-80%)&lt;br&gt;Hepatic artery (20-25%)</td>
<td>Sympathetic innervation via fibers of the celiac plexus&lt;br&gt;Parasympathetic innervation via fibers of the anterior and posterior vagal trunks</td>
<td>Largest internal organ&lt;br&gt;Composed of 4 lobes (left, right, caudate, quadrate) and divided into 8 segments</td>
</tr>
<tr>
<td>Biliary Tract</td>
<td>Gallbladder functions to store and release bile that is produced in the liver&lt;br&gt;Bile is used to emulsify fat and is composed of cholesterol, lecithin, bile acids and bilirubin&lt;br&gt;CCK stimulates gallbladder emptying while trypsin and chymotrypsin inhibit bile release</td>
<td>Cystic artery</td>
<td>Parasympathetic innervation via vagus nerve&lt;br&gt;Sympathetic and visceral innervation via celiac nerve plexus&lt;br&gt;Somatic afferent fibers via right phrenic nerve</td>
<td>Consists of the hepatic ducts (intrahepatic, left, right and common), gallbladder, cystic duct, common bile duct and ampulla of Vater</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Endocrine function: islets of Langerhans produce glucagon, insulin and somatostatin (from the α, β and δ cells, respectively)&lt;br&gt;Exocrine function: digestive enzymes are produced including amylase, lipase, trypsin, chymotrypsin and carboxypeptidase</td>
<td>Anterior superior pancreaticoduodenal artery (from the celiac trunk)&lt;br&gt;Anterior inferior pancreaticoduodenal artery (from the superior mesenteric artery)&lt;br&gt;Dorsal pancreatic artery (from the splenic artery)&lt;br&gt;Pancreatic veins drain into the portal, splenic and superior mesenteric veins</td>
<td>Parasympathetic innervation via vagus nerve&lt;br&gt;Sympathetic innervation via abdominopelvic splanchnic nerves</td>
<td>4 parts of pancreas: head (includes uncinate process), neck, body, and tail&lt;br&gt;(Major) Pancreatic duct connecting to common bile duct prior to ampulla of Vater&lt;br&gt;Accessory pancreatic duct connecting directly to duodenum</td>
</tr>
</tbody>
</table>

### Visualizing the GI Tract

- see also Medical Imaging, MI10

**Esophagus, Stomach, Duodenum**

- oesophagogastroduodenoscopy (OGD): best visualization of mucosa; also allows for therapeutic intervention (banding varices, cauterizing/clipping/injecting bleeding ulcers, and dilating esophageal strictures)
- consider barium swallow first if dysphagia, decreased level of consciousness (increases risk of aspiration), inability to cooperate (increases risk of pharyngeal trauma during intubation)
- endotracheal intubation first if massive upper GI bleed, acidosis or unable to protect airway

---

**Retroperitoneal Structures**

- SAD PUCKER
  - Suprarenal glands (adrenal glands)
  - Aorta/IVC
  - Duodenum (second to fourth segments)
  - Pancreas (tail is intraperitoneal)
  - Ureters
  - Colon (only the ascending and descending branches)
  - Kidneys
  - Esophagus
  - Rectum

**Only the ileum (not jejunum), can absorb vitamin B₁₂ and bile acids.**

---
Small Bowel
- most difficult to visualize, especially if mucosal detail is needed
- CT enterography more accurate than small bowel follow through, but both have low sensitivity
- MRI enteroclysis increasingly available (use enteroclysis if dilation of the small bowel might improve sensitivity, such as diverticulosis, or if stricture suspected)
- “double balloon” enteroscopy (enteroscope with balloons proximally and distally to propel endoscope into jejunum from mouth or into ileum from anus) may be most sensitive but currently available only in selected centres; technically demanding
- wireless endoscopy capsule (26 x 11 mm capsule is swallowed, transmits images to a computer; contraindicated in bowel obstruction) is also accurate in diagnosis but unable to provide any therapeutic intervention

Colon and Terminal Ileum
- colonoscopy, with biopsy if required; contraindicated in perforation, acute diverticulitis and severe colitis (increased risk of perforation)
- CT colonoscopy (“virtual colonoscopy”) more accurate in diagnosing diverticulosis, extrinsic pressure on colon (e.g. ovarian cancer compressing sigmoid colon) and fistulae; increasing evidence for use in colorectal cancer screening

Pancreatic/Biliary Duct
- MRCP almost as sensitive as ERCP in determining if bile duct obstruction present, but less accurate in determining cause of obstruction (tumour, stone, stricture)
- ERCP if endoscopic draining necessary, strong suspicion of stone, obstruction requiring stenting, or if tissue sampling required

Differential Diagnosis of Common Presenting Complaints

### Table 2. Differential Diagnosis of Common Presenting Complaints

<table>
<thead>
<tr>
<th>NAUSEA/ VOMITING</th>
<th>With Abdominal Pain</th>
<th>Without Abdominal Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relieved by Vomiting</td>
<td>Not Relieved by Vomiting</td>
</tr>
<tr>
<td>Gastric outlet obstruction</td>
<td>Gallbladder disease</td>
<td>Cerebral tumour</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>Pancreatitis</td>
<td>Migraine</td>
</tr>
<tr>
<td>GERD (regurgitation more common)</td>
<td>Myocardial infarction</td>
<td>Vestibular disease</td>
</tr>
<tr>
<td></td>
<td>Hepatitis</td>
<td>Increased ICP</td>
</tr>
<tr>
<td></td>
<td>Infectious gastroenteritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DYSPHAGIA</th>
<th>Mechanical (Solids)</th>
<th>Motility (Solids and Liquids)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic stricture/cancer</td>
<td>Achalasia</td>
<td>Foreign Body</td>
<td>Eosinophilic esophagitis</td>
</tr>
<tr>
<td>Eosinophilic esophagitis</td>
<td>Diffuse esophageal spasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrinsic compression</td>
<td>Scleroderma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schatzki ring/esophageal web</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zenker’s diverticulum</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ODYNOPHAGIA</th>
<th>Infection</th>
<th>Inflammation/Ulceration</th>
<th>Drugs</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida</td>
<td>Caustic damage</td>
<td>Quinidine</td>
<td>Radiation</td>
<td></td>
</tr>
<tr>
<td>Herpes</td>
<td>Eosinophilic esophagitis</td>
<td>Iron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV (common only in those who are immunosuppressed)</td>
<td></td>
<td>Vitamin C</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antibiotics (e.g. tetracycline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bisphosphonates</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ABDOMINAL DISTENTION</th>
<th>Fluid (Ascites)</th>
<th>Flatulence</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal HTN</td>
<td>Cancer (esp. ovarian)</td>
<td>Functional bowel disease (e.g. IBS)</td>
<td>Constipation</td>
</tr>
<tr>
<td>Normal Portal Pressure</td>
<td>Pancreatitis TB</td>
<td>Fibre</td>
<td>Colonic obstruction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lactose intolerance</td>
<td>Dysmotility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chewing gum (e.g. sorbitol, mannitol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Obesity (fat)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Blood</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Large tumours (fatal growth)</td>
</tr>
</tbody>
</table>

**Commonly Forgotten Causes of Vomiting**
- Drugs
- Uremia
- CNS Disease
- Pregnancy

**Differential Diagnosis of Abdominal Distention**
- 6 Fs
- Fat
- Feces
- Fetus
- Flatus
- Fluid
- Fatty Growth

**Acute Upper Abdominal Pain**
Remember to rule out thoracic sources, e.g. myocardial infarction, pneumonia, dissecting aneurysm.
### Table 2. Differential Diagnosis of Common Presenting Complaints (continued)

#### ACUTE ABDOMINAL PAIN

<table>
<thead>
<tr>
<th>Upper/Mid-Abdomen</th>
<th>Lower Abdomen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenteritis</td>
<td>Gastroenteritis</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>Appendicitis</td>
</tr>
<tr>
<td>Perforated peptic ulcer</td>
<td>Diverticulitis</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>Pelvic inflammatory disease</td>
</tr>
<tr>
<td>Mesenteric ischemia</td>
<td>Ectopic pregnancy</td>
</tr>
<tr>
<td>Ruptured aortic aneurysm</td>
<td></td>
</tr>
</tbody>
</table>

#### CHRONIC/RECURRENT ABDOMINAL PAIN

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Neoplastic/Vascular</th>
<th>Toxic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUD</td>
<td>Recurrent bowel obstruction</td>
<td>Lead poisoning</td>
<td>Mittelschmerz</td>
</tr>
<tr>
<td>Biliary colic</td>
<td>Biliary colic ischemia</td>
<td>Sickle cell anemia</td>
<td>Endometriosis</td>
</tr>
<tr>
<td>IBD</td>
<td>IBD</td>
<td>Ischemic *</td>
<td>Porphyria</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>Chronic pancreatitis</td>
<td></td>
<td>IBS</td>
</tr>
</tbody>
</table>

#### ACUTE DIARRHEA

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Non-Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>Bacterial</td>
</tr>
<tr>
<td>Shigella*</td>
<td>S. aureus</td>
</tr>
<tr>
<td>Salmonella*</td>
<td>C. perfringens</td>
</tr>
<tr>
<td>Campylobacter*</td>
<td>B. cereus</td>
</tr>
<tr>
<td>Yersinia*</td>
<td>E. coli (ETEC, EPEC)</td>
</tr>
<tr>
<td>E. coli (0157:H7)*</td>
<td>Salmonella enteralis</td>
</tr>
<tr>
<td>C. difficile</td>
<td>Vibrio cholera</td>
</tr>
<tr>
<td></td>
<td>Protozoal</td>
</tr>
<tr>
<td></td>
<td>E. histolytica (amebiasis)</td>
</tr>
<tr>
<td></td>
<td>Strongyloides</td>
</tr>
<tr>
<td></td>
<td>Others</td>
</tr>
<tr>
<td></td>
<td>NSAIDs</td>
</tr>
<tr>
<td></td>
<td>IBD*</td>
</tr>
<tr>
<td></td>
<td>Ischemic *</td>
</tr>
</tbody>
</table>

#### CHRONIC DIARRHEA

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>(a) Organic</th>
<th>(b) Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD</td>
<td>Stimulant laxatives</td>
<td>Giardia lamblia</td>
</tr>
<tr>
<td>Infectious</td>
<td>Post-ileal resection/cholecystectomy (bile salts)</td>
<td>Celiac sprue</td>
</tr>
<tr>
<td>(C. difficile, TB, CMV, HSV)</td>
<td></td>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td>Ischemic bowel</td>
<td>Neoplasia</td>
<td>Chronic cholestasis</td>
</tr>
<tr>
<td>Radiation colitis</td>
<td>Neoplasia (Colon Ca, Carcinoid, VIPoma)</td>
<td></td>
</tr>
<tr>
<td>Neoplasia</td>
<td>Addison’s disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Congenital syndromes</td>
<td></td>
</tr>
</tbody>
</table>

#### CONSTIPATION: if no associated rectal bleeding/weight loss, etc., usually no cause found

| Colorectal cancer | Medications (narcotics, antidepressants, calcium channel blockers) | Neurological (Parkinson’s, multiple sclerosis, stroke) |
| Stricture        | Metabolic (diabetes, thyroid, hypercalciemia) | Collagen vascular disease (scleroderma, dermatomyositis) |
| Extrinsic compression | | |
| Anal disease     | | |
| Rectosigmoid     | | |

#### DYSPEPSIA

| Functional dyspepsia | Angina | Gastric antral vascular ectasia |
| Drug side effect    | Crohn’s disease | Esophageal varices |
| Peptic ulcer (GERD) | Cancer | Mallory-Weiss tears |

#### UPPER GI BLEED

| Ulcers (H. pylori, ASA, NSAIDs) | Tumours | Gastric antral vascular ectasia |
| Esophageal varices | Arteriovenous malformation | Portal hypertensive gastropathy |
| Mallory-Weiss tears | Dieulafoy’s lesion | |
| Erosive esophagitis | Gastric antral vascular ectasia | |
| Erosive gastritis | Gastric antral vascular ectasia | |

#### LOWER GI BLEED

| Diverticulosis | Upper GI bleed (brisk) |
| Ischemia      | Post-polypectomy |
| Angiodysplasia (elderly) | Radiation colitis |
| Infectious    | IBD | |
| Anorectal (hemorrhoids, fissure, ulcer) | | |

**Obscure But Treatable Causes of Abdominal Pain**
- Porphyria
- Angioedema
- Familial Mediterranean Fever
- Vasculitis (e.g. polyarteritis nodosa)

*Rule out IBD when patient presents with bloody diarrhea.*
Table 2. Differential Diagnosis of Common Presenting Complaints (continued)

<table>
<thead>
<tr>
<th>JAUNDICE</th>
<th>Overproduction</th>
<th>Decreased Hepatic Intake</th>
<th>Decreased Conjugation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(UNCONJUGATED BILIRUBIN)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemolysis</td>
<td>Gilbert’s syndrome</td>
<td>Drug inhibition (e.g. chloramphenicol)</td>
</tr>
<tr>
<td></td>
<td>Ineffective erythropoiesis (e.g. megaloblastic anemias)</td>
<td>Drugs (e.g. rifampin)</td>
<td>Crigler-Najjar syndromes type I and II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gilbert’s syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neonatal jaundice</td>
</tr>
<tr>
<td>JAUNDICE</td>
<td>Impaired Hepatic Secretion</td>
<td>Extrahepatic Biliary Obstruction</td>
<td></td>
</tr>
<tr>
<td>(CONJUGATED BILIRUBIN)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatocellular disease – by far the most common</td>
<td>Intraductal obstruction:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Familial disorders (e.g. Rotor syndrome, Dubin-Johnson syndrome, cholestasis of pregnancy)</td>
<td>Gallstones</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug-induced cholestasis (e.g. oral contraceptives, chlorpromazine)</td>
<td>Biliary stricture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary biliary cirrhosis (PBC)</td>
<td>Parasites</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary sclerosing cholangitis (PSC)</td>
<td>Malignancy (choolangiocarcinoma)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Septis</td>
<td>Sclerosing cholangitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-operative</td>
<td>Extraductal obstruction:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malignancy (e.g. pancreatic cancer, lymphoma)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metastases in peri-portal nodes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inflammation (e.g. pancreatitis)</td>
<td></td>
</tr>
</tbody>
</table>

Esophagus

Gastroesophageal Reflux Disease (GERD)

Definition
- condition in which the stomach contents (solid or liquid) leak backwards from the stomach into the esophagus (the tube from the mouth to the stomach)

Etiology
- inappropriate transient relaxations of lower esophageal sphincter (LES) – most common
- low basal LES tone (especially in scleroderma)
- contributing factors include: delayed esophageal clearance, delayed gastric emptying, increased intra-abdominal pressure
- acid hypersecretion (rare): Zollinger-Ellison syndrome (gastrin-secreting tumour)
- hiatus hernia worsens reflux, does not cause it (see General Surgery, GS22)

Clinical Features
- “heartburn” (pyrosis) and acid regurgitation (together are 80% sensitive and specific for reflux) ± sour regurgitation, water brash, sensation of a lump in the throat (bolus sensation) and frequent belching
- non-esophageal symptoms (see below) are increasingly recognized of being poor predictors of reflux

Investigations
- usually a clinical diagnosis based on symptom history and relief following a trial of pharmacotherapy (proton pump inhibitor (PPI): symptom relief 80% sensitive for reflux)
  - absolute indications:
    - heartburn accompanied by red-flags (bleeding, weight loss, etc.)
    - persistent reflux symptoms or previous severe erosive esophagitis after therapeutic trial of 4-8 wk of PPI 2x daily
    - history of esophageal stricture with persistent dysphagia
  - repeat endoscopy indicated only if known Barrett’s (or recurrence of symptoms) because future likelihood of Barrett’s and esophagitis is minimal if the first endoscopy is normal

Figure 2. Signs and symptoms of GERD

Gastroesophageal Reflux Disease (GERD)

Non-erosive reflux disease (NERD)
- Normal esophagus
- Aim for symptom relief only; proton pump inhibitor PRN

Esophagitis
- Normal esophagus
- Esophageal inflammation
- Aim to heal inflammation; proton pump inhibitor indefinitely or surgical fundoplication

Esophageal damage from reflux is most severe at first gastroscopy, therefore necessary only once for patients with NERD.
• esophageal manometry (study of esophageal motility)
  ▪ may be done to diagnose abnormal peristalsis and/or decreased LES tone, but cannot detect presence of reflux; indicated before surgical fundoplication to ensure esophageal functional
  ▪ surgical fundoplication (wrapping of gastric fundus around the lower end of the esophagus) more likely to be successful if lower esophageal pressure is diminished; less likely to be successful if abnormal peristalsis
• 24-h pH monitoring: most accurate test, but rarely required or performed
  ▪ most useful if PPIs do not improve symptoms

Management
• PPIs are the most effective therapy and usually need to be continued as maintenance therapy
• on-demand: antacids (Mg(OH)₂, Al(OH)₃, alginate), H₂-blockers or PPIs can be used for NERD
• diet helps symptoms, not the disease; avoid alcohol, coffee, spices, tomatoes and citrus juices
• only beneficial lifestyle changes are weight loss (if obese) and elevating the head of bed (if nocturnal symptoms)
• dyspepsia may recur if therapy is discontinued

Complications
• esophageal stricture disease – scarring can lead to dysphagia (solids)
• ulcer
• bleeding
• Barrett’s esophagus (see below) and esophageal adenocarcinoma – gastroscopy is recommended for patients with chronic GERD or symptoms suggestive of complicated disease (e.g. anorexia, weight loss, bleeding, dysphagia)

Barrett’s Esophagus

Definition
• metaplasia of normal squamous esophageal epithelium to abnormal columnar epithelium containing intestinal metaplasia

Etiology
• thought to be acquired via long-standing GERD and consequent damage to squamous epithelium

Epidemiology
• in North America and Western Europe, 0.5-2.0% of adults are thought to have Barrett’s esophagus
• up to 10% of GERD patients will have already developed BE by the time they seek medical attention
• more common in males, age >50, Caucasians, smokers, overweight, hiatus hernia and long history of reflux symptoms

Pathophysiology
• endoscopy shows erythematous epithelium in distal esophagus; diagnosis of BE relies on biopsy demonstrating the presence of specialized intestinal epithelium of any length within the esophagus
• BE predisposes to premalignant changes in abnormal columnar epithelium, characterized as low- or high-grade dysplasia

Significance
• rate of malignant transformation is approximately 0.12% per year for all BE patients prior to dysplasia
• risk of malignant transformation in high-grade dysplasia is significantly higher; studies have reported a 32-59% transformation rate over 5-8 yr of surveillance
• increased gastric acid secretion is more frequently associated with Barrett’s esophagus as opposed to reflux alone

Management
• acid suppressive therapy with high-dose PPI indefinitely (or surgical fundoplication)
• endoscopy every 3 yr if no dysplasia
• high grade dysplasia: regular and frequent surveillance with intensive biopsy, endoscopic ablation/resection, or esophagectomy produce similar outcomes; however, evidence increasingly favouring endoscopic ablation with mucosal resection or radiofrequency ablation
• if low grade dysplasia, both surveillance and endoscopic ablation/resection are satisfactory options

Complications
• esophageal stricture disease – scarring can lead to dysphagia (solids)
• ulcer
• bleeding
• Barrett’s esophagus (see below) and esophageal adenocarcinoma – gastroscopy is recommended for patients with chronic GERD or symptoms suggestive of complicated disease (e.g. anorexia, weight loss, bleeding, dysphagia)
Eosinophilic Esophagitis

Definition
- inflammatory condition with prominence of eosinophils on esophageal biopsy
- most commonly found in children, but increasingly recognized in adults

Etiology
- unknown; may be an "allergic" disorder in children
- cytokines cause edema and fibrosis

Clinical Features
- odynophagia or dysphagia (solids); history often dates back to childhood
- first presentation may be to ER with food bolus impaction
- allergies common

Investigations
- endoscopy may reveal multiple rings or "crepe-paper" appearance
- biopsy showing increased eosinophils is necessary to confirm diagnosis

Management
- corticosteroid (e.g. fluticasone) spray (swallowed not inhaled)
- budesonide in a matrix to increase contact time with esophageal mucosa
- leukotriene B4 inhibitors (e.g. Montelukast)
- rule out food allergies: elimination diets have been an effective therapy in children

Complications
- increased risk of perforation with endoscopic dilatation procedures

Dysphagia

Definition
- difficulty swallowing, sensation of food "sticking" after swallowing

Esophageal Motor Disorders

Symptoms
- dysphagia with solids and liquids
- chest pain (in some disorders)

Diagnosis
- motility study (esophageal manometry)
- barium swallow sometimes helpful

Causes (Table 3)
- idiopathic
- achalasia (painless)
- scleroderma (painless)
- diabetes
- diffuse esophageal spasm (DES); rare and can be difficult to diagnose due to intermittent presentation

Key Questions in Dysphagia
- Difficulty in starting swallowing?
- Associated symptoms? (regurgitation, change in voice pitch, weight loss)
- Solids, liquids or both?
- Intermittent or progressive?
- History of heartburn?
- Change in eating habits/diet?

Dysphagia = Difficulty in swallowing
Odynophagia = Pain on swallowing
Table 3. Esophageal Motor Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Achalasia</th>
<th>Scleroderma</th>
<th>Diffuse Esophageal Spasm (DES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>• Failure of smooth muscle relaxation at LES</td>
<td>• See Rheumatology, RH13</td>
<td>• Normal peristalsis interspersed with frequent, repetitive, spontaneous, high pressure, non-peristaltic waves (tertiary peristalsis)</td>
</tr>
<tr>
<td>Etiology</td>
<td>• Usually idiopathic</td>
<td>• Involves autoimmune, genetic, hormonal, and environmental factors</td>
<td>• Idiopathic</td>
</tr>
<tr>
<td></td>
<td>• 2nd pseudo-achalasia: e.g. malignancy, Chagas disease (Trypanosoma cruzi)</td>
<td>• Dysphagia: caused by reflux, dysmotility, or both</td>
<td></td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>• Inflammatory degeneration of Auerbach’s plexus → increase in LES pressure, incomplete relaxation of LES with swallowing, aperistalsis</td>
<td>• Blood vessel damage → intramural neuronal dysfunction → distal esophageal muscle weakening → aperistalsis and loss of LES tone → reflux → stricture → dysphagia</td>
<td>• Potential mechanisms include impaired inhibitory innervation to esophageal body, malfunction in endogenous nitric oxide synthesis</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>• CXR: no air in stomach, dilated esophagus</td>
<td>• Clinical features of scleroderma</td>
<td>• Barium x-ray: “Corkscrew pattern”</td>
</tr>
<tr>
<td></td>
<td>• Barium studies: esophagus terminates in narrowing at LES (“bird’s beak”)</td>
<td>• Manometry: decreased pressure in LES, decreased peristalsis in body of esophagus</td>
<td>• Manometry: &gt;30% (but &lt;100%) of esophageal contractions are aperistaltic</td>
</tr>
<tr>
<td></td>
<td>• Endoscopy: r/o malignancy</td>
<td>• Injection of botulinum toxin into LES (temporary)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Manometry: definitive diagnosis (signs listed above)</td>
<td>• Surgery (myomectomy)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>• Dilatation of LES with balloon, ≥ GERD prophylaxis, 50% good response, can repeat, risk of perforation (5%)</td>
<td>• Medical: aggressive GERD therapy (PPIs bid)</td>
<td>• Reassurance not cardiac pain</td>
</tr>
<tr>
<td></td>
<td>• Injection of botulinum toxin into LES (temporary)</td>
<td>• Surgery: anti-reflux surgery (gastroplasty, last resort)</td>
<td>• Medical: nitrates, calcium channel blockers, anticholinergics have variable benefit</td>
</tr>
<tr>
<td></td>
<td>• Surgery (myomectomy)</td>
<td></td>
<td>• Surgical: long esophageal myotomy if unresponsive to above treatment (rarely helpful); balloon dilatation</td>
</tr>
</tbody>
</table>

**Esophageal Diverticula**

**Definition**
- outpouchings of one or more layers of the esophageal tract

**Clinical Features**
- commonly associated with motility disorders
- dysphagia, regurgitation, retrosternal pain, intermittent vomiting, may be asymptomatic

**Classification**
- classified according to location
  - pharyngoesophageal (Zenker’s) diverticulum
  - most frequent form of esophageal diverticulum
  - posterior pharyngeal outpouching most often on the left side, above cricopharyngeal muscle and below the inferior pharyngeal constrictor muscle
  - symptoms: dysphagia, regurgitation of undigested food, halitosis
  - treatment: endoscopic or surgical myotomy of cricopharyngeal muscle ± surgical excision of sac
- mid-esophageal diverticulum
  - secondary to mediastinal inflammation, motor disorders
  - usually asymptomatic; no treatment required
- just proximal to LES (pulsatile type)
  - usually associated with motor disorders
  - usually asymptomatic; no treatment required

**Peptic Stricture (from Esophagitis)**
- presents as dysphagia alongside a long history of reflux symptoms, but reflux symptoms may disappear as stricture develops
- diagnosed with endoscopy or barium study if endoscopy contraindicated or unavailable

**Treatment**
- endoscopic dilatation and indefinite PPI
- anti-reflux surgery if above treatment unsuccessful
Esophageal Carcinoma

- see General Surgery, GS14

Webs and Rings

- web = partial occlusion (upper esophagus)
- ring = circumferential narrowing (lower esophagus)

Clinical Features
- asymptomatic with lumen diameter >12 mm, provided peristalsis is normal
- dysphagia with large food boluses
- Plummer-Vinson (or Patterson-Kelly syndrome)
  - upper esophageal web with iron deficiency, plus cheilosis (dry scaling and fissuring of the lips) and koilonychia (concave outer nail surface)
  - usually in middle-aged females (>40 yr)
  - elevated risk of hypopharyngeal carcinoma
- Schatzki's ring
  - mucosal ring at squamo-columnar junction above a hiatus hernia
  - causes intermittent dysphagia with solids
  - treatment involves disrupting ring with endoscopic bougie

Infectious Esophagitis

Definition
- severe mucosal inflammation and ulceration as a result of a viral or a fungal infection

Risk Factors
- diabetes
- chemotherapeutic agents
- immunocompromised states

Symptoms
- characteristically odynophagia, less often dysphagia
- diagnosis is via endoscopic visualization and biopsy

Appearance
- Candida (most common): whitish-yellow plaques without visible ulceration or inflammation
- Herpes (second most common), CMV: focal ulcers

Treatment
- Candida: nystatin swish and swallow, ketoconazole, fluconazole
- Herpes: often self-limiting; acyclovir, valacyclovir, famciclovir
- CMV: IV gancyclovir, famciclovir or oral valganciclovir

Stomach and Duodenum

Dyspepsia

Definition
- intermittent epigastric discomfort, characteristically develops after eating

History and Physical
- history: most important are age, associated symptoms (such as weight loss and vomiting), and drugs (especially NSAIDs)
- physical examination: adenopathy, abdominal mass/organomegaly, Carnett's sign (if pain is due to abdominal wall muscle problem then the pain will increase during muscle contraction, such as during a sit-up)

Investigations
- laboratory: usual (CBC, liver enzymes, glucose, Cr, etc.) plus amylase, albumin
- consider trial of empiric anti-secretory drug therapy, non-invasive testing for H. pylori infection, endoscopy, barium radiography

The most common cause of dyspepsia is functional (idiopathic) dyspepsia. “Neither clinical impression nor computer models can adequately distinguish between organic disease and functional disease in patients referred for endoscopic evaluation of dyspepsia.”

JAMA 2006;295:1566-1576
Gastric Acid Secretion

Stomach
- primary function is mechanical grinding of food facilitating early enzymatic digestion into chyme and propulsion into duodenum

Table 4. Cells of the Gastric Mucosa

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Secretory Product</th>
<th>Important Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietal cells</td>
<td>Gastric acid (HCl)</td>
<td>Stimulated by histamine, ACh, gastrin</td>
</tr>
<tr>
<td></td>
<td>Intrinsic factor</td>
<td></td>
</tr>
<tr>
<td>Chief cells</td>
<td>Pepsinogen</td>
<td>Stimulated by vagal input and local acid</td>
</tr>
<tr>
<td>G-cells</td>
<td>Gastrin</td>
<td>Stimulates H+ production from parietal cells</td>
</tr>
<tr>
<td>Superficial epithelial cells</td>
<td>Mucus, HCO3⁻</td>
<td>Protect gastric mucosa</td>
</tr>
<tr>
<td>Neuroendocrine cells</td>
<td>Multiple (e.g. somatostatin, inhibits cell secretion)</td>
<td>Involved in neural, hormonal and paracrine pathways</td>
</tr>
</tbody>
</table>

Figure 5. Stimulation of H⁺ secretion from the parietal cell

Gastritis

Definition
- defined histologically: inflammation of the stomach mucosa

Etiology
- some causative agents may play a role in more than one type of gastritis and an individual patient may have histopathological evidence of more than one type of gastritis

Table 5. Updated Sydney Classification of Gastritis

<table>
<thead>
<tr>
<th>Type</th>
<th>Common Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Gastritis</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic/erosive gastritis</td>
<td>Alcohol⁹⁸, Aspirin⁹⁷/NSAID⁹⁸, shock/physiological stress⁹⁸ (seen in ICU patients)</td>
</tr>
<tr>
<td>Helicobacter gastritis</td>
<td>Helicobacter pylori⁹⁸</td>
</tr>
<tr>
<td>Chronic Gastritis</td>
<td></td>
</tr>
<tr>
<td>Non-atrophic</td>
<td>Helicobacter pylori⁹⁸</td>
</tr>
<tr>
<td>Atrophic</td>
<td>Helicobacter pylori⁹⁸, dietary, environmental factors (multi-focal), autoimmunity</td>
</tr>
<tr>
<td>Chemical</td>
<td>NSAID⁹⁸, bile</td>
</tr>
<tr>
<td>Radiation</td>
<td>Radiation injury</td>
</tr>
<tr>
<td>Lymphocytic</td>
<td>Celiac disease, drug</td>
</tr>
<tr>
<td>Eosinophilic</td>
<td>Food allergies</td>
</tr>
<tr>
<td>Non-infectious granulomatous</td>
<td>Crohn’s disease, sarcoidosis</td>
</tr>
<tr>
<td>Other infectious gastritides</td>
<td>Bacteria, viruses, fungi, parasite, TB, syphilis</td>
</tr>
</tbody>
</table>

*Most common causes
Clinical Features
- non-erosive gastritis is asymptomatic (except in certain rare causes like Crohn's Disease); difficult to diagnose clinically or endoscopically
- erosive gastritis can cause bleeding (pain only if progresses to ulcers – rare); can be seen endoscopically

Management
- determined by etiology (see H. Pylori section, G13, NSAID section, G14 and Stress-Induced Ulceration section, G14)
- non-pharmacological: avoidance of mucosal irritants such as alcohol, NSAIDs and foods that trigger symptoms

Peptic Ulcer Disease (PUD)

Definition
- focal defects in the mucosal that penetrate the muscularis mucosal layer results in scarring (defects superficial to the muscularis mucosa have erosions and no scarring)
- peptic ulcer disease includes defects located in the stomach (gastric ulcers) and duodenum (duodenal ulcers)

Etiology

Table 6. Etiology of Peptic Ulcer Disease

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Duodenal</th>
<th>Gastric</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori infection</td>
<td>90%</td>
<td>60%</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>7%</td>
<td>35%</td>
</tr>
<tr>
<td>Physiologic stress-induced</td>
<td>&lt;3%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Zollinger-Ellison (ZE) syndrome</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>

- NSAID negative, H. pylori negative ulcers becoming more commonly recognized
- others: CMV, ischemic, idiopathic
- alcohol: damages gastric mucosa but rarely causes ulcers
- peptic ulcer associated with tobacco, cirrhosis of liver, COPD and chronic renal failure

Clinical Features
- dyspepsia: most common presenting symptom
  - only 20% of patients with dyspepsia have ulcers, while most have functional disease
- may present with complications
  - bleeding 10% (severe if from gastroduodenal artery) (see Bleeding Peptic Ulcer, G13)
  - perforation 2% (usually anterior ulcers)
  - gastric outlet obstruction 2%
  - penetration (posterior) 2%; may also cause pancreatitis
- duodenal ulcers: 6 classical features, but history alone cannot distinguish from functional dyspepsia
  - epigastric pain; may localize to tip of xiphoid
  - burning
  - develops 1-3 h after meals
  - relieved by eating and antacids
  - interrupts sleep
  - periodicity (tends to occur in clusters over wk with subsequent periods of remission)
- gastric ulcers: more atypical symptoms; a biopsy is necessary to exclude malignancy

Investigations
- endoscopy (most accurate)
- upper GI series
- H. pylori tests (see Table 7)
- fasting serum gastrin measurement if Zollinger-Ellison (ZE) syndrome suspected

Treatment
- specific management depends on etiology; (see H. Pylori section, G13, NSAID section, G14 and Stress-Induced Ulceration section, G14)
- eradicate H. pylori if present, chief advantage is to lower ulcer recurrence rate
- stop NSAIDs if possible
- start PPI: inhibits parietal cell H^+/K^-ATPase pump which secretes acid
  - heals most ulcers, even if NSAIDs are continued
- other meds (e.g. histamine H2-antagonists) less effective
- discontinue tobacco
- no diet modifications required but some people have fewer symptoms if they avoid caffeine, alcohol and spices
Management of Bleeding Peptic Ulcers
- OGD to explore upper GI tract (see Figure 6)
- establish risk of rebleeding/continuous bleed
  - clinical risk factors: increased age (>60), bleeding diathesis, history of PUD, comorbid disease, hemodynamically unstable
  - endoscopic signs of recurrent bleeding (active bleeding, visible vessel, clot, red spot) more predictive than clinical risk factors
  - if high risk, consider ICU admission

Figure 6. Approach to management of suspected bleeding peptic ulcer
Adapted from: Gralnek I, Barkun A, Bardou M. Management of acute bleeding from a peptic ulcer. NEJM 2008;359:928-937

**H. pylori-Induced Peptic Ulceration**

Pathophysiology
- *H. pylori*: Gram-negative flagellated rod that resides on but does not invade the gastric mucosa
- acid secreted by parietal cells (stimulated by vagal acetylcholine, gastrin, histamine) necessary for most ulcers
- mucosal defenses moderated by PGE2 and blood flow, mucus, etc.
- theories of how *H. pylori* causes ulcers: none satisfactory, but pattern of colonization correlates with outcome
  - gastritis only in antrum (15% of patients), high gastric acid, associated with peptic ulcer, may progress to gastric metaplasia of duodenum where ulcer forms
  - gastritis throughout stomach (“pangastritis” – 85% of patients), low gastric acid, associated with cancer

Epidemiology
- *H. pylori* is found in about 20% of all Canadians
  - highest prevalence in those raised during 1930s
  - infection most commonly acquired in childhood, presumably by fecal-oral route
  - high prevalence in developing countries, low socioeconomic status (poor sanitation and overcrowding)

Outcome
- gastritis (non-erosive) in 100% of patients but asymptomatic
- peptic ulcer in 15% of patients
- gastric malignancy [gastric carcinoma and mucosal associated lymphomatous tissue (MALT) lymphoma in 0.5% of patients]
- most are asymptomatic but still worthwhile eradicating to lower future risk of peptic ulcer/gastric malignancy and prevent spread to others (mostly children <5 yr of age)
Investigations

Table 7. Diagnosis of *H. pylori* Infection

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive Tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea breath test</td>
<td>90-100%</td>
<td>89-100%</td>
<td>Affected by PPI therapy (false negatives)</td>
</tr>
<tr>
<td>Serology</td>
<td>88-99%</td>
<td>89-95%</td>
<td>Can remain positive after treatment</td>
</tr>
<tr>
<td>Stool antigen test</td>
<td>95-97%</td>
<td>94-98%</td>
<td>Useful for diagnosing acute infection</td>
</tr>
<tr>
<td>Invasive Tests (require endoscopy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>93-99%</td>
<td>95-99%</td>
<td>Gold standard; affected by PPI therapy (false negatives)</td>
</tr>
<tr>
<td>Rapid urease test (on biopsy)</td>
<td>89-98%</td>
<td>93-100%</td>
<td>Rapid</td>
</tr>
<tr>
<td>Microbiology culture</td>
<td>98%</td>
<td>95-100%</td>
<td>Research only</td>
</tr>
</tbody>
</table>

Treatment: *H. pylori* Eradication

- **triple therapy for 7-14 d (Hp-Pac®):** PPI bid (e.g. lansoprazole 30 mg bid) + amoxicillin 1 g bid + clarithromycin 500 mg bid
  - 80% success rate
- **quadruple therapy for 10-14 d:** PPI bid + bismuth 525 mg qid + tetracycline 500 mg qid + metronidazole 250 mg qid
  - only recommended as first line therapy if resistance to clarithromycin or metronidazole is high, or in patients with recent or repeated exposure to these drugs
  - levofloxacin can replace metronidazole or tetracycline
- **sequential therapy**
  - days 1-5: PPI bid + amoxicillin 1 g bid
  - days 6-10: PPI bid + clarithromycin 500 mg bid + tinidazole 500 mg bid
- 5-15% of cases are resistant to all known therapies

**NSAID-Induced Ulceration**

- NSAID use causes gastric mucosal petechiae in virtually all, erosions in most, ulcers in some (25%)—erosions bleed, but usually only ulcers cause significant clinical problems
- most NSAID ulcers are clinically silent: dyspepsia is as common in patients with ulcers as in patients without ulcers; NSAID-induced ulcers characteristically present with complications (bleeding, perforation, obstruction)
- NSAIDs more commonly cause gastric ulcers than duodenal ulcers
- may exacerbate underlying duodenal ulcer disease

**Pathophysiology**

- direct: erosions/petechiae – are due to local (direct) effect of drug on gastric mucosa
- indirect: systemic NSAID effect (intravenous NSAID causes ulcers, but not erosions), inhibits mucosal cyclooxygenase, leading to decreased synthesis of protective prostaglandins, thus leading to ulcers

**Risk Factors For NSAID Causing Peptic Ulcer**

- previous peptic ulcers/UGIB
- age
- high dose of NSAID/multiple NSAIDs being taken
- concomitant corticosteroid use
- concomitant cardiovascular disease/other significant diseases

**Treatment**

- prophylactic cytoprotective therapy with a PPI is recommended if any of the above risk factors exist concomitantly with ASA/NSAID use
- lower NSAID dose or stop all together and replace with acetaminophen
- combine NSAID with PPI or misoprostol
- enteric coating of Aspirin® (ECASA) provides minor benefit since this decreases incidence of erosion, not incidence of ulceration

**Stress-Induced Ulceration**

**Definition**

- ulceration or erosion in the upper GI tract of ill patients, usually in ICU
- lesions most commonly in fundus of stomach

**Pathophysiology**

- unclear: likely involves ischemia; may be caused by CNS disease, acid hypersecretion, Cushing ulcers
- physiological stress (e.g. fever, severe illness, complex post-op course) causes ulcers and erosions
Risk Factors
- mechanical ventilation
- anti-coagulation
- multi-organ failure
- septicemia
- severe surgery/trauma
- CNS injury ("Cushing's ulcers")
- burns involving more than 35% of body surface

Clinical Features
- UGIB (see Upper Gastrointestinal Bleeding, G25)
- painless

Treatment
- prophylaxis with gastric acid suppressants (H$_2$-blockers or PPI) decreases risk of UGIB, but may increase risk of pneumonia
- treatment same as for bleeding peptic ulcer but often less successful

Gastric Carcinoma
- see General Surgery, GS18

Small and Large Bowel

Classification of Diarrhea

Definition
- clinically: diarrhea defined as stools that are looser and/or more frequent than normal; physiologically: 24 h stool weight >200 g (less useful clinically)

Classification
- acute vs. chronic
- small volume (tablespoons of stool; typical of colonic diseases) versus large volume (>1/2 cup stool; typical of small bowel diseases)
- watery (bowel disease) vs. steatorrhea
- secretory (diarrhea persists with fasting) vs. osmotic (diarrhea stops with fasting)

Acute Diarrhea

Definition
- passage of frequent unformed stools for <14 d

Etiology
- most commonly due to infections
- most infections are self-limiting and resolve within 7 d

Risk Factors
- food (seafood, chicken, turkey, eggs, beef)
- medications: antibiotics, laxatives
- others: high risk sexual activity, infectious outbreaks, family history (IBD)

Classification
- broadly divided and classified into inflammatory and non-inflammatory diarrhea
- mechanisms:
  - stimulation of intestinal water secretion and inhibition of water absorption (i.e. secretory problem)
  - in inflammatory diarrhea, organisms and cytotoxins invade mucosa, killing mucosal cells, further perpetuating the diarrhea

<table>
<thead>
<tr>
<th>Table 8. Classification of Acute Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory</strong></td>
</tr>
<tr>
<td>Definition</td>
</tr>
<tr>
<td>Site</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Investigations</td>
</tr>
</tbody>
</table>

Useful Questions in Acute Diarrhea
- Those Fads Wilt
- Travel
- Homosexual contacts
- Outbreaks
- Seafood
- Extra-intestinal signs of IBD
- Family history
- Antibiotics
- Diet
- Steatorrhea
- Weight loss
- Immunosuppressed
- Laxatives
- Tumour history

Infectious Causes of Inflammatory Diarrhea
- "Your Stool Smells Extremely Crappy"
- Yersinia
- Shigella
- Salmonella
- E. coli (EHEC 0157:H7), E. histolytica
- Campylobacter, C. difficile
Table 8. Classification of Acute Diarrhea (continued)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Inflammatory</th>
<th>Non-Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>See Differential Diagnosis of Common Presenting Complaints, G4</td>
<td>See Differential Diagnosis of Common Presenting Complaints, G4</td>
</tr>
<tr>
<td>Differential Diagnosis</td>
<td>Acute presentation of idiopathic inflammatory bowel disease</td>
<td>Acute presentation of non-inflammatory chronic diarrhea (e.g. celiac disease)</td>
</tr>
<tr>
<td>Significance</td>
<td>Higher yield with stool C&amp;S</td>
<td>Lower yield with stool C&amp;S</td>
</tr>
<tr>
<td></td>
<td>Can progress to life-threatening megacolon, perforation, hemorrhage</td>
<td>Chief life-threatening problem is electrolyte disturbances/ fluid depletion</td>
</tr>
<tr>
<td></td>
<td>Antibiotics may benefit</td>
<td>Antibiotics unlikely to be helpful</td>
</tr>
</tbody>
</table>

Investigations
- stool cultures/microscopy (C&S/O&P) are required only if diarrhea is inflammatory, severe, or for epidemiological purposes (day care worker, nursing home resident, etc.)
  - C&S only tests Campylobacter, Salmonella, Shigella, E. Coli
  - other organisms must be ordered separately
- flexible sigmoidoscopy: useful if inflammatory diarrhea suspected
  - biopsies are the most useful method of distinguishing idiopathic IBD (Crohn's disease and ulcerative colitis) from infectious colitis or acute self-limited colitis
- C. difficile toxin: indicated when recent/remote antibiotic use, hospitalization, nursing home or recent chemotherapy

Treatment
- fluid and electrolyte replacement orally in most cases, intravenous if severe extremes of age/coma
- anti-diarrheals
  - antimitoty agents: diphenoxylate, loperamide (Imodium®); contraindicated in mucosal inflammation
    - side effects: abdominal cramps, toxic megacolon
  - absorbants: kaolin/pectin (Kaopectate®), methylcellulose, activated attapulgite
    - act by absorbing intestinal toxins/micro-organisms, or by coating intestinal mucosa
    - much less effective than antimitoty agents
  - modifiers of fluid transport: bismuth subsalicylate (Pepto-Bismol®) may be helpful
- antibiotics: rarely indicated
  - risks
    - prolonged excretion of enteric pathogen (especially Salmonella)
    - drug side effects (including C. difficile infection)
    - development of resistant strains
    - renal failure/hemolyis (enterohemorrhagic E. Coli O157:H7)
- indications for antimicrobial agents in acute diarrhea:
  - septicemia
  - prolonged fever with fecal blood or leukocytes
  - clearly indicated: Shigella, V. cholerae, C. difficile, traveller’s diarrhea [enterotoxigenic E. coli (ETEC)], Giardia, Entamoeba histolytica, Cyclospora
  - situational: Salmonella, Campylobacter, Yersinia, non-enterotoxigenic E. coli
  - Salmonella: always treat Salmonella typhi (typhoid or enteric fever); treat other Salmonella only if there is underlying immunodeficiency, hemolytic anemia, extremes of age, aneurysms, prosthetic valve grafts/joints, sickle cell disease

Traveller’s Diarrhea
- see Infectious Diseases, ID14

Chronic Diarrhea

Definition
- passage of frequent unformed stool for >14 d
- approach is similar to that of acute diarrhea except that the majority of cases are non-infectious

Etiology/Classification
- see Differential Diagnosis of Common Presenting Complaints, G4

Investigations
- guided by history
- stool analysis for: C. difficile toxin, C&S, O&P ± fecal fat, WBC.
- blood for: CBC, electrolytes, CRP, TSH, celiac serology (anti-tTG, protein electrophoresis, IgA)
- colonoscopy and ileoscopy with biopsy
- upper GI endoscopy with duodenal biopsy
- wireless small bowel endoscopy capsule (last resort – very costly)
- trial of lactose free diet
  - caveat: may delay diagnosis of IBD and celiac disease
Maldigestion and Malabsorption

Definition
- **maldigestion**: inability to break down large molecules in the lumen of the intestine into their component small molecules
- **malabsorption**: inability to transport molecules across the intestinal mucosa into circulation
- **malassimilation**: encompasses both maldigestion and malabsorption

Etiology
- **maldigestion**
  - inadequate mixing of food with enzymes (e.g. post-gastrectomy)
  - pancreatic exocrine deficiency
  - primary diseases of the pancreas (e.g. cystic fibrosis, pancreatitis, cancer)
  - bile salt deficiency
    - terminal ileal disease (impairment recycling), bacterial overgrowth (deconjugation of bile salts), rarely liver disease (cholestasis)
  - specific enzyme deficiencies (e.g. lactase)
- **malabsorption**
  - inadequate absorptive surface
    - infections/infestations (e.g. Whipple’s disease, Giardia)
    - immunologic or allergic injury (e.g. celiac disease)
    - infiltration (e.g. lymphoma, amyloidosis)
    - fibrosis (e.g. systemic sclerosis, radiation enteritis)
    - bowel resection
    - extensive Crohn’s disease
  - drug-induced
    - cholestyramine, ethanol, neomycin, tetracycline and other antibiotics
  - endocrine
    - diabetes (complex pathogenesis)

Clinical Features
- symptoms usually vague unless disease is severe
- weight loss, diarrhea, steatorrhea, weakness, fatigue
- manifestations of malabsorption/deficiency (see Table 9)

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Absorption</th>
<th>Signs and Symptoms</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Duodenum, upper jejunum</td>
<td>Hypochromic, microcytic anemia, glossitis, koilonychia (spoon nails), pica</td>
<td>↓ Hb, ↓ serum Fe, ↓ serum ferritin</td>
</tr>
<tr>
<td>Calcium</td>
<td>Duodenum, upper jejunum (binds to Ca&lt;sup&gt;2+&lt;/sup&gt; binding-protein in cells; levels increased by Vit D)</td>
<td>Metabolic bone disease, may get tetany and paresthesias if serum calcium falls (see Endocrinology, E40)</td>
<td>↓ serum Ca&lt;sup&gt;2+&lt;/sup&gt;, ↓ serum Mg&lt;sup&gt;2+&lt;/sup&gt;, and ↑ ALP Evaluate for ↓ bone mineralization radiographically (DEXA)</td>
</tr>
<tr>
<td>Folic acid</td>
<td>Jejunum</td>
<td>Megaloblastic anemia, glossitis, ↓ red cell folate (may see ↑ folic acid with bacterial overgrowth)</td>
<td>↓ serum folic acid</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>B&lt;sub&gt;12&lt;/sub&gt; ingested and bound to R proteins mainly from salivary glands; stomach secretes intrinsic factor (IF) in acidic medium; in basic medium, proteases from the pancreas cleave R protein and B&lt;sub&gt;12&lt;/sub&gt;-IF complex forms, protecting B&lt;sub&gt;12&lt;/sub&gt; from further protease attack; B&lt;sub&gt;12&lt;/sub&gt; absorbed in ileum and binds to transcobalamine (TC)</td>
<td>Subacute combined degeneration of the spinal cord, peripheral/optic neuropathy, dementia, megaloblastic anemia, glossitis</td>
<td>Differentiate causes by Schilling test when available Positive anti-intrinsic factor antibodies and atrophic gastritis point toward pernicious anemia (see Hematology, H22)</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>Complex polysaccharides hydrolyzed to oligosaccharides and disaccharides by salivary and pancreatic enzymes Monosaccharides absorbed in duodenum/jejunum</td>
<td>Generalized malnutrition, weight loss, flatulence and diarrhea</td>
<td>Hydrogen breath test Trial of carbohydrate-restricted diet D-xylene test</td>
</tr>
<tr>
<td>Protein</td>
<td>Digestion at stomach, brush border, and inside cell Absorption occurs primarily in the jejunum</td>
<td>General malnutrition and weight loss, amenorrhea and ↓ libido if severe</td>
<td>↓ serum albumin (low sensitivity)</td>
</tr>
<tr>
<td>Fat</td>
<td>Lipase, colipase, phospholipase A (pancreatic enzymes) and bile salts needed for digestion Products of lipolysis form micelles which solubilize fat and aid in absorption Fatty acids diffuse into cell cytoplasm</td>
<td>Generalized malnutrition, weight loss and diarrhea Foul-smelling feces + gas Steatorrhea</td>
<td>Small bowel biopsy MRCP, ERCP, pancreatic function tests Quantitative stool fat test (72 h) (Sudan stain of stool) (C-triolein breath test)</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Dietary sources (e.g. milk, eggs, liver, carrots, sweet potatoes)</td>
<td>Night blindness Dry skin Keratomalacia</td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Skin (via UV light) or diet (e.g. eggs, fish oil, fortified milk)</td>
<td>Osteomalacia in adults Rickets in children</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Dietary sources (e.g. vegetable oils, nuts, leafy green vegetables)</td>
<td>Retinopathy, neurological problems</td>
<td></td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Synthesized by intestinal flora ↑ risk of deficiency after prolonged use of broad spectrum antibiotics and/or starvation</td>
<td>Prolonged INR causes bleeding</td>
<td></td>
</tr>
</tbody>
</table>

* Calcium malabsorption more commonly causes decreased bone density rather than hypocalcemia because serum calcium levels are protected by leaching calcium from the bone
Investigations
- transglutaminase serology/protein electrophoresis and abdominal imaging are most useful because celiac disease and chronic pancreatitis are the two most common causes of steatorrhea
- 72 h stool collection (weight, fat content) documents steatorrhea
- serum carotene, folate, Ca\(^{2+}\), Mg\(^{2+}\), vitamin B\(_{12}\), albumin, ferritin, serum iron solution, INR/PTT
- stool fat globules on fecal smear stained with Sudan (rarely used)
- other tests specific for etiology (e.g. CT scan/MRI to visualize pancreas)
- trial of therapy with pancreatic enzymes

Treatment
- dependent on underlying etiology

Celiac Disease (Gluten Enteropathy/Sprue)

Definition
- abnormal small intestine mucosa due to intestinal reaction to gliadin, a component of gluten found in cereal grains

Etiology
- only autoimmune disease in which antigen (α-gliadin) is recognized
- associated with other autoimmune diseases, especially thyroid disease
- gluten, a protein in cereal grains, broken down to gliadin, is toxic factor
- HLA-DQ2 (chromosome 6) found in 80-90% of patients compared with 20% in general population; also associated with HLA-DQ8

Epidemiology
- more common in women
- family history: 15% of first-degree relatives
- may present any time from infancy (when cereals introduced) to elderly
- peak presentation in infancy

Clinical Features
- classically: diarrhea, weight loss, anemia, symptoms of vitamin/mineral deficiency, failure to thrive; now more commonly bloating, gas, iron deficiency
- improves with gluten-free diet, deteriorates when gluten reintroduced
- disease is usually most severe in proximal bowel
  - thus iron, calcium and folic acid deficiency more common than vitamin B\(_{12}\) deficiency
- gluten enteropathy may be associated with dermatitis herpetiformis skin eruption, epilepsy, myopathy, depression, paranoia, infertility, bone fractures/metabolic bone disease

Investigations
- small bowel mucosal biopsy (usually duodenum) is diagnostic with:
  - villous atrophy and crypt hyperplasia
  - increased number of plasma cells and lymphocytes in lamina propria
  - increased intraepithelial lymphocytes
  - villous atrophy also seen in small bowel overgrowth, Crohn's, lymphoma, Giardia, HIV
- consider CT enterography to visualize small bowel to rule out lymphoma
- evidence of malabsorption (localized or generalized)
  - steatorrhea
  - low levels of ferritin/iron saturation, Ca\(^{2+}\), Fe, albumin, cholesterol, carotene, B\(_{12}\) absorption
- improvement with a gluten-free diet; should not be started before anti-tTG and biopsy
- serological tests
  - serum anti-tTG antibody, IgA, is 90-98% sensitive, 94-97% specific
  - IgA deficient patients have false-negative anti-tTG
  - thus measure serum IgA concomitantly (via serum protein electrophoresis)
  - fecal fat >7%

Treatment
- dietary counselling
  - gluten free diet: avoid barley, rye, wheat
    - oats allowed if not contaminated by other grains
  - rice and corn flour are acceptable
  - iron, folate supplementation (with supplementation of other vitamins as needed)
- if poor response to diet change, consider:
  - alternate diagnosis
  - non-adherence to gluten-free diet
  - concurrent disease (e.g. microscopic colitis, pancreatic insufficiency)

Gluten found in “BROW”
Barley
Rye
Oats (controversial)
Wheat

Gluten Microchallenge with Wheat-based Starch Hydrolysates in Celiac Disease Patients
Aliment Pharm Therap 2008;28:1240-1248
Study: Randomized, placebo-controlled, prospective study with 24 wk follow-up.
Participants: 90 patients with celiac disease in remission.
Intervention: Patients either received glucose syrups, maltodextrins or placebo.
Primary Outcome: Small bowel mucosal morphology and inflammation, symptoms, celiac serology and malabsorption.
Results: There were no significant differences between the intervention and control group in small-bowel morphology and inflammation, gastrointestinal symptoms, serology or malabsorption parameters.
Conclusion: Celiac patients can safely continue to consume wheat-based starch hydrolysates, glucose syrups and maltodextrins.
- development of intestinal (enteropathy-associated T-cell) lymphoma (abdominal pain, weight loss, palpable mass)
- development of diffuse intestinal ulceration, characterized by aberrant intraepithelial T-cell population (precursor to lymphoma)

**Prognosis**
- associated with increased risk of lymphoma, carcinoma (e.g. small bowel and colon)
- risk of malignancy may be lowered by dietary gluten restriction

---

**Inflammatory Bowel Disease (IBD)**

**Definition**
- Crohn’s disease, ulcerative colitis, indeterminate colitis

**Pathophysiology**
- poorly understood
- sustained response of the immune system, perhaps to enteric flora in a genetically predisposed individual
- current hypothesis: lack of appropriate down-regulation of immune responsiveness

**Genetics**
- increased risk of both UC and CD in relatives of patients with either disease, especially siblings, early onset disease
  - familial risk greater if proband has CD rather than UC
- likely polygenomic pattern: 9 gene loci described to be associated
- CARD15/NOD2 gene mutation associated with CD (relative risk in heterozygote is 3, in homozygote is 40), especially Ashkenazi Jews, early onset disease, ileal involvement, fistulizing and stenotic disease
  - CARD15 gene product modulates NFκB, which is required for the innate immune response to microbial pathogens, best expressed in monocytes-macrophages

**Clinical Features**

**Table 10. Clinical Differentiation of Ulcerative Colitis from Crohn’s Disease**

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Any part of GI tract</td>
<td>Isolated to large bowel</td>
</tr>
<tr>
<td></td>
<td>- Small bowel + colon: 50%</td>
<td>Always involves rectum, may progress proximally</td>
</tr>
<tr>
<td></td>
<td>- Small bowel only: 30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Colon only: 20%</td>
<td></td>
</tr>
<tr>
<td><strong>Rectal Bleeding</strong></td>
<td>Uncommon</td>
<td>Very common (80%)</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>Less prevalent</td>
<td>Frequent small stools</td>
</tr>
<tr>
<td><strong>Abdominal Pain</strong></td>
<td>Post-prandial/colicky</td>
<td>Less common</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Urgency/Tenesmus</strong></td>
<td>Uncommon (unless rectum involved)</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Palpable Mass</strong></td>
<td>Frequent (25%), RLO</td>
<td>Rare (if present, cecum full of stool)</td>
</tr>
<tr>
<td><strong>Recurrence After Surgery</strong></td>
<td>Common</td>
<td>None post-colectomy</td>
</tr>
<tr>
<td><strong>Endoscopic Features</strong></td>
<td>Ulcers (aphthous, stellate, linear), patchy lesions, pseudopolyps, cobblestoning</td>
<td>Continuous diffuse inflammation, erythema, friability, loss of normal vascular pattern, pseudopolyps</td>
</tr>
<tr>
<td><strong>Histologic Features</strong></td>
<td>Transmural distribution with skip lesions</td>
<td>Mucosal distribution, continuous disease (no skip lesions)</td>
</tr>
<tr>
<td></td>
<td>Focal inflammation</td>
<td>Granulomas absent</td>
</tr>
<tr>
<td></td>
<td>± noncaseating granulomas, deep</td>
<td>Gland destruction, crypt abscess</td>
</tr>
<tr>
<td></td>
<td>fissuring + aphthous ulcerations, strictures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glands intact</td>
<td></td>
</tr>
<tr>
<td><strong>Radiologic Features</strong></td>
<td>Cobblestone mucosa</td>
<td>Lack of haustra</td>
</tr>
<tr>
<td></td>
<td>Frequent strictures and fistulae</td>
<td>Strictures rare and suggests complicating cancer</td>
</tr>
<tr>
<td></td>
<td>AXR: Bowel wall thickening “string sign”</td>
<td></td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Strictures, fistulae, perianal disease</td>
<td>Toxic megacolon</td>
</tr>
<tr>
<td><strong>Colon Cancer Risk</strong></td>
<td>Increased if &gt;30% of colon involved</td>
<td>Increased except in proctitis</td>
</tr>
</tbody>
</table>
Table 11. Extraintestinal Manifestations (EIM) of IBD

<table>
<thead>
<tr>
<th>System</th>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema Nodosum</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Pyoderma Gangrenosum</td>
<td>10%</td>
<td>Less common</td>
</tr>
<tr>
<td>Perianal skin tags</td>
<td>75-80%</td>
<td>Rare</td>
</tr>
<tr>
<td>Oral mucosal lesions</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Statistically associated in 5-10% of those with IBD but not an EIM</td>
<td></td>
</tr>
<tr>
<td>Rheumatologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>15-20% of those with IBD (CD&gt;UC)</td>
<td></td>
</tr>
<tr>
<td>Ankylosing Spondylitis</td>
<td>10% of those with IBD (CD&gt;UC)</td>
<td></td>
</tr>
<tr>
<td>Sacroilitis</td>
<td>Occurs equally in CD and UC</td>
<td></td>
</tr>
<tr>
<td>Ocular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uveitis (vision threatening)</td>
<td>3-4% of IBD patients (CD&gt;UC)</td>
<td></td>
</tr>
<tr>
<td>Episcleritis (benign)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>15-35% of patients with ileal Crohn’s</td>
<td></td>
</tr>
<tr>
<td>Primary sclerosing cholangitis (PSC)</td>
<td>1-5% of IBD cases involving colon</td>
<td></td>
</tr>
<tr>
<td>Fatty liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculi</td>
<td>Most common in CD, especially following ileal resection</td>
<td></td>
</tr>
<tr>
<td>Ureteric obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fistulae</td>
<td>Characteristic of Crohn’s</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin deficiencies (B₁₂, Vit ADEK)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatitis (rare)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Crohn’s Disease (CD)

Definition
- chronic transmural inflammatory disorder potentially affecting the entire gut from mouth to perianal region (“gum to bum”)

Epidemiology
- incidence 1-6/100,000; prevalence 10-100/100,000
- bimodal: onset before 30 yr, second smaller peak age 60; M=F
- incidence of Crohn’s increasing (relative to UC) especially in young females
- more common in Caucasians, Ashkenazi Jews
  - risk in Asians increases with move to Western countries
- smoking incidence in Crohn’s patients is higher than general population

Clinical Features
- natural history unpredictable; young age, perianal disease, and need for corticosteroids have been associated with poor prognosis, but associations are not strong enough to guide clinical decisions
- most often presents as recurrent episodes of abdominal cramps, diarrhea and weight loss
- most common location: ileum + ascending colon
- ileitis may present with post-prandial pain, vomiting, RLQ mass; mimics acute appendicitis
- fistulae, fissures, abscesses are common
- extra-intestinal manifestations (see Table 11) are more common with colonic involvement
- linear ulcers leading to mucosal islands and “cobblestone” appearance
- deep fissures with risk of perforation into contiguous viscera (leads to fistulae and abscesses)
- enteric fistulae may communicate with skin, bladder, vagina and other parts of bowel
- granulomas are found in 50% of surgical specimens, 15% of mucosal biopsies

Investigations
- colonoscopy with biopsy to visualize (less often gastroscopy)
- CT/MR enterography to visualize small bowel
- CRP elevated in most new cases, useful to monitor treatment response
- bacterial cultures, O&P, C. difficile toxin to exclude other causes of inflammatory diarrhea

Figure 7. Traditional graded approach to induction therapy in Crohn’s disease

Note: Starting with immunosuppressives plus immunomodulators (“bottom-up approach”) increasingly being used (Lancet 2009;373:180-187). Combination of azathioprine and infliximab has the highest remission rate yet described with medical treatment (NEJM 2010;362:1383-1395).

Characteristically more than 1 yr between onset of symptoms and diagnosis of Crohn’s disease.
Management (also see Figure 7)

Table 12. Management of Crohn’s Disease

<table>
<thead>
<tr>
<th>Management</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle/Diet</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td></td>
<td>Fluids only during acute exacerbation</td>
</tr>
<tr>
<td></td>
<td>Enteral diets may aid in remission</td>
</tr>
<tr>
<td></td>
<td>No evidence for any non-enteral diet changing the natural history of Crohn’s disease, but may affect symptoms</td>
</tr>
<tr>
<td></td>
<td>Those with extensive small bowel involvement or extensive resection require electrolyte, mineral and vitamin supplements (vit D, Ca²⁺, Mg²⁺, Fe, B₁₂)</td>
</tr>
<tr>
<td></td>
<td>G21</td>
</tr>
<tr>
<td></td>
<td>Gastroenterology</td>
</tr>
<tr>
<td></td>
<td>Biologics</td>
</tr>
<tr>
<td></td>
<td>Infliximab IV (Remicade®) or adalimumab SC (Humira®): both = antibody to TNF-α</td>
</tr>
<tr>
<td></td>
<td>Efficacy controversial: most evidence for mild colonic disease</td>
</tr>
<tr>
<td></td>
<td>Antidiarrheal agents*</td>
</tr>
<tr>
<td></td>
<td>Loperamide (Imodium®) &gt; diphenoxylate (Lomotil®) &gt; codeine (cheap but addictive)</td>
</tr>
<tr>
<td></td>
<td>All work by decreasing small bowel motility</td>
</tr>
<tr>
<td></td>
<td>Caution if colitis is severe (risk of precipitating toxic megacolon), therefore avoid during flare-ups</td>
</tr>
<tr>
<td></td>
<td>5-ASA</td>
</tr>
<tr>
<td></td>
<td>Efficacy controversal: most evidence for mild colonic disease</td>
</tr>
<tr>
<td></td>
<td>Sulfasalazine (Salazopyrin®): 5-ASA bound to sulfapyridine</td>
</tr>
<tr>
<td></td>
<td>Hydrolysis by intestinal bacteria releases 5-ASA (active component)</td>
</tr>
<tr>
<td></td>
<td>Dose-dependent efficacy</td>
</tr>
<tr>
<td></td>
<td>Mesalamine (Pentasa®): coated 5-ASA releases 5-ASA in the ileum and colon</td>
</tr>
<tr>
<td></td>
<td>Antibiotics</td>
</tr>
<tr>
<td></td>
<td>e.g. metronidazole (20 mg/kg/d, bid or tid dosing) or ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td>Best described for perianal Crohn’s, although characteristically relapse when discontinued</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Prednisone: starting dose 40 mg OD for acute exacerbations; IV methylprednisolone if severe</td>
</tr>
<tr>
<td></td>
<td>No proven role for steroids in maintaining remissions; masks intra-abdominal sepsis</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressives</td>
</tr>
<tr>
<td></td>
<td>6-mercaptopurine (6-MP), azathioprine (Imuran®); methotrexate (used less often)</td>
</tr>
<tr>
<td></td>
<td>More often used to maintain remission than to treat active inflammation</td>
</tr>
<tr>
<td></td>
<td>Most commonly used as steroid-sparing agents</td>
</tr>
<tr>
<td></td>
<td>i.e. to lower risk of relapse as corticosteroids are withdrawn</td>
</tr>
<tr>
<td></td>
<td>May require &gt;3 mo to have beneficial effect; usually continued for several years</td>
</tr>
<tr>
<td></td>
<td>May help to heal fistulae, decrease disease activity</td>
</tr>
<tr>
<td></td>
<td>Side effects: vomiting, pancreatitis, bone marrow suppression, increased risk of malignancy</td>
</tr>
<tr>
<td></td>
<td>Biologics</td>
</tr>
<tr>
<td></td>
<td>Infliximab IV (Remicade®) or adalimumab SC (Humira®): both = antibody to TNF-α</td>
</tr>
<tr>
<td></td>
<td>Proven effective for treatment of fistulae and patients with medically refractory CD</td>
</tr>
<tr>
<td></td>
<td>First-line immunosuppressive therapy with infliximab + azathioprine more effective than using either alone</td>
</tr>
<tr>
<td></td>
<td>Surgical/Experimental</td>
</tr>
<tr>
<td></td>
<td>Surgical treatment (see General Surgery, GS30)</td>
</tr>
<tr>
<td></td>
<td>Surgery generally reserved for complications such as fistulae, obstruction, abscess, perforation, bleeding and for medically refractory disease</td>
</tr>
<tr>
<td></td>
<td>If &lt;50% or &lt;200 cm of functional small intestine, risk of short bowel syndrome</td>
</tr>
<tr>
<td></td>
<td>At least 50% clinical recurrence within 5 yr; 85% within 15 yr; endoscopic recurrence rate even higher</td>
</tr>
<tr>
<td></td>
<td>40% likelihood of second bowel resection, 30% likelihood of third bowel resection</td>
</tr>
<tr>
<td></td>
<td>Complications of ileal resection:</td>
</tr>
<tr>
<td></td>
<td>&lt;100 cm resected → watery diarrhea (impaired bile salt absorption)</td>
</tr>
<tr>
<td></td>
<td>Treatment: cholestyramine or anti-diarrheals e.g. loperamide</td>
</tr>
<tr>
<td></td>
<td>&gt;100 cm resected → steatorrhea (reduced mucosal surface area, bile salt deficiency)</td>
</tr>
<tr>
<td></td>
<td>Treatment: fat restriction, medium chain triglycerides</td>
</tr>
<tr>
<td></td>
<td>Biological Therapies for Inflammatory Bowel Diseases</td>
</tr>
<tr>
<td></td>
<td>Gastroenterology 2009;136:1182-1197</td>
</tr>
<tr>
<td></td>
<td>Although the etiology of inflammatory bowel disease (IBD) is unknown, biological therapies (BT) that target key molecules in innate and adaptive immune pathways have been designed.</td>
</tr>
<tr>
<td></td>
<td>Anti-TNF Agents (infliximab, adalimumab, certolizumab): effective in CD, less effective for UC. Increase mucosal healing, decrease need for hospitalizations and surgeries, and can induce steroid-free remission. At least 10% of patients annually develop irremont due to BT and/or a loss of response.</td>
</tr>
<tr>
<td></td>
<td>Promising New BT: Anti-Interleukin-12/Interleukin-23 p40 target factors more often associated with CD, while anti–IFN-antibodies may treat CD and UC.</td>
</tr>
<tr>
<td></td>
<td>Selective Anti-Adhesion Molecules</td>
</tr>
<tr>
<td></td>
<td>BT Without Established Efficacy: Recombinant human cytokines, blockade of T-cell activation (daclizumab and basiliximab) and stimulators of the innate immune system.</td>
</tr>
<tr>
<td></td>
<td>Conclusion: Anti-TNF agents are effective treatments for IBD. There is a need to develop salvage biologic therapies for patients who do not respond to a first biological drug. BT’s have a safety risk, so their place in treatment algorithms must be defined carefully.</td>
</tr>
</tbody>
</table>

*Cholestyramine: a bile-salt binding resin; for watery diarrhea with <100 cm of terminal ileum diseased or resected; however, non-specific anti-diarrheals are more convenient and often more potent.

Prognosis

- highly variable course
- 10% disabled by the disease eventually, spontaneous remission also described
- increased mortality, especially with more proximal disease, greatest in the first 4-5 yr
- complications include:
  - intestinal obstruction/perforation
  - fistula formation
  - malignancy (lower risk compared to UC)
- surveillance colonoscopy same as ulcerative colitis (see below) if more than 1/3 of colon involved
Ulcerative Colitis (UC)

Definition
- inflammatory disease affecting colonic mucosa anywhere from rectum (always involved) to cecum

Epidemiology
- incidence 2-10/100,000; prevalence 35-100/100,000 (more common than Crohn’s)
- 2/3 onset by age 30 (with second peak after 50); M=F
- small hereditary contribution (15% of cases have 1st degree relative with disease)
- risk is less in smokers
- inflammation limited to rectum or left colon is more common than pancolitis

Pathology
- disease can involve any portion of lower bowel ranging from rectum only (proctitis) to entire colon (pancolitis)
- inflammation seen is diffuse, continuous and confined to mucosa

Clinical Features
- rectal bleeding is the hallmark feature, however diarrhea may be present if more than the rectum is involved
  - can also have abdominal cramps/pain, especially with defecation
  - severity of colonic inflammation correlates with symptoms (stool volume, amount of blood in stool)
  - tenesmus, urgency, incontinence
  - systemic symptoms: fever, anorexia, weight loss, fatigue in severe cases
  - extra-intestinal manifestations (see Table 11)
  - characteristic exacerbations and remissions; 5% of cases are fulminant

Investigations
- sigmoidoscopy with mucosal biopsy (to exclude self-limited colitis) without bowel prep often sufficient for diagnosis
- colonoscopy helpful to determine extent of disease; contraindicated in severe exacerbation
- CT colonography (formerly barium enema) if colonoscopy cannot be done; contraindicated in severe disease
- stool culture, microscopy, C. difficile toxin assay necessary to exclude infection
- no single confirmatory test

Management
- mainstays of treatment: 5-ASA (mesalamine) derivatives and corticosteroids, with azathioprine used in steroid-dependent or resistant cases
- diet of little value in decreasing inflammation but may alleviate symptoms
- antidiarrheal medications generally not indicated in UC
- 5-ASA
  - topical (suppository or enema): very effective for distal disease (distal to splenic flexure), preferable to corticosteroids
  - oral: effective for mild to moderate, but not severe colitis (4 g/d)
  - e.g. sulfasalazine 3-4 g/d, mesalamine 4 g/d
  - commonly used in maintaining remission (decreases yearly relapse rate from 60% to 15%)
  - may decrease rate of colorectal cancer
- corticosteroids
  - to remit acute disease, especially if severe or first attack; may need maximum dose IV steroids initially (e.g. methylprednisolone 30 mg IV q12h)
  - limited role as maintenance therapy
  - use suppositories for proctitis, enemas for proctosigmoiditis
  - topical steroids (e.g. hydrocortisone foam, budesonide enemas) for inflammation distal to splenic flexure
- immunosuppressants (steroid-sparing)
  - if severe UC is refractory to steroid therapy, consider adding IV cyclosporine or IV infliximab within 3-5 d of recognition of need for salvage – rapidly effective, but helpful only in a minority of patients
  - azathioprine: too slow to rapidly resolve acute relapse
    - most commonly used to induce and maintain remission as corticosteroids withdrawn
- surgical treatment
  - early in severe UC, especially fulminant cases and toxic megacolon – consider operation if no response after 3-5 d of corticosteroids, or after 4-7 d of immunosuppressive medical therapy
  - aim for cure with colectomy; bowel continuity can be restored with ileal pouch-anal anastomosis
  - indications: failure of adequate medical therapy, toxic megacolon, uncontrollable bleeding, pre-cancerous changes detected either by endoscopy or endoscopic biopsies (dysplasia), inability to taper corticosteroids

In UC, non-bloody diarrhea is frequently the initial presentation; eventually progressing to bloody diarrhea.
Figure 8. Medical management of severe ulcerative colitis

Complications
- similar to CD, except:
  - more liver problems (especially primary sclerosing cholangitis in men)
  - greater risk of colorectal cancer
    - risk increases with duration and extent of disease (5% at 10 yr, 15% at 20 yr for pancolitis; overall relative risk is 8%) 
    - risk also increases with active mucosal inflammation and sclerosing cholangitis 
    - thus, regular colonoscopy and biopsy in pancolitis of ≥8 yr is indicated
  - toxic megacolon (transverse colon diameter >6 cm on abdominal x-ray) with immediate danger of perforation (see General Surgery, GS26)

Prognosis
- chronic relapsing pattern in most patients 
- 10-15% chronic continuous pattern 
- >1 attack in almost all patients 
- more colonic involvement in the 1st year correlates with increased severity of attacks and increased colectomy rate 
  - colectomy rate = 1% for all patients after the 1st year; 20-25% eventually undergo colectomy 
  - normal life expectancy 
  - if proctitis only, usually benign course

Irritable Bowel Syndrome (IBS)

Definition
- a form of functional bowel disease, more than just a label for GI symptoms unexplained after investigations

Epidemiology
- 20% of North Americans 
- onset of symptoms usually in young adulthood 
- F>M
Pathophysiology

- associated with either abnormal perception of intestinal activity or abnormal intestinal motility
- abnormal motility: multiple abnormalities described; unclear if associations or if causative
- psychological: stress may increase IBS symptoms but does not cause IBS

Diagnosis

**Table 13. Rome III Criteria for Diagnosing Irritable Bowel Syndrome**

<table>
<thead>
<tr>
<th>IBS Rome III Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥12 wk in the past 12 mo of abdominal discomfort or pain that has 2 out of 3 features:</td>
</tr>
<tr>
<td>• Relieved with defecation</td>
</tr>
<tr>
<td>• Associated with a change in frequency of stool</td>
</tr>
<tr>
<td>• Associated with a change in consistency of stool</td>
</tr>
</tbody>
</table>

- The following are supportive, but not essential to the diagnosis:
  • Abnormal stool frequency (>3/d or <3/wk)
  • Abnormal stool form (lumpy/hard/loose/watery) >1/4 of defecations
  • Abnormal stool passage (straining, urgency, feeling of incomplete evacuation) >1/4 of defecations
  • Passage of mucus >1/4 of defecations
  • Bloating

**Diagnosis of IBS Less Likely in Presence of “Red Flag” Features**

- Weight loss
- Fever
- Nocturnal defecation
- Abnormal gross findings on flexible sigmoidoscopy

Normal Physical Exam

**Investigations**

- if history consistent with Rome III criteria, no alarm symptoms, and no family history of IBD or colorectal cancer, limited investigations required
- aim is to rule out diseases which mimic IBS
  • CBC, TSH, albumin, CRP, tTG serology with protein electrophoresis
  • stool for C&S, O&P, fat excretion if diarrhea present
  • consider sigmoidoscopy

**Management**

- reassurance, explanation, support, aim for realistic goals
- relaxation therapy, biofeedback, hypnosis, stress reduction
- no therapeutic agent consistently effective, pain most difficult to control
- symptom-guided treatment
  - pain predominant
    • antispasmodic medication before meals (e.g. hyoscine, pinaverium, trimebutine)
    • increase dietary fibre (bran or psyllium)
    • tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI)
  - diarrhoea predominant
    • increase dietary fibre (bran or psyllium) to increase stool consistency
    • loperamide (Imodium®)
    • diphenoxylate (Lomotil®)
    • cholestyramine 4 g QID
  - constipation predominant
    • exercise and increase fibre in diet
    • osmotic or other laxatives

**Prognosis**

- 80% improve over time
- most have intermittent episodes
- normal life expectancy

**Constipation**

**Definition**

- passage of infrequent or hard stools with straining (stool water <50 mL/d); bowel frequency <3 times/wk

**Epidemiology**

- increasing prevalence with age; F>M
- rare in Africa and India where stool weight is 3-4x greater than in Western countries
Etiology
• most common: idiopathic attributed to colon dysmotility but this is difficult to measure
• organic causes
  • medication side effects (narcotics, antidepressants) are the most common
  • intestinal obstruction, left sided colon cancer (consider in older patients) and fecal impaction
  • metabolic
    • diabetes mellitus
    • hyperthyroidism
    • hypercalcemia, hypokalemia, uremia
  • neurological
    • intestinal pseudo-obstruction
    • Parkinson's disease
    • multiple sclerosis
  • collagen vascular disease (e.g. scleroderma)
  • painful anal conditions (e.g. fissures)

Clinical Presentation
• overlaps with irritable bowel syndrome
• abdominal pain relieved by defecation, hard stools, straining and pain with defecation,
  flatulence, overflow diarrhea, tenesmus (sense of incomplete evacuation), abdominal distention,
  <3 BM/wk

Investigations
• consider colon visualization (colonoscopy, CT colonography), although chronic constipation by
  itself is rarely due to colonic mucosal disease
• classification based on colon transit time, can be quantitated by swallowing radio-opaque
  markers to measure colonic transit time (normal: 70 h)
  (1) normal = misperception of normal defecation (irritable bowel syndrome)
  (2) prolonged throughout = "colonic inertia" (infrequent bowel movements with gas/bloating,
    tends to occur in youth)
  (3) outlet obstruction = inability to coordinate pelvic floor muscles to empty rectum, straining,
    stool in rectum on digital exam, tends to occur in old age
• combination of (2) and (3) common

Treatment (in order of increasing potency)
• dietary fibre
  • useful if mild or moderate constipation, but not if severe
  • aim for 30 g daily, increase dose slowly
• surface-acting (soften and lubricate)
  • docusate salts, mineral oils
• osmotic agents (effective in 2-3 d)
  • lactulose, sorbitol, magnesium salts (e.g. magnesium hydroxide, aka milk of magnesia),
    lactitol, polyethylene glycol 3350
• cathartics/stimulants (effective in 24 h)
  • castor oil, senna (avoid prolonged use to prevent melanosis coli), bisacodyl
• enemas and suppositories (e.g. saline enema, phosphate enema, glycerin suppository, bisacodyl
  suppository)

Upper Gastrointestinal Bleeding

Definition
• bleeding proximal to the ligament of Treitz (75% of GI bleeds)
  • ligament of Treitz: suspensory ligament where fourth portion of the duodenum transitions to
    jejunum

Etiology
• above the GE junction
  • epistaxis
  • esophageal varices (10-30%)
  • esophagitis
  • esophageal cancer
  • Mallory-Weiss tear (10%)
• stomach
  • gastric ulcer (20%) (see Peptic Ulcer Disease, G12)
  • gastritis (e.g. from alcohol or post-surgery) (20%)
  • gastric cancer
  • gastric antral vascular ectasia (rare, associated with cirrhosis and CTD)
  • dieulofoy lesion (very rare)
• duodenum
  • ulcer in bulb (25%)
  • aortoenteric fistula: usually only if previous aortic graft (see sidebar)
• coagulopathy (drugs, renal disease, liver disease)
• vascular malformation (Dieulafoy’s lesion, AVM)

Clinical Features
• in order of decreasing severity of the bleed: hematochezia > hematemesis > coffee ground emesis > melena > occult blood in stool

Management (initial)
• stabilize patient (1-2 large bore IVs, IV fluids, monitor)
• send blood for CBC, cross and type, platelets, PT, PTT, electrolytes, BUN, Cr, LFTs
• keep NPO
• consider NG tube to determine upper vs. lower GI bleeding in some cases
• endoscopy (OGD): establish bleeding site + treat lesion
  • if bleeding peptic ulcer: most commonly used method of controlling bleeding is injection of epinephrine around bleeding point + thermal hemostasis (bipolar electrocoagulation or heater probe); less often thermal hemostasis may be used alone, but injection alone not recommended
  • endoclips
• IV PPI: decrease risk of rebleed if endoscopic predictors of rebleeding seen (see prognosis section)
  • given to stabilize clot, not to accelerate ulcer healing
  • if given before endoscopy, decreases need for endoscopic therapeutic intervention
• for variceal bleeds, octreotide 50 μg loading dose followed by constant infusion of 50 μg/h
• consider IV erythromycin (or metoclopramide) to accelerate gastric emptying prior to gastroscopy to remove clots from stomach

Prognosis
• 80% stop spontaneously
• peptic ulcer bleeding: low mortality (2%) unless rebleeding occurs (25% of patients, 10% mortality)
• endoscopic predictors of rebleeding: spurt or ooze, visible vessel, fibrin clot
• can send home if clinically stable, bleed is minor, no comorbidities, endoscopy shows clean ulcer with no predictors of rebleeding
• H₂–antagonists have little impact on rebleeding rates and need for surgery
• esophageal varices have a high rebleeding rate (55%) and mortality (29%)

Approach to Iron Deficiency Anemia

Overt GI bleeding (hematochezia, melena)

- Yes
  - Upper and lower endoscopy
  - Rule out non-GI sources of bleeding (e.g., hemorrhage, hemolysis)
  - Has the anemia resolved?
- No
  - Wireless endoscopy capsule/ double balloon endoscopy

* Wireless endoscopy capsule results help double balloon endoscopy localize source of bleeding
  • Angiography if overt bleeding hemodynamically significant, estimated >0.5 cc/min
  • CT enterography if wireless endoscopy capsule/double balloon endoscopy not available

Figure 9. Approach to iron deficiency anemia

Esophageal Varices

Etiology
• almost always due to portal hypertension
• often accompanied by varices in stomach

Clinical Features
• characteristically massive upper GI bleeding

Prognosis
• risk of bleeding: 30% in first year
• risk of rebleeding: 50-70% (20% mortality at 6 wk)

Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

<table>
<thead>
<tr>
<th>Forrest Classification of Bleeding Peptic Ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forrest</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>l</td>
</tr>
<tr>
<td>l</td>
</tr>
<tr>
<td>l</td>
</tr>
<tr>
<td>l</td>
</tr>
</tbody>
</table>

Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

- better survival, and fewer adverse events.
- Fewer patients in the restrictive group required transfusion (57% vs. 15%; P < 0.001). The hazard ratio for death for restrictive compared to liberal transfusion was 0.55; 95% CI, 0.33 to 0.92; P = 0.02. Further bleeding occurred in 10% vs. 16% (P = 0.01) of patients, while adverse effects occurred in 40% vs. 48% (P = 0.02) of patients in the restrictive and liberal strategies, respectively.
- The restrictive strategy had a better survival rate in patients with bleeding associated with cirrhosis Child-Pugh class A or B (HR: 0.30; 95% CI, 0.11 to 0.80), but not in cirrhosis Child-Pugh class C (HR: 1.04; 95% CI, 0.45 to 2.37) or a peptic ulcer (HR: 0.70; 95% CI, 0.26 to 1.95).
- Conclusions: Transfusing patients with an acute upper GI bleed at hemoglobin of <70 g/L rather than 90 g/L is associated with fewer transfusions, better survival, and fewer adverse events.

Review Article: Improved Survival with Patients with Variceal Bleeds

- Better survival, and fewer adverse events.
- Fewer patients in the restrictive group required transfusion (57% vs. 15%; P < 0.001). The hazard ratio for death for restrictive compared to liberal transfusion was 0.55; 95% CI, 0.33 to 0.92; P = 0.02. Further bleeding occurred in 10% vs. 16% (P = 0.01) of patients, while adverse effects occurred in 40% vs. 48% (P = 0.02) of patients in the restrictive and liberal strategies, respectively.
- The restrictive strategy had a better survival rate in patients with bleeding associated with cirrhosis Child-Pugh class A or B (HR: 0.30; 95% CI, 0.11 to 0.80), but not in cirrhosis Child-Pugh class C (HR: 1.04; 95% CI, 0.45 to 2.37) or a peptic ulcer (HR: 0.70; 95% CI, 0.26 to 1.95).
- Conclusions: Transfusing patients with an acute upper GI bleed at hemoglobin of <70 g/L rather than 90 g/L is associated with fewer transfusions, better survival, and fewer adverse events.

Esophageal varices are a common complication of portal hypertension, and their management includes medical, endoscopic, and surgical interventions. The Forrest classification provides a framework for understanding the severity of bleeding and guiding treatment decisions. The use of restrictive transfusion strategies has been shown to improve survival and reduce adverse events compared to liberal transfusion, especially in patients with cirrhosis. Always consider the underlying cause of variceal bleeding and tailor treatment accordingly. Always ask about NSAID/Aspirin or anticoagulant therapy in GI bleed.
Investigations
• endoscopy

Management

**Mallory-Weiss Tear**

**Definition**
• longitudinal laceration in gastric mucosa on lesser curvature near GE junction (20% straddle junction, 5% in distal esophagus)

**Etiology**
• due to rapid increases in gastric pressure from retching/vomiting against a closed glottis
• hiatus hernia usually present

**Clinical Features**
• hematemesis ± melena, classically following an episode of retching without blood
• can lead to fatal hematemesis

**Management**
• 90% stop spontaneously
• if persistent: endoscopy with epinephrine injection ± clips or surgical repair

**Lower Gastrointestinal Bleeding**

**Definition**
• bleed distal to ligament of Treitz

**Etiology**
• rule out upper GI source
• diverticular (60% from right colon)
• vascular
  • angiodysplasia
  • anorectal (hemorrhoids, fissures)
• neoplasm
• cancer
• polyps
• inflammation
  • colitis (ulcerative, infectious, radiation, ischemic)
• post-polypectomy

**Clinical Features**
• hematochezia (see Figure 11)
• anemia
• occult blood in stool
• rarely melena

**Management**
• treat underlying cause
**Figure 11. Approach to hematochezia**

### Colorectal Carcinoma (CRC)
- see [General Surgery, GS34](#)

### Colorectal Polyps
- see [General Surgery, GS33](#)

### Familial Colon Cancer Syndromes
- see [General Surgery, GS33](#)

### Benign Anorectal Disease
- see [General Surgery, GS38](#)

### Liver

#### Investigations of Hepatobiliary Disease

**A. TEST OF LIVER FUNCTION**

**Prothrombin Time (PT or INR)**
- a marker of hepatic protein synthesis
- increased by:
  - impaired hepatic protein synthesis (>80%) (including all coagulation factors except VIII) i.e. hepatocellular dysfunction
  - vitamin K deficiency
  - vitamin K administration promptly corrects PT in vitamin K deficiency (malnutrition, malabsorption, etc.) but not in hepatocellular dysfunction; thus in the absence of vitamin K deficiency, PT is a reliable index of hepatocellular dysfunction

**Serum Albumin Level**
- a marker of hepatic protein synthesis; must exclude malnutrition, renal or GI losses and significant inflammatory or malignant illness of any organ system

**Serum Bilirubin**
- marker of hepatic excretion; transport from hepatocyte to bile
- canaliculus breakdown product of hemoglobin; metabolized in the reticuloendothelial system of liver, transported through biliary system, excreted via gut
- direct bilirubin = conjugated; indirect = unconjugated bilirubin
- liver dysfunction causes hyperbilirubinemia (elevated direct bilirubin) since conjugation preserved even in end stage liver failure

ALT > AST = most causes of hepatitis
AST > ALT = alcoholic liver disease or other causes of hepatitis that have progressed to advanced cirrhosis
B. TESTS OF LIVER DAMAGE
- disproportionately increased AST or ALT = hepatocellular damage
  - ALT more specific to liver; AST from multiple sources (especially muscle)
  - elevation of both highly suggestive of liver injury
  - most common cause of elevated ALT is fatty liver
- disproportionately increased ALP and GGT = cholestasis
  - if ALP is elevated alone, rule out bone disease by fractionating ALP
  - if ALP elevation out of proportion to ALT/AST elevation, consider:
    1. obstruction of common bile duct (extraluminal = pancreatic Ca, lymphoma; intraluminal = stones, cholangiocarcinoma, sclerosing cholangitis, helminths)
    2. destruction of microscopic ducts (e.g. PBC)
    3. bile acid transporter defects (drugs, intrahepatic cholestasis of pregnancy)
    4. infiltration of the liver (liver metastases, lymphoma, granulomas, amyloid)

Acute Viral Hepatitis (General)

Definition
- viral hepatitis lasting <6 mo

Clinical Features
- most are subclinical
- flu-like prodrome may precede jaundice by 1-2 wk
  - nausea, vomiting, anorexia, taste/smell disturbance, headaches, fatigue, myalgia, low-grade fever
  - arthralgia and urticaria (especially HBV)
- only some progress to icteric (clinical jaundice) phase, lasting days to weeks
  - pale stools and dark urine 1-5 d prior to icteric phase
  - hepatomegaly and RUQ pain
  - splenomegaly and cervical lymphadenopathy (10-20% of cases)

Investigations
- AST and ALT (>10-20x normal in hepatocellular necrosis)
- ALP and bilirubin minimally elevated
- viral serology, IgM

Treatment
- supportive (hydration, diet)
- indications for hospitalization: encephalopathy, coagulopathy severe vomiting, hypoglycemia

Prognosis
- poor prognostic indicators: comorbidities, persistently high bilirubin (>340 mmol; 20 mg/dL), increased INR, decreased albumin, hypoglycemia
- cholestasis (most commonly with HAV infection)

Complications
- hepatocellular necrosis: AST, ALT >10-20x normal, ALP and bilirubin minimally increased, increased cholestasis

Hepatitis A Virus (HAV)

- RNA virus
- fecal-oral transmission; incubation period 4-6 wk
- diagnosed by elevated transaminases, positive anti-HAV IgM
- in children: characteristically asymptomatic
- in adults: fatigue, nausea, arthralgia, fever, jaundice
- can cause fulminant hepatic failure and subsequent death (<1-5%)
- can relapse, but never becomes chronic

Hepatitis B Virus (HBV)

<table>
<thead>
<tr>
<th>Table 14. Hepatitis B Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Acute HBV</td>
</tr>
<tr>
<td>Chronic HBV (high HBV DNA)</td>
</tr>
<tr>
<td>Chronic HBV (low HBV DNA)</td>
</tr>
<tr>
<td>Resolved infection</td>
</tr>
<tr>
<td>Immunization</td>
</tr>
</tbody>
</table>
Epidemiology
• 4 phases of chronic hepatitis B: not all will go through all 4 phases, but all will have positive HBsAg
  1. immune tolerance: extremely high HBV-DNA (>20,000 IU/mL), HBeAg positive, but normal ALT/AST; due to little immune control and minimal immune-mediated liver damage; characteristic of perinatal infection (or 'incubation period' in adult with newly-acquired HBV)
  2. immune clearance (or immunoactive): falling but still elevated HBV-DNA levels (>20,000 IU/mL), HBeAg positive; due to immune attack on the virus and immune-mediated liver damage; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment
  3. immune control: lower HBV-DNA (<20,000 IU/mL), HBeAg negative, anti-HBe positive, ALT/AST normal; due to immune control without immune-mediated liver damage; risk of reactivation to phase 2 (clinically resembles acute hepatitis B), especially with immunosuppression e.g. corticosteroids or chemotherapy
  4. immune escape (“core or precore mutant”): elevated HBV-DNA (>2,000 IU/mL), HBeAg negative because of pre-core or core promoter gene mutation, anti-HBe positive, ALT/AST high; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment

Management
• counselling: 40% of men and 10% of women with perinatal infection will die from HBV-related complications
• prolonged immune-mediated damage leads to higher risk of liver fibrosis
• hepatocellular carcinoma screening with ultrasound q6mo, especially if high serum HBV-DNA levels, cirrhosis, men, (age >40 in Asian men, >50 in Asian women, and >20 in African descent)
• consider pharmacological therapy if: 1. HBeAg positive + HBV-DNA >20,000 IU/mL + ALT >90; or 2. HBeAg negative + HBV-DNA >2,000 IU/mL + ALT >90 + stage ≥2 fibrosis on liver biopsy
• treat to prevent flare when placed on immunosuppressive therapy such as prednisone
• treatment goal: reduce serum HBV-DNA to undetectable level
• treatment options: interferon, tenofovir, entacavir, lamivudine, adefovir
• vaccinate against HAV if serology negative (to prevent further liver damage)
• follow blood and sexual precautions

Hepatitis D
• defective RNA virus requiring HBsAg for entry into hepatocyte, therefore infects only patients with hepatitis B; causes more aggressive disease than hepatitis B virus alone
• co-infection: acquire HDV and HBV at the same time
  ▪ better prognosis than superinfection (acute HDV infection on pre-existing HBV infection)
• HDV can present as fulminant hepatic failure (FHF) and/or accelerate progression to cirrhosis
• management: low-dose interferon (20% response) and liver transplant for end-stage disease

Hepatitis C Virus (HCV)
• RNA virus
• blood-borne transmission; sexual transmission is "inefficient"
• major risk factor: injection drug use
• other risk factors: blood transfusion received before 1992 (or received in developing world), tattoos, intranasal cocaine use
• clinical manifestation develops 6-8 wk after exposure
  ▪ symptoms mild and vague (fatigue, malaise, nausea) therefore not commonly diagnosed in acute stage

Risk of hepatocellular carcinoma in HBV increases with increasing age, which is likely a surrogate for increasing liver fibrosis/cirrhosis.

Risk of hepatocellular carcinoma in HCV increases only after cirrhosis develops.

Without treatment, 8-20% of those with ongoing immunoactive chronic hepatitis can develop cirrhosis within 5 yr. In contrast, those in the immune tolerant phase (with extremely high HBV-DNA levels) are at minimal risk for liver fibrosis as they do not have immune-mediated liver injury.

In acute hepatitis B, HDV co-infection increases severity of hepatitis but does not increase risk of progression to chronic hepatitis. However in the context of chronic hepatitis B, superinfection with HDV increases progression to cirrhosis.
Diagnosis
- suspected on basis of elevated ALT/AST and positive serum anti-HCV
- diagnosis established by detectable HCV-RNA in serum
- virus genotype correlates with response to treatment but not prognosis
- serum HCV-RNA inversely correlates with response to treatment
- normal transaminases can have underlying cirrhosis on biopsy, but otherwise excellent prognosis

Management
- blood-borne precautions; vaccinate for hepatitis B and A if serology negative, avoid alcohol
- clearest indication for treatment is in subgroup likely to develop clinically significant liver disease
- persistently elevated transaminases, liver biopsy shows fibrosis/cirrhosis and at least moderately severe necrosis/inflammation
- indicators of poor response to treatment: cirrhosis, genotype 1, high HCV-RNA, co-infection with HIV, African-American race
- pegylated interferon-α + ribavirin aims to clear HCV infection, but only 50-80% success rate and side effects common (therefore not all patients are treated)
  - general adverse effects: depression/fatigue, hemolysis, bone marrow suppression (monitor CBC regularly), fevers/myalgia, precipitates autoimmune diseases (rare), skin rashes
  - recently introduced protease inhibitors for genotype I (most common, least amenable to treatment) have significantly increased sustained remission rate to up to 70%

Prognosis
- 80% of acute hepatitis C become chronic (of these 20% evolve to cirrhosis)
- risk of hepatocellular carcinoma increases if cirrhotic
- can cause cryoglobulinemia; associated with membranoproliferative glomerulonephritis, lymphoma

Table 15. Characteristics of the Viral Hepatitis

<table>
<thead>
<tr>
<th>Virus Family</th>
<th>Genotype</th>
<th>Incubation</th>
<th>Onset</th>
<th>Communicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picornaviridae</td>
<td>HAV</td>
<td>4-6 wk</td>
<td>Usually abrupt</td>
<td>HBsAg state highly communicable</td>
</tr>
<tr>
<td>Hepadnaviridae</td>
<td>HBV</td>
<td>6 wk-6 mo</td>
<td>Usually insidious</td>
<td>communicable during 3rd trimester/early post-partum</td>
</tr>
<tr>
<td>Flaviviridae</td>
<td>HCV</td>
<td>2-6 wk</td>
<td>Insidious</td>
<td>Communicable prior to overt symptoms and throughout chronic illness</td>
</tr>
<tr>
<td>Deltaviridae</td>
<td>HDV</td>
<td>3-13 wk</td>
<td>Usually abrupt</td>
<td>Infectious only in presence of HBV (HBsAg required for replication)</td>
</tr>
<tr>
<td>Caliciviridae</td>
<td>HEV</td>
<td></td>
<td>Usually abrupt</td>
<td>Unknown</td>
</tr>
<tr>
<td>Herpesviridae</td>
<td>CMV</td>
<td></td>
<td></td>
<td>Variable – dormant or persistent</td>
</tr>
<tr>
<td>Flavivirus</td>
<td>EBV</td>
<td></td>
<td></td>
<td>Communicable highest during year after primary infection but never zero</td>
</tr>
<tr>
<td>Herpesviridae</td>
<td>Yellow Fever</td>
<td></td>
<td></td>
<td>Variable, vector-dependent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Virus Family</th>
<th>Genotype</th>
<th>Chronicity</th>
<th>Serology</th>
<th>Immunity</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picornaviridae</td>
<td>HAV</td>
<td>None, although can relapse</td>
<td>Anti-HAV (IgM)</td>
<td>Yes</td>
<td>Havrix, 2 doses q6mo, combined with Twinrix at 0, 7, and 21 d</td>
</tr>
<tr>
<td>Hepadnaviridae</td>
<td>HBV</td>
<td>5% adults, 90% infants</td>
<td>See Table 15</td>
<td>?</td>
<td>Recombivax HBV/HTM, age 11-15, 2 doses q6mo</td>
</tr>
<tr>
<td>Flaviviridae</td>
<td>HCV</td>
<td>80%, 20% of which develop cirrhosis</td>
<td>HCV-RNA Anti-HCV (IgG/IgM)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Deltaviridae</td>
<td>HDV</td>
<td>6%</td>
<td>HBsAg Anti-HDV (IgG/IgM)</td>
<td>?</td>
<td>No</td>
</tr>
<tr>
<td>Flavivirus</td>
<td>HEV</td>
<td></td>
<td></td>
<td>Anti-HEV (IgG/IgM)</td>
<td>?</td>
</tr>
<tr>
<td>Caliciviridae</td>
<td>CMV</td>
<td></td>
<td></td>
<td>Anti-CMV (IgG/IgM)</td>
<td>?</td>
</tr>
<tr>
<td>Herpesviridae</td>
<td>EBV</td>
<td></td>
<td></td>
<td>Monospot; anti-EBV IgM/ IgG, EBV DNA quantitation</td>
<td>?</td>
</tr>
<tr>
<td>Flavivirus</td>
<td>Yellow Fever</td>
<td></td>
<td></td>
<td>Anti-YF (IgM/IgG)</td>
<td>?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Factors for Progression</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old age at diagnosis</td>
<td>General hygiene Treat close contacts (anti-HAV Ig) Phylaxis for high-risk groups (HAV vaccine ± HAV Ig) unless immune</td>
</tr>
<tr>
<td>HIV co-infection</td>
<td>Prevention: HBV vaccine and/or hepatitis B Ig (HBIG) for needlestick, sexual contact, infants of infected mothers unless already immune</td>
</tr>
<tr>
<td>EOIH</td>
<td>Prevention: no vaccine Rx: IFN + ribavirin</td>
</tr>
<tr>
<td>In high risk transplant patients: CMV Ig and anti-virals (ganciclovir, vanganciclovir)</td>
<td>Prevention: general hygiene, no vaccine</td>
</tr>
<tr>
<td>Supportive treatment post infection</td>
<td>Supportive treatment post infection</td>
</tr>
</tbody>
</table>

HCV treatment lowers the risk of hepatocellular carcinoma.
Table 15. Characteristics of the Viral Hepatitides (continued)

<table>
<thead>
<tr>
<th></th>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
<th>HDV</th>
<th>HEV</th>
<th>CMV</th>
<th>EBV</th>
<th>Yellow Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute mortality</td>
<td>0.1-0.3%</td>
<td>0.5-2%</td>
<td>1%</td>
<td>2-20% coinfection with HBV, 30% superinfection</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>20-60% in developing countries</td>
</tr>
<tr>
<td>Oncogenicity</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Complications</td>
<td>Can cause fulminant hepatic failure and subsequent death (&lt;1-5%)</td>
<td>Hepatocellular carcinoma secondary to cirrhosis, Serum sickness-like syndrome, glomerulonephritis, cryoglobulinemia, polyarteritis nodosa, porphyria cutanea tarda</td>
<td>Hepatocellular carcinoma in 2-5% of cirrhosis per year, cryoglobulinemia, B-cell non-Hodgkin lymphoma</td>
<td>Leukocytoclastic vasculitis, membranous glomerulonephropathy</td>
<td>Mild, except in third trimester (10-20% fulminant liver failure)</td>
<td>5% of newborns with multiple handicaps</td>
<td>Associated with Burkitt’s lymphoma and nasopharyngeal carcinoma (rare in Western world)</td>
<td>Can cause a recurrent toxic phase with liver damage, GI bleeding, and high mortality rates</td>
</tr>
</tbody>
</table>

Autoimmune Chronic Active Hepatitis

- Diagnosis of exclusion: rule out viruses, drugs, metabolic or genetic causes
- Can be severe: 40% mortality at 6 mo without treatment
- Extrahepatic manifestations
  - sicca, Raynaud’s, thyroiditis, Sjögren’s, arthralgias
  - Hypergammaglobulinemia
    - Anti-smooth muscle antibody elevation is most characteristic; also elevations in anti-LKM (liver, kidney microsome, especially in children)
    - Less specific: elevated ANA, RF
    - Can have false positive viral serology (especially anti-HCV)
    - Biopsy – periportal (zone 1) and “interface” inflammation and necrosis
- Management: corticosteroids (80% respond) ± azathioprine (without this, most will relapse as corticosteroids are withdrawn)

Drug-Induced Liver Disease

Table 16. Classification of Hepatotoxins

<table>
<thead>
<tr>
<th></th>
<th>Direct</th>
<th>Indirect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>Acetaminophen, CCl₄</td>
<td>Phenytoin, INH</td>
</tr>
<tr>
<td>Dose-dependence</td>
<td>Usual</td>
<td>Unusual</td>
</tr>
<tr>
<td>Latent period</td>
<td>Hours-days</td>
<td>Weeks-months</td>
</tr>
<tr>
<td>Host factors</td>
<td>Not important</td>
<td>Very important</td>
</tr>
<tr>
<td>Predictable</td>
<td>Yes</td>
<td>No (idiopathic)</td>
</tr>
</tbody>
</table>

Specific Drugs

- Acetaminophen
  - Metabolized by hepatic cytochrome P450 system
  - Can cause FHF (transaminases >1,000 U/L followed by jaundice and encephalopathy)
  - Requires 10-15 g in healthy, 4-6 g in alcoholics/anticonvulsant users
  - Mechanism: high acetaminophen dose saturates glucuronidation and sulfation elimination pathways → reactive metabolite is formed → covalently binds to hepatocyte membrane
  - Presentation:
    - First 24 h: nausea and vomiting (usually within 4-12 h of overdose)
    - 24-48 h: asymptomatic, but ongoing hepatic necrosis resulting in increased transaminases
    - >48 h: continued hepatic necrosis possibly complicated with FHF or resolution
  - Note: potential delay in presentation in sustained-release products
  - Blood levels of acetaminophen correlate with the severity of hepatic injury, particularly if time of ingestion known
  - Therapy:
    - Gastric lavage/emesis (if <2 h after ingestion)
    - Oral activated charcoal
    - N-acetylcysteine (NAC, Mucomyst*) can be given PO or IV (most effective within 8-10 h of ingestion, but should be given no matter when time of ingestion)
      - Promotes hepatic glutathione regeneration
    - No recorded fatal outcomes if NAC given before increase in transaminases
    - Chlorpromazine: cholestasis in 1% after 4 wk; often with fever, rash, jaundice, pruritus and eosinophilia
• INH (isoniazid)
  ▪ 20% develop elevated transaminases but <1% develop clinically significant disease
  ▪ susceptibility to injury increases with age
• methotrexate
  ▪ causes cirrhosis; increased risk in the presence of obesity, diabetes, alcoholism (i.e. with
    underlying risk for pre-existing fatty liver)
  ▪ scarring develops without symptoms or changes in liver enzymes, therefore biopsy may be
    needed in long-term treatment
• amiodarone: can cause same histology and clinical outcome as alcoholic hepatitis
• others: azoles, statins, methyldopa, phenytoin, propylthiouracil (PTU), rifampin, sulfonamides,
  tetracyclines
• herbs: chaparral, Chinese herbs (e.g. germander, comfrey, bush tea)

Wilson’s Disease

Definition
• autosomal recessive defect in copper metabolism (gene ATP7B)

Pathology
• decreased biliary excretion of copper plus decreased incorporation of copper into ceruloplasmin

Clinical Manifestations
• liver: acute hepatitis, fulminant liver failure, chronic active hepatitis, cirrhosis, low risk of
  hepatocellular carcinoma
• eyes: Kayser-Fleischer rings (copper deposits in Descemet’s membrane); more common in
  patients with CNS involvement, present in 50% if only liver involvement
• CNS: basal ganglia (wing flapping tremor, Parkinsonism), cerebellum (dysarthria, dysphagia,
  incoordination, ataxia), cerebrum (psychosis, affective disorder)
• kidneys: Fanconi’s syndrome (proximal tubule transport defects) and stones
• blood: intravascular hemolysis; may be initial presentation in fulminant hepatitis
• joints: arthritis, bone demineralization, calcifications

Investigations
• suspect if increased liver enzymes with clinical manifestations at young age (<30); especially
  combination of liver disease with dystonia, psychiatric symptoms
• screening tests:
  1. reduced serum ceruloplasmin (<50% of normal)
  2. Kayser-Fleischer rings (usually require slit-lamp examination)
  3. increased urinary copper excretion
• gold standard:
  1. increased copper on liver biopsy by quantitative assay
  2. genetic analysis imperfect as many mutations in ATP7B are possible

Treatment
• 4 drugs available:
  1. penicillamine chelates copper, poorly tolerated
  2. trientine chelates copper
  3. zinc impairs copper excretion in stool/ decreases copper absorption from gut
  4. tetrathiomolybdate preferred if neurological involvement
• screen relatives
• liver transplant in severe cases

Hemochromatosis

Definition
• excessive iron storage causing multiorgan system dysfunction (liver, in particular) with total
  body stores of iron increased to 20-40 g (normal 1 g)

Etiology
• primary hemochromatosis
  ▪ primarily due to common recessive gene (HFE, 5%); 1/400 patients are homozygotes
  ▪ results in ongoing gut absorption of iron despite adequate iron stores
• secondary hemochromatosis
  ▪ parenteral iron overload (e.g. transfusions)
  ▪ chronic hemolytic anemia: thalassemia, pyruvate kinase deficiency
  ▪ excessive iron intake

Gene mutation not 100% penetrant: so not all with homozygous gene defect have clinically significant iron overload.
Clinical Features
- usually presents with trivial elevation in serum transaminases
- liver: cirrhosis (30%), HCC (200x increased risk) – most common cause of death (1/3 of patients)
- pancreas: diabetes, chronic pancreatitis
- skin: bronze or grey (due to melanin, not iron)
- heart: dilated cardiomyopathy
- pituitary: hypogonadotropic hypogonadism (impotence, decreased libido, amenorrhea)
- joints: arthralgia (any joint, but especially MCP joints), chondrocalcinosis

Investigations
- screening for individuals with clinical features and/or family history (1/4 chance of sibling having the disease)
  - transferrin saturation (free Fe²⁺/TIBC) >50%
  - serum ferritin >400 ng/mL
  - HFE gene analysis: 90% of primary hemochromatosis involves C282Y allele, while H63D and S65C alleles also commonly involved and screened
- liver biopsy (to define degree of iron overload and to detect cirrhosis)
  - usually indicated if age >40, ALT/AST more than 2.5 times the upper limit of normal, or ferritin >1000
- HCC screening if cirrhosis

Treatment
- phlebotomy: weekly or q2wk then lifelong maintenance phlebotomies q2-6mo
- deferoxamine if phlebotomy contraindicated (e.g. cardiomyopathy, anemia)
- primary hemochromatosis responds well to phlebotomy
- secondary hemochromatosis usually requires chelation therapy (administration of agents that bind and sequester iron, and then excreted)

Prognosis
- normal life expectancy if treated before the development of cirrhosis or diabetes

Alcoholic Liver Disease

Types of Lesions
- fatty liver (all alcoholics): always reversible if alcohol stopped
- alcoholic hepatitis (35% of alcoholics): usually reversible if alcohol stopped
- cirrhosis (10-15% of alcoholics): potentially irreversible

Pathophysiology
- several mechanisms, poorly understood
- ethanol oxidation to acetaldehyde:
  - reduces NAD⁺ to NADH; increased NADH decreases ATP supply to liver, impairing lipolysis so fatty acids and triglycerides accumulate in liver
  - binds to hepatocytes evoking an immune reaction
- ethanol increases gut permeability leading to increased bacterial translocation
- alcohol metabolism causes:
  - relative hypoxia in liver zone III > zone I
  - necrosis and hepatic vein sclerosis
- histology of alcoholic hepatitis:
  - ballooned (swollen) hepatocytes often containing Mallory bodies, characteristically surrounded by neutrophils
  - large fat globules
  - fibrosis: space of Disse and perivenular

Clinical Features
- >2-3 standard drinks/d in females and >3-6 standard drinks/d in men for >10 yr leads to cirrhosis, but only in about 10 to 20% of those who consume this amount daily on a continuous basis; cirrhosis risk increases with amount of alcohol consumed above threshold
- clinical findings do not accurately predict type of liver involvement
  - fatty liver:
    - mildly tender hepatomegaly; jaundice rare
    - mildly increased transaminases <5x normal
  - alcoholic hepatitis:
    - variable severity: mild to fatal liver failure
    - mild: stops drinking because feels unwell, resumes when feeling better (if assessed, findings of hepatitis, potentially mild jaundice and mildly elevated INR)
    - severe: stops drinking but feels unwell, low grade fever, RUQ discomfort, increased white blood cell count – mimics RLL pneumonia and cholecystitis

Standard Drink Equivalent
- 1 standard drink= 14 g EtOH
  = 12 oz beer (5% alcohol)
  = 5 oz wine (12-17%)
  = 3 oz fortified wine (17-22%)
  = 1.5 oz liquor (40%)
Tip: Percentage alcohol multiplied by oz roughly equals 60
- Blood tests are non-specific, but in general:
  - AST/ALT > 2:1 (usually < 300)
  - Increased GGT
  - CBC: Increased MCV (mean corpuscular volume), increased WBC
- Prognosis: Maddrey's discriminant function (based on PT and bilirubin) predicts mortality

### Treatment
- Alcohol cessation (see Psychiatry, PS22)
  - Alcoholics Anonymous, disulfiram, naltrexone, acamprosate
- Multivitamin supplements (especially thiamine)
- Caution with drugs metabolized by the liver
- Prednisone 40 mg OD x 28 d (taper over 2-4 wk) in subgroup with elevated bilirubin and INR, or if encephalopathy; but contraindicated in GI bleeding, renal failure, infection
- Pentoxyphilline decreases TNF, shown in one trial to reduce death, albeit only from renal failure, favourable side-effect profile

### Prognosis
- Fatty liver: complete resolution with cessation of alcohol intake
- Alcoholic hepatitis mortality
  - Immediate: 30%-60% in the first 6 mo if severe
  - With continued alcohol: 70% in 5 yr
  - With cessation: 30% in 5 yr

### Non-Alcoholic Fatty Liver Disease (NAFLD)

#### Etiology/Epidemiology
- Spectrum of disorders characterized by macrovesicular hepatic steatosis
- Most common cause of liver disease in North America

#### Pathophysiology
- Pathogenesis not well elucidated; insulin resistance implicated as key mechanism, leading to hepatic steatosis
- Changes indistinguishable from those of alcoholic hepatitis despite negligible history of alcohol consumption

#### Risk Factors
- Likely a component of the metabolic syndrome along with type II diabetes, hypertension, hypertriglyceridemia
- Rapid weight loss or weight gain

#### Clinical Features/Investigations
- Often asymptomatic
- May present with fatigue, malaise and vague RUQ discomfort
- Elevated serum triglyceride/cholesterol levels and insulin resistance
- Elevated serum AST, ALT ± ALP; AST/ALT < 1
- Presents as echogenic liver texture on ultrasound
- Liver biopsy diagnostic, but often necessary only for prognosis

#### Management
- No proven effective therapy other than gradual weight loss
- Some evidence for vitamin E (800 U daily); pioglitazone if diabetes concomitantly present
- Modification of risk factors is generally recommended, especially gradual weight reduction
- Optimization of therapy for diabetes, hyperlipidemia, hypertension

#### Prognosis
- Most die from cardiovascular or cerebrovascular disease
- Better prognosis than alcoholic hepatitis
  - < 25% progress to cirrhosis over a 7-10 yr period
- Risk of progression increases if inflammation or scarring occurs alongside fat infiltration (non-alcoholic steatohepatitis)
- Other clinical indicators of unfavourable prognosis: diabetes, age, metabolic syndrome
Acute Liver Failure (ALF; Formerly Fulminant Hepatic Failure)

Definition
- severe decline in liver function characterized by coagulation abnormality (INR>1.5) and encephalopathy
- in setting of previously normal liver
- rapid (<26 wk duration)

Etiology
- drugs (especially acetaminophen), hepatitis B (measure IgM anti-HBc because sometimes HBV-DNA and even HBsAg rapidly becomes negative), hepatitis A, hepatitis C (rare), ischemic, idiopathic

Management
- correct hypoglycemia, monitor level of consciousness, prevent GI bleeding with PPI, vigilant for infection and multiorgan failure (usually requires ICU)
- consider liver biopsy before INR becomes too high
- chief value is to exclude chronic disease, less helpful for prognosis
- liver transplant: consider early, especially if time from jaundice to encephalopathy >7 d (e.g. not extremely rapid), age <10 or >40, cause is drug or unknown, bilirubin >300 µmol/L, INR >3.5, creatinine >200 µmol/L

Cirrhosis

Definition
- liver damage characterized by diffuse distortion of the basic architecture and replacement with scar tissue and formation of regenerative nodules
- Stage 1 cirrhosis is compensated and asymptomatic, can last for 10-20 yr with almost normal life expectancy
- Stage 2 cirrhosis is the onset of first decompensation, typically development of ascites (most common), varical bleeding, encephalopathy

Etiology
- fatty liver (alcohol, metabolic syndrome)
- chronic viral hepatitis (B, B+D, C; not A or E)
- autoimmune hepatitis
- hemochromatosis
- α1-antitrypsin deficiency
- primary biliary cirrhosis
- chronic hepatic congestion
  - cardiac cirrhosis (chronic right heart failure, constrictive pericarditis)
  - hepatic vein thrombosis (Budd-Chiari)
- idiopathic
- rare: Wilson's disease, Gaucher's disease

Diagnosis
- definitive diagnosis is histologic (liver biopsy)
- other tests may be suggestive:
  - blood work: fall in platelet count <150 is the earliest finding, followed many yr later with rise in INR, fall in albumin, rise in bilirubin, fall in glucose level (pre-terminal event; see Figure 13)
  - FibroTest: combination of various clinical and biochemical markers that can predict degree of fibrosis
  - imaging:
    - U/S is the primary imaging modality but only finds advanced cirrhosis
    - CT to look for varices, nodular liver texture, splenomegaly, ascites
    - FibroScan: non-invasive tool using elastography (variable availability)
    - gastroscopy: varices or portal gastropathy

Management
- treat underlying disorder
- decrease insults (e.g. alcohol cessation, hepatotoxic drugs)
- follow patient for complications (esophageal varices, ascites, HCC defines stage 2 cirrhosis)
- prognosis: Child-Pugh Score (see Table 17)
- liver transplantation for end-stage disease if no alcohol for >6 mo; use MELD stratification (see sidebar)

**MELD (Model for End Stage Liver Disease)**
- Predicts 3-mo survival and used to stratify patients on transplant list
- Based on creatinine, INR and total bilirubin
Table 17. Child-Pugh Score and Interpretation

<table>
<thead>
<tr>
<th>Classification</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (µmol/L)</td>
<td>&lt;34</td>
<td>34-51</td>
<td>&gt;51</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>&gt;35</td>
<td>28-35</td>
<td>&lt;28</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
<tr>
<td>Presence of ascites</td>
<td>Absent</td>
<td>Controllable</td>
<td>Refractory</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Absent</td>
<td>Minimal</td>
<td>Severe</td>
</tr>
</tbody>
</table>

**Interpretation**

<table>
<thead>
<tr>
<th>Points</th>
<th>Class</th>
<th>Life Expectancy</th>
<th>Perioperative Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>A</td>
<td>15-50 yr</td>
<td>10%</td>
</tr>
<tr>
<td>7-9</td>
<td>B</td>
<td>Candidate for transplant</td>
<td>30%</td>
</tr>
<tr>
<td>10-15</td>
<td>C</td>
<td>1-3 mo</td>
<td>82%</td>
</tr>
</tbody>
</table>

Score: 5-6 (Child’s A), 7-9 (Child’s B), 10-15 (Child’s C)

*Note: Child’s classification is rarely used for shunting, but is still useful to quantitate the severity of cirrhosis

**Complications**

- hematologic changes in cirrhosis
  - pancytopenia from hypersplenism: platelets first, then WBC, then hemoglobin
  - decreased clotting factors resulting in elevated INR, thus tendency for bruising and bleeding
- variceal bleeds
  - half of patients with cirrhosis have gastroesophageal varices and one-third of these develop hemorrhage with an overall mortality of >30%
  - hepatic venous pressure gradient (HVPG) ≥10 mmHg is the strongest predictor of variceal development
  - management: resuscitation, antibiotic prophylaxis, vasoactive drugs combined with endoscopic band ligation or sclerotherapy, TIPS
- renal failure in cirrhosis
  - classifications
    - pre-renal (usually due to over-diuresis)
    - acute tubular necrosis (ATN)
    - hepatorenal syndrome (HRS)
      - Type I: sudden and acute renal failure (rapid doubling of creatinine over 2 wk)
      - Type II: gradual increase in creatinine with worsening liver function (creatinine doubling over years)
    - HRS can occur at any time in severe liver disease, especially after:
      - overdiuresis or dehydration, such as diarrhea, vomiting, etc.
      - GI bleed
      - sepsis
    - treatment for hepatorenal syndrome (generally unsuccessful at improving long term survival)
      - for type I HRS: octreotide + midodrine + albumin (increases renal blood flow by increasing systemic vascular resistance)
      - definitive treatment is liver transplant
- hepatopulmonary syndrome
  - majority of cases due to cirrhosis, though can be due to other chronic liver diseases, such as non-cirrhotic portal hypertension
  - thought to arise from ventilation-perfusion mismatch, intrapulmonary shunting and limitation of oxygen diffusion, failure of damaged liver to clear circulating pulmonary vasodilators vs. production of a vasodilating substance by the liver
  - clinical features:
    - hyperdynamic circulation with cardiac output >7 L/min at rest and decreased pulmonary + systemic resistance (intrapulmonary shunting)
    - dyspnea, platypnea (increase in dyspnea in upright position, improved by recumbency) and orthodeoxia (desaturation in the upright position, improved by recumbency)
    - diagnosis via contrast-enhanced echocardiography: inject air bubbles into peripheral vein; air bubbles appear in left ventricle after third heartbeat (normal = no air bubbles; in ventricular septal defect, air bubbles seen <3 heart beats)
    - only proven treatment is liver transplantation

**Hepatorenal Syndrome vs. Pre-renal Failure – difficult to differentiate:**

- Similar blood and urine findings, (see Nephrology, NP33)
- Urine sodium: very low in hepatorenal; low in pre-renal
- Intravenous fluid challenge: giving volume expanders improves pre-renal failure, but not hepatorenal syndrome
Hepatocellular Carcinoma (HCC)

- see General Surgery, GS43

Liver Transplantation

- see General Surgery, GS44

Portal Hypertension

Definition
- pressure gradient between hepatic vein pressure and wedged hepatic vein pressure (corrected sinusoidal pressure) >5 mmHg

Pathophysiology
- 3 sites of increased resistance (remember pressure = flow x resistance)
  - pre-sinusoidal (e.g. portal vein thrombosis, schistosomiasis, sarcoidosis)
  - sinusoidal (e.g. cirrhosis, alcoholic hepatitis)
  - post-sinusoidal (e.g. right-sided heart failure, hepatic vein thrombosis, veno-occlusive disease, constrictive pericarditis)

Complications
- GI bleeding from varices in esophagus, less commonly in stomach, even less frequently from portal hypertensive gastropathy
- ascites
- hepatic encephalopathy
- thrombocytopenia
- renal dysfunction
- sepsis
- arterial hypoxemia

Management
- non-selective β-blockers (propanolol, nadolol) decrease risk of bleeding from varices
- transjugular intrahepatic portosystemic shunt (TIPS): to decrease portal venous pressure
  - shunt between portal and hepatic vein via transjugular vein catheterization and percutaneous puncture of portal vein
  - can be used to stop acute bleeding or prevent rebleeding or treat ascites
  - shunt usually remains open for <1 yr
  - complications: hepatic encephalopathy, deterioration of hepatic function
  - contraindicated with severe liver dysfunction
  - most commonly used as a “bridge” to liver transplant
- other surgically created shunts (rare): portacaval, distal spleno-renal (Warren shunt)

Hepatic Encephalopathy

Definition
- spectrum of potentially reversible neuropsychiatric syndromes secondary to liver disease diagnosed after ruling out other causes for symptoms (e.g. structural/metabolic)

Pathophysiology
- portosystemic shunt around hepatocytes and decreased hepatocellular function increase level of systemic toxins (believed to be ammonia from gut, mercaptans, fatty acids, amino acids) which go to the brain
Precipitating Factors
- nitrogen load (GI bleed, protein load from food intake, renal failure, constipation)
- drugs (narcotics, CNS depressants)
- electrolyte disturbance (hypokalemia, alkalosis, hypoxia, hypovolemia)
- infection (spontaneous bacterial peritonitis)
- deterioration in hepatic function or superimposed liver disease

Stages
- I: apathy, restlessness, reversal of sleep-wake cycle, slowed intellect, impaired computational abilities, impaired handwriting
- II: asterixis, lethargy, drowsiness, disorientation
- III: stupor (rousable), hyperactive reflexes, extensor plantar responses
- IV: coma (response to painful stimuli only)

Investigations
- clinical diagnosis: supported by laboratory findings and exclusion of other neuropsychiatric diseases
- rule out:
  - non-liver-related neuropsychiatric disease in a patient with liver problems (e.g. alcohol withdrawal or intoxication, sedatives, subdural hematoma, metabolic encephalopathy)
  - causes of metabolic encephalopathy (e.g. renal failure, respiratory failure, severe hyponatremia, hypoglycemia)
- characteristic EEG findings: diffuse (non-focal), slow, high amplitude waves

Treatment
- treat underlying precipitating factors
- decrease generation of nitrogenous compounds
  - decrease dietary protein to 50 g/d; vegetable protein is better tolerated than animal protein
  - lactulose: titrated to achieve 2 to 3 soft stools per day
    - prevents diffusion of NH₃ (ammonia) from the colon into blood by lowering pH and forming non-diffusible NH₄ (ammonium)
    - serves as a substrate for incorporation of ammonia by bacteria, promotes growth in bowel lumen of bacteria which produce minimal ammonia
    - also acts as a laxative to eliminate nitrogen-producing bacteria from colon
  - if inadequate response with lactulose may try antibiotics
    - broad-spectrum antibiotics (metronidazole, rifaximin) eliminate ammonia producing bacteria from bowel lumen
    - non-absorbable antibiotic rifaximin probably most effective treatment but only available through special access in Canada
- best acute treatment in comatose patient is tap water or lactulose enemas

Ascites

Definition
- accumulation of excess fluid in the peritoneal cavity

Etiology

Table 18. Serum-Ascites Albumin Gradient as an Indicator of the Causes of Ascites

<table>
<thead>
<tr>
<th>Serum [Alb] – Ascitic [Alb] &gt; 11 g/L (1.1 g/dL)</th>
<th>Serum [Alb] – Ascitic [Alb] &lt; 11 g/L (1.1 g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal Hypertension Related</td>
<td>Non-portal Hypertension Related</td>
</tr>
<tr>
<td>Cirrhosis/severe hepatitis</td>
<td>Peritoneal carcinomatosis</td>
</tr>
<tr>
<td>Chronic hepatic congestion (right heart failure, Budd-Chiari)</td>
<td>TB</td>
</tr>
<tr>
<td>Massive liver metastases</td>
<td>Pancreatic disease</td>
</tr>
<tr>
<td>Myxedema</td>
<td>Serositis</td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome*</td>
</tr>
</tbody>
</table>

* In nephrotic syndrome: decreased serum [Alb] to begin with therefore gradient not helpful

Pathogenesis
- key factor in pathogenesis is increased sodium (and water) retention by the kidney for reasons not fully understood. Theories include:
  - underfill hypothesis: first step in ascites formation is increased portal pressure and low oncotic pressure (e.g. low serum albumin) driving water out of the splanchnic portal circulation into abdominal cavity; the resulting decreased circulating volume causes secondary sodium retention by the kidney
  - overfill hypothesis: cirrhosis directly causes increased sodium retention by the kidney in the absence of hypovolemia and ascites arises secondarily
  - peripheral arterial vasodilation theory (most popular): as portal hypertension develops in cirrhosis, production of local mediators such as nitric oxide lead to splanchnic arterial vasodilation which ultimately results in reduction of effective arterial volume and compensatory sodium and fluid retention by the kidneys (i.e. circulation volume is increased, as per overflow hypothesis, but relatively underfilled, as per underfill hypothesis)
Diagnosis
- abdominal ultrasound
- physical exam (clinically detectable when >500 mL):
  - bulging flanks, shifting dullness, fluid-wave test positive
  - most sensitive symptom: ankle swelling

Investigations
- diagnostic paracentesis
  - 1st aliquot: cells and differential
  - 2nd aliquot: chemistry (especially albumin, but also total protein; amylase if pancreatitis, TG if turbid and suspect chylous ascites)
  - 3rd aliquot: C&S, Gram stain
  - 4th aliquot: cytology (usually positive in peritoneal carcinomatosis)

Treatment
- non-refractory ascites:
  - Na+ restriction (daily sodium intake <2 g)
  - diuretics: spironolactone, furosemide
  - aim for weight loss 0.5-1 kg/d, more if concomitant peripheral edema (which is mobilized quicker than ascitic fluid); overly rapid weight loss increases risk of renal failure
  - double diuretic dose every 2-4 wk to achieve weight loss target
- refractory ascites (treatment with diuretics are inadequate or not tolerated):
  - therapeutic/palliative paracentesis indicated
  - IV albumin (not indicated if <5 L removed by paracentesis)
  - TIPS usually provides temporary benefit in controlling ascites but no survival advantage
  - liver transplantation should be considered in every case, since development of ascites in patients with cirrhosis are associated with 50% 2-yr mortality

Complication: Primary/Spontaneous Bacterial Peritonitis (SBP)
- primary/spontaneous bacterial peritonitis (SBP)
- complicates ascites, but does not cause it (occurs in 10% of cirrhotic ascites); higher risk in patients with GI bleed
- 1/3 of patients are asymptomatic, thus do not hesitate to do a diagnostic paracentesis in ascites even if no clinical indication of infection
- fever, chills, abdominal pain, ileus, hypotension, worsening encephalopathy, acute kidney injury
- Gram-negatives compose 70% of pathogens: E. coli (most common), Streptococcus, Klebsiella

• diagnosis
  - absolute neutrophil count in peritoneal fluid >0.25x10⁹ cells/L (250 cells/mm³)
  - Gram stain positive in only 10-50% of patients
  - culture positive in <80% of patients (not needed for diagnosis)

• prophylaxis: consider in patients with
  - cirrhosis or GI bleed: IV ceftriaxone daily or norfloxacin bid x 7 d
  - previous episode of SBP, long-term prophylaxis with daily norfloxacin or TMP-SMX

• treatment
  - IV antibiotics (cefotaxime 2 g IV q8h is the treatment of choice for 5 d; modify if response inadequate or culture shows resistant organisms)
  - IV albumin (1.5 g/kg at time of diagnosis and 1 g/kg on day 3) decreases mortality by lowering risk of acute renal failure

Primary Prophylaxis of Spontaneous Bacterial Peritonitis Delays Hepatorenal Syndrome and Improves Survival in Cirrhosis
Gastroenterology 2007;133:818-824

Study: RCT, double-blinded study with 1 yr follow-up.
Population: 68 patients with cirrhosis, ascites, ascitic fluid protein <15 g/L and impaired renal function or severe liver failure.
Intervention: General, regional or combined anesthesia to patients undergoing a surgical procedure.
Main Outcome: Norfloxacin versus placebo.
Results: There was a significant reduction of patients developing spontaneous bacterial peritonitis (SBP) (6% vs. 30%, p=0.02) and spontaneous bacteremia (6% vs. 12%, p=0.05) with norfloxacin therapy. There were significantly fewer patients who developed all-cause renal failure (7 vs. 16, p=0.03) and hepatorenal syndrome (HRS) with norfloxacin therapy. Probability of survival at 3 mo (94% vs. 62%, p=0.02) and 1 yr (60% vs. 48%, p=0.003) were high in patients treated with norfloxacin.
Conclusion: Primary prophylaxis with norfloxacin in patients with advanced cirrhosis reduced SBP, HRS, and improved 1 yr survival.

Biliary Tract

Jaundice
- see Table 2, Figures 15 and 16

Signs and Symptoms
- dark urine, pale stools: suggests that bilirubin elevation is from direct fraction
- pruritus: suggests chronic disease, cholestasis
- abdominal pain: suggests biliary tract obstruction from stone or pancreatic tumour (obstructive jaundice)
- painless jaundice in the elderly: think of pancreatic cancer, although most patients with pancreatic cancer have pain
- kerneicterus: rarely seen in adults due to maturation of blood brain barrier
Investigations
- blood work: CBC, bilirubin (direct and total), liver enzymes (AST, ALT, ALP, GGT), liver function tests (INR/PT, PTT, albumin), amylase
- U/S or CT for evidence of bile duct obstruction (e.g. bile duct dilation)
- direct bile duct visualization
  - magnetic resonance cholangiopancreatography (MRCP): non-invasive
  - endoscopic ultrasound (EUS): sensitive for stones and pancreatic tumours
  - endoscopic retrograde cholangiopancreatography (ERCP): invasive, most accurate, allows for therapeutic intervention
  - percutaneous transhepatic cholangiography (PTC): if ERCP fails, if obstruction is in liver

Figure 16. Approach to jaundice

Gilbert’s Syndrome

Definition
- mild decrease in glucuronyltransferase activity leading to defective conjugation of bilirubin

Etiology/Epidemiology
- some patients have decreased hepatobiliary uptake
- affects 7% of population, especially males
- autosomal dominant, 70% due to a mutation in the UGT gene

Signs and Symptoms
- presents in teens-20s, often an incidental finding
- only manifestation is intermittent jaundice with increased serum unconjugated bilirubin developing most characteristically while fasting; no other clinical implications

Treatment
- none indicated (entirely benign)

Sclerosing Cholangitis

Definition
- inflammation of biliary tree (intra and/or extrahepatic bile ducts) leading to scarring and lumen obliteration

Etiology
- primary/idiopathic (most common)
  - associated with IBD, more commonly UC, in up to 70% of patients (usually male)
  - one of the most common indications for transplant
- secondary (less common)
  - long-term choledocholithiasis
  - cholangiocarcinoma
  - surgical/traumatic injury (iatrogenic)
  - contiguous inflammatory process
  - post-ERCP
  - associated with HIV/AIDS (“HIV cholangiopathy”)
Signs and Symptoms
- often insidious, may present with fatigue and pruritus
- may present with signs of episodic bacterial cholangitis secondary to biliary obstruction

Diagnosis
- increased ALP (hallmark), less often increased bilirubin
- mildly increased AST, usually <300 U/L
- p-ANCA (30-80%), elevated IgM (40-50%)
- ERCP shows narrowing and dilatations of bile ducts that may result in “beading”, both intrahepatic and extrahepatic bile ducts
  - if intrahepatic narrowing only, do anti-mitochondrial antibody to rule out PBC

Complications
- repeated bouts of cholangitis may lead to complete biliary obstruction with resultant secondary biliary cirrhosis and hepatic failure
- increased incidence of cholangiocarcinoma (10-15%): difficult to diagnose and treat

Management
- image bile duct (MRCP) at least annually for early detection of cholangiocarcinoma
- endoscopic sphincterotomy, biliary stent in selected cases of dominant CBD stricture
- antibiotics for cholangitis
- suppurative cholangitis requires emergency drainage of pus in CBD
- liver transplantation appears the best treatment for advanced sclerosing cholangitis (nearly 90% 1-yr survival; mean follow-up from time of diagnosis to need for transplant is 10 yr)
- ursodiol: previously recommended, but studies suggest that at least in high doses it increases mortality

Prognosis
- unfavourable regardless of treatment
- mean survival after diagnosis remains 4-10 yr

Primary Biliary Cirrhosis (PBC)

Definition
- chronic inflammation and fibrous obliteration of intrahepatic bile ductules

Etiology/Epidemiology
- likely autoimmune (associated with Sjögren’s syndrome, scleroderma, CREST syndrome, RA, thyroiditis)
- affects mainly middle-aged women (M:F = 1:9)

Signs and Symptoms
- often asymptomatic
- initial symptoms: pruritus, fatigue
- chronic: jaundice and melanosis (darkening skin) and other signs of cholestasis
- end-stage: hepatocellular failure, portal hypertension, ascites
- high incidence of osteoporosis

Investigations
- increased ALP, GGT; bilirubin rises in later stage
- positive anti-mitochondrial antibodies (AMA; 95% specificity and sensitivity)
- increased serum cholesterol (mild increase in LDL, larger increase in HDL)
  - may have: xanthelasmas, xanthomas
- liver biopsy confirms diagnosis and stages severity
- normal bile duct on MRCP rules out bile duct obstruction which can mimic PBC
- recently described “overlap” syndromes with autoimmune cholangitis, autoimmune hepatitis, sclerosing cholangitis

Clinical Course
- can be fatal, although not all asymptomatic patients show progression

Treatment
- treat with ursodiol (less frequently colchicine, methotrexate)
- cholestyramine (for pruritus and hypercholesterolemia)
- calcium and vitamin D for low bone density; bisphosphonates if osteoporosis severe
- monitor for thyroid disease
- liver transplant if disease severe, progressive
Table 19. Primary Sclerosing Cholangitis vs. Primary Biliary Cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>Primary Sclerosing Cholangitis</th>
<th>Primary Biliary Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominant gender</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Associated comorbidities</td>
<td>IBD, especially UC</td>
<td>Other autoimmune disorders (Sjögren’s, CREST, RA)</td>
</tr>
<tr>
<td>Affected ducts</td>
<td>Both intra- and extra-hepatic</td>
<td>Intrahepatic only</td>
</tr>
<tr>
<td>Investigations</td>
<td>ERCP/MRCP (narrowing and dilatations of ducts visualized)</td>
<td>Anti-mitochondrial antibodies, IgM, increased lipids, liver biopsy (absence of duct narrowing on ERCP)</td>
</tr>
</tbody>
</table>

**Secondary Biliary Cirrhosis**

**Definition**
- cirrhosis from prolonged partial or total obstruction of major bile ducts

**Etiology**
- acquired: post-op strictures, chronic pancreatitis, sclerosing cholangitis, stone in bile duct
- congenital: cystic fibrosis (CF), congenital biliary atresia, choledochal cysts

**Diagnosis**
- cholangiography and liver biopsy

**Treatment**
- treat obstruction, give antibiotics for cholangitis prophylaxis

**Biliary Colic, Cholecystitis**

- see General Surgery, GS46

**Ascending Cholangitis**

- see General Surgery, GS48

**Definition**
- infection of the biliary tree

**Etiology**
- stasis in the biliary tract due to obstruction or stricture (usually from previous cholecystectomy)
- infection originates in the duodenum or spreads hematogenously from the portal vein
- bacteria
  - *E. coli*, *Klebsiella*, *Enterobacter*, *Enterococcus*
  - co-infection with *Bacteroides* and *Clostridia* can occur

**Signs and Symptoms**
- Charcot’s triad: fever, RUQ pain, jaundice (50-70%)
- Reynold’s Pentad in patients with suppurative cholangitis: fever, RUQ pain, jaundice, hypotension, altered mental status

**Diagnosis**
- increased WBC
- usually increased ALP and bilirubin, ALT variably elevated
- blood culture
- abdominal U/S: CBD dilation, stones

**Treatment**
- most important is drainage, ideally via ERCP, but if necessary by percutaneous biliary or surgical routes
- antibiotic therapy: broad spectrum to cover Gram-negatives, *Enterococcus*, and anaerobes (especially if CBD manipulation); no clear consensus on antibiotic choice but consider:
  - ampicillin + sulbactam or piperacillin/tazobactam
  - metronidazole + 3rd generation cephalosporin (e.g. ceftriaxone) or fluoroquinolone (e.g. ciprofloxacin or levofloxacin)
  - carbapenem monotherapy (e.g. imipenem or meropenem)

**Prognosis**
- good with effective drainage and antibiotics in mild to moderate cases
- high mortality (~50%) in patients with Reynold’s Pentad
Pancreatic Enzyme Abnormalities

Causes of Increased Serum Amylase

- pancreatic disease
  - pancreatic diseases: pancreatitis, pancreatic duct obstruction (e.g. ampullary cancer), pseudocyst, abscess, ascites, trauma, cancer
- non-pancreatic abdominal disease
  - biliary tract disease, bowel obstruction/ischemia, perforated or penetrating ulcer, ruptured ectopic pregnancy, aneurysm, chronic liver disease, peritonitis
- non-abdominal disease
  - cancer (lung, ovary, esophagus, etc.), salivary gland lesions, bulimia, renal transplant/insufficiency, burns, ketoacidosis
  - macroamylasemia

Causes of Increased Serum Lipase

- pancreatic disease: same as above
- non-pancreatic abdominal disease (mild elevations only): same as above
- non-abdominal disease
  - macrolipasemia
  - renal failure

Acute Pancreatitis

Etiology

Idiopathic: thought to be hypertensive sphincter or microlithiasis
Gallstones (45%)
Ethanol (35%)
Tumours: pancreas, ampulla, choledochocoele
Scorpion stings
Microbiological
  - bacterial: Mycoplasma, Campylobacter, TB, M. avium intracellulare, Legionella, leptospirosis
  - viral: mumps, rubella, varicella, viral hepatitis, CMV, EBV, HIV, Coxsackie virus, echovirus, adenovirus
  - parasites: ascariasis, clonorchiasis, echinococcosis
Autoimmune: SLE, polyarteritis nodosa (PAN), Crohn's
Surgery/trauma
  - manipulation of sphincter of Oddi (e.g. ERCP), post-cardiac surgery, blunt trauma to abdomen, penetrating peptic ulcer
Hyperlipidemia (TG >11.3 mmol/L; >1000 mg/dL), Hypercalcemia, Hypothermia
Emboli or Ischemia
Drugs/toxins
  - azathioprine, mercaptopurine, furosemide, estrogens, methyl dopa, H2-blockers, valproic acid, antibiotics, acetaminophen, salicylates, methanol, organophosphates, steroids (controversial)

Pathogenesis

- activation of proteolytic enzymes within pancreatic cells, starting with trypsin, leading to local and systemic inflammatory response
- in gallstone pancreatitis, this is due to mechanical obstruction of the pancreatic duct by stones
- in ethanol-related pancreatitis, pathogenesis is unknown
- in rare genetic diseases, mutations prevent the physiological breakdown of trypsin required normally to stop proteolysis (e.g. mutant trypsin in hereditary pancreatitis or mutation in SPINK 1 gene which normally inhibits activated trypsin); may be model for ethanol-related pancreatitis

Pathology

- mild (interstitial)
  - peri-pancreatic fat necrosis
  - interstitial edema
- severe (necrotic)
  - extensive peri-pancreatic and intra-pancreatic fat necrosis
  - parenchymal necrosis and hemorrhage → infection in 60%
  - release of toxic factors into systemic circulation and peritoneal space (causes multi-organ failure)
- severity of clinical features may not always correlate with pathology
• 3 phases:
  ▪ local inflammation + necrosis → hypovolemia
  ▪ systemic inflammation in multiple organs, especially in lungs, usually after IV fluids given → pulmonary edema
  ▪ local complications 2 wk after presentation → pancreatic sepsis/abscess

### Signs and Symptoms

- pain: epigastric, noncolicky, constant
- can raditate to back
- may improve when leaning forward (Inglefinger’s sign)
- tender rigid abdomen; guarding
- nausea and vomiting
- abdominal distention from paralytic ileus
- fever: chemical, not due to infection
- jaundice: compression or obstruction of bile duct
- Cullen/Grey-Turner’s signs
- tetany: transient hypocalcemia
- hypovolemic shock: can lead to renal failure
- acute respiratory distress syndrome
- coma

### Investigations

- increased serum pancreatic enzymes: amylase, lipase (more specific)
- ALT >150 specific for biliary cause
- increased WBC, glucose, low calcium
- imaging: CT most useful for diagnosis and prognosis
  - x-ray: “sentinel loop” (dilated proximal jejunum), calcification and “colon cut-off sign” (colonic spasm)
  - U/S: useful for evaluating biliary tree (67% sensitivity, 100% specificity)
  - CT scan with IV contrast: useful for diagnosis and prognosis because contrast seen only in viable pancreatic tissue, non-viable areas can be biopsied percutaneously to differentiate sterile from infected necrosis
  - ERCP or MRCP if cause uncertain, assess for duct stone, pancreatic or ampullary tumour, pancreas divisum

### Prognosis

- usually a benign, self-limiting course, single or recurrent
- occasionally severe leading to:
  ▪ shock
  ▪ pulmonary edema
  ▪ multi-organ dysfunction syndrome
  ▪ GI ulceration due to stress
  ▪ death
- mortality according to Ranson’s criteria (see sidebar)
  ▪ ≤2 criteria = <5% mortality
  ▪ 3–4 criteria = 15–20%
  ▪ 5–6 criteria = 40%
  ▪ ≥7 criteria = >99%
- multiple other prognostic indices available, more accurate than Ranson but difficult to remember (e.g. APACHE)

### Treatment

- goals (only supportive therapy available):
  (1) hemodynamic stability
  (2) analgesia
  (3) oxygen
  (4) stop progression of damage (difficult)
  (5) treat local and systemic complications
- antibiotics controversial except in documented infection (use cephalosporins, imipenem)
- aspirate necrotic areas of pancreas to diagnose infection; drain if infected
- IV fluids (crystalloid or colloid)
- beware third spacing of fluid, monitor urine output carefully
- NG suction (rests pancreas) if vomiting, stomach very dilated
- endoscopic sphincterotomy if severe gallstone pancreatitis (i.e. cholangitis or ongoing obstruction)
- nutritional support: nasojejunal feeding tube or TPN if cannot tolerate enteric feeds
- recent evidence supports nasogastric enteral (or oral if feasible) feeds
- no benefit: glucagon, atropine, aprotinin, H2-blockers, peritoneal lavage
- follow clinically and CT/ultrasound to exclude complications
- chief role of surgery is to drain fluid or excise necrotic tissue (necrosectomy) in the case of infected pancreatic necrosis (try to delay for >2 wk to allow demarcation between viable and necrotic tissue)

---

G45 Gastroenterology Pancreas Toronto Notes 2014

---

**Prophylactic Antibiotics Cannot Reduce Infected Pancreatic Necrosis and Mortality in Acute Necrotizing Pancreatitis: Evidence from a Meta-analysis of Randomized Controlled Trials**

**An J Gastroenterol 2008;103:104-110**

**Study Selection:** RCTs comparing antibiotics with placebo or no treatment.

**Results:** Seven trials (n = 463) were included. Antibiotics were not statistically superior to controls in reduction of infected necrosis and mortality.

**Conclusion:** Prophylactic antibiotics cannot reduce infected pancreatic necrosis and mortality in patients with acute necrotizing pancreatitis.

---

**Ranson’s Criteria: Prognostic Indicator of Mortality in Pancreatitis not due to Gallstones**

**At Admission**

- G: Blood Glucose >11 mmol/L (>200 mg/dL) (with no history of hyperglycemia)
- A: Age >55
- L: Serum LDH >350 IU/L
- W: WBC >6x10^9/L (60,000/mm^3)

**During First 48 h**

- C: Serum Calcium <2 mmol/L (<8 mEq/L)
- B: Base deficit >4 mmol/L (>4 mEq/L)
- S: Estimated fluid Sequestration >6 L

- ≥7 criteria present
- High mortality if ≥3 criteria present

---

**Increased Amylase**

- Sensitive, not specific

**Increased Lipase**

- Higher sensitivity and specificity
- Stays elevated longer

---

**Rep 2009;11:104-110**

**Increased Pancreatic Enzymes**

- Specific for biliary cause

**Increased Serum Lipase**

- Specific for biliary cause

---

**Infectious Complications of Necrotizing Pancreatitis**

- Pneumonia
- Peritonitis
- Sepsis

---

**Pancreatic Ulcers**

- Often diagnosed by CT scan

---

**Pancreatic Sepsis/Abscess**

- Common complications

---

**Prognosis of Necrotizing Pancreatitis**

- Mortality according to Ranson’s criteria

---

**Surgical Complications of Necrotizing Pancreatitis**

- Pancreatic ascites
- Pancreatic pseudocyst

---

**Management of Necrotizing Pancreatitis**

- Early operative intervention

---

**Prognostic Indices of Necrotizing Pancreatitis**

- Ranson’s Criteria
- GPR
- Rep 2009;11:104-110

---

**Incidence of Necrotizing Pancreatitis**

- 20% of patients with acute pancreatitis

---

**Epidemiology of Necrotizing Pancreatitis**

- More common in developed countries

---

**Risk Factors for Necrotizing Pancreatitis**

- Alcohol use
- Hyperlipidemia
- Diabetes mellitus

---

**Pathophysiology of Necrotizing Pancreatitis**

- Autodigestion of pancreas

---

**Pathology of Necrotizing Pancreatitis**

- Necrotic tissue
- Infected pancreatic necrosis

---

**Treatment of Necrotizing Pancreatitis**

- Conservative management

---

**Conclusion of Necrotizing Pancreatitis**

- Management remains challenging
Late Complications
- pseudocysts: follow if asymptomatic, drain if symptomatic or growing
  - drain: choice of endoscopic, percutaneous under radiological guidance, or surgical
- infected necrosis/abscesses: antibiotics + percutaneous drainage, endoscopic vs. surgical
- bleeding: (1) gastric varices if splenic vein thrombosis, (2) pseudoaneurysm of vessels in areas of necrosis, especially splenic artery, (3) duodenal ulcer related to compression of duodenum by enlarged pancreas
- splenic and portal vein thrombosis: no effective therapy described, anticoagulation not proven, hazardous
- rare: diabetes, pancreatic duct damage

Chronic Pancreatitis

Definition
- irreversible damage to pancreas characterized by:
  1. pancreatic cell loss (from necrosis)
  2. inflammation
  3. fibrosis

Etiology/Pathophysiology
- alcohol (most common):
  - causes a larger proportion (>90%) of chronic pancreatitis than acute pancreatitis
  - changes composition of pancreatic juice (e.g. increases viscosity)
  - decreases pancreatic secretion of pancreatic stone protein (lithostathine) which normally solubilizes calcium salts
    - precipitation of calcium within pancreatic duct results in duct and gland destruction
  - toxic effect on acinar and duct cells – directly or via increasing free radicals
    - acinar cell injury leads to cytokine release, which stimulates pancreatic stellate cells to form collagen (leading to fibrosis)
  - varying degrees of ductular dilatation, strictures, protein plugs, calcification
  - no satisfactory theory to explain why only a minority of alcoholics develop pancreatitis
- unusual causes
  - cystic fibrosis
  - severe protein-calorie malnutrition
  - hereditary
  - idiopathic

Signs and Symptoms
- early stages:
  - recurrent attacks of severe abdominal pain (upper abdomen and back)
  - chronic painless pancreatitis: 10%
- late stages: occurs in 15% of patients
  - malabsorption syndrome when >90% of function is lost, steatorrhea
  - diabetes, calcification, jaundice, weight loss, pseudocyst, ascites, GI bleed

Investigations
- laboratory:
  - increase in serum glucose
  - increase in serum ALP, less commonly bilirubin (jaundice)
  - serum amylase and lipase usually normal
- AXR: looking for pancreatic calcifications
- U/S or CT: calcification, dilated pancreatic ducts, pseudocyst
- MRCP or ERCP: abnormalities of pancreatic ducts-narrowing and dilatation
- EUS: abnormalities of pancreatic parenchyma and pancreatic ducts
- secretin test: gold standard, measures exocrine function but difficult to perform, unpleasant for patient, expensive
- fecal pancreatic enzyme measurement (elastase-1, chymotrypsin) available only in selected centres

Management
- most common problem is pain, difficult to control
- general management:
  - total abstinence from alcohol
  - enzyme replacement may help pain by resting pancreas via negative feedback
  - analgesics
  - celiac ganglion blocks
  - time: pain decreases with time as pancreas "burns out"
- endoscopy: sphincterotomy, stent if duct dilated, remove stones from pancreatic duct
• surgery: drain pancreatic duct (pancreaticojejunostomy) if duct dilated (more effective than endoscopy); resect pancreas if duct contracted
• steatorrhea:
  ▪ pancreatic enzyme replacement
  ▪ restrict fat, increase carbohydrate and protein (may also decrease pain)
  ▪ neither endoscopy nor surgery can improve pancreatic function

**Autoimmune Pancreatitis**

• most commonly presents as a mimicker of pancreatic cancer (pancreatic mass detected because of jaundice & abdominal pain)

**Investigations**

• histology: lymphocyte and plasma cell infiltration of pancreas
• imaging: focal or diffuse enlargement of pancreas on CT or MRI, sausage shaped, low density rim around pancreas
• serology: increased serum IgG4
• other organs involvement: sialadenitis, retroperitoneal fibrosis, biliary duct narrowing, nephritis

**Treatment**

• responds to prednisone

---

**Clinical Nutrition**

**Determination of Nutritional Status**

• corrected weight loss [expressed as body mass index (kg/m²)] is most important parameter in assessing need for nutritional support

**Investigations**

• plasma proteins: albumin, pre-albumin (shorter half life than albumin), transferrin
  ▪ decrease may indicate decreased nutritional status or disease state
• thyroid-binding globulin, retinol-binding protein (may be too sensitive)
• anthropometry (e.g. triceps skinfold thickness), grip strength less often used

**Table 20. Areas of Absorption of Nutrients**

<table>
<thead>
<tr>
<th></th>
<th>Fe</th>
<th>CHO</th>
<th>Proteins, Lipids</th>
<th>Na⁺, H₂O</th>
<th>Bile Acids</th>
<th>Vit B₁₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Jejunum</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Ileum</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td></td>
</tr>
</tbody>
</table>

**Enteral Nutrition (EN)**

**Definition**

• enteral nutrition (tube feeding) is a way of providing food through a tube placed in the stomach or the small intestine
• choice of tubes: nasogastric (NG), nasojejunal (NJ), percutaneous endoscopic gastrostomy (G-tube), percutaneous endoscopic jejunostomy (J-tube) or tubes can be placed radiologically, surgically

**Indications**

• oral feeding inadequate or contraindicated

**Feeds**

• polymeric feeds contain whole protein, carbohydrate, fat as a liquid, with or without fibre
• elemental feeds contain protein as amino acids, carbohydrate as simple sugars, fat content low (therefore high osmolarity)
• specific diets: low carbohydrate/high fat solution for ventilated patients (carbohydrate has a high respiratory quotient so minimizes carbon dioxide production), high energy, low electrolyte solutions for dialysis patients

**Relative Contraindications**

• non-functioning gut (e.g. intestinal obstruction, enterocutaneous or enterocutaneous fistulae)
• uncontrolled diarrhea
• GI bleeding
Complications
- aspiration
- diarrhea
- refeeding syndrome (rare): carbohydrate can stimulate excessive insulin release, leading to cellular uptake and low serum levels of phosphate, magnesium, potassium
- overfeeding syndrome (rare): hypertonic dehydration, hyperglycemia, hypercapnea, azotemia (from excess protein)

Enteral Nutrition Advantages over Parenteral Nutrition
- far fewer serious complications (especially sepsis)
- nutritional requirements for enterally administered nutrition better understood
- can supply gut-specific fuels such as glutamine and short chain fatty acids
- nutrients in the intestinal lumen prevent atrophy of the gut and pancreas
- prevents gallstones by stimulating gallbladder motility
- much less expensive

Parenteral Nutrition (PN)

Definition
- parenteral nutrition is the practice of feeding a person intravenously, bypassing the usual process of eating and digestion

Indications
- short term (<1 mo)
  - whenever GI tract not functioning
    - only situations where PN has been well shown to increase survival are after bone marrow transplant and in short bowel syndrome, some evidence for benefit in gastric cancer, but often used in ICU, perioperatively and difficult to control sepsis
  - preoperative: only useful in severely malnourished (e.g. loss of >15% of pre-morbid weight, serum albumin <28 g/L or <2.8 g/dL), and only if given for ≥2 wk
  - renal failure: PN shown to increase rate of recovery; no increase in survival
  - liver disease: branched chain amino acids may shorten duration of encephalopathy; no increase in survival
  - IBD: PN closes fistulae and heals acute exacerbations of mucosal inflammation, but effect is transient (EN is equally effective)
  - some evidence for efficacy, but convincing data not available for:
    - radiation/chemotherapy-induced enteritis
    - AIDS with wasting diarrhea
    - severe acute pancreatitis
- long term (>1 mo): can be given at home
  - severe untreatable small bowel disease (e.g. radiation enteritis, extensive CD, high output fistulae)
  - following surgical resection of >70% of bowel (e.g. bowel infarction)
  - severe motility diseases (e.g. scleroderma affecting bowel)

Relative Contraindications
- functional GI tract for enteral nutrition
- active infection; at least until appropriate antibiotic coverage
- inadequate venous access; triple-lumen central venous lines usually prevent this problem
- unreliable patient or clinical setting

Complications of PN
- sepsis: most serious of the common complications
- mechanical pneumothorax from insertion of central line, catheter migration and thrombosis, air embolus
- metabolic: CHF, hyperglycemia, gallstones, cholestasis

Enteral versus Parenteral Nutrition for Acute Pancreatitis
Cochrane DB of Syst Rev 2010;1:CD002037

Purpose: Compare EN versus TPN on mortality, morbidity and hospital stay in patients with pancreatitis.
Study Selection: RCTs of TPN versus EN in pancreatitis.
Results: Eight trials (n=348) were included. Enteral nutrition decreases RR of death (0.50), multiple organ failure (0.55), infection (0.39) and other local complications (0.70). It also decreased hospital stay by 2.37 d.
Conclusion: EN reduces mortality, organ failure, infections and length of hospital stay in patients with pancreatitis.

Whenever possible, enteral nutrition is ALWAYS preferable over parenteral nutrition!
### Common Medications

#### Table 21. Common Drugs Prescribed in Gastroenterology

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proton Pump Inhibitors</strong></td>
<td>omeprazole</td>
<td>Losec®, Prilosec®</td>
<td>20 mg PO OD</td>
<td>Inhibits gastric enzymes H⁺/K⁺ - ATPase (proton pump)</td>
<td>Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, reflux esophagitis, symptomatic GERD, dyspepsia, Zollinger-Ellison syndrome, eradication of H. pylori (combined with antibiotics)</td>
<td>Hypersensitivity to drug</td>
<td>Dizziness, headache, flatulence, abdominal pain, nausea, rash, increased risk of osteoporotic fracture (secondary to impaired calcium absorption)</td>
</tr>
<tr>
<td><strong>Histamine H₂-receptor Antagonists</strong></td>
<td>ranitidine</td>
<td>Zantac®</td>
<td>300 mg PO OD or 150 mg bid</td>
<td>Inhibits gastric histamine H₂-receptors</td>
<td>Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, ulcer prophylaxis, reflux esophagitis, symptomatic GERD, Zollinger-Ellison syndrome</td>
<td>Hypersensitivity to drug</td>
<td>Confusion, dizziness, headache, arthralgias, constipation, nausea, agranulocytosis, pancytopenia, depression</td>
</tr>
<tr>
<td><strong>Stool Softener</strong></td>
<td>docusate sodium</td>
<td>Colace®</td>
<td>100-400 mg daily, divided in 1-4 doses</td>
<td>Promotes incorporation of water into stool</td>
<td>Relief of constipation</td>
<td>Presence of abdominal pain, fever, nausea and vomiting</td>
<td>Throat irritation, abdominal cramps, rashes</td>
</tr>
<tr>
<td><strong>Osmotic Laxatives</strong></td>
<td>lactulose</td>
<td>Lactulose/Constulose®</td>
<td>Constipation: 15-30 mL OD to bid</td>
<td>Constipation: 15-30 mL OD to bid</td>
<td>Chronic constipation, prevention and treatment of portal-systemic encephalopathy</td>
<td>Patients who require a low galactose diet</td>
<td>Flatulence, intestinal cramps, nausea, diarrhea if excessive dosage</td>
</tr>
<tr>
<td>PEG3350</td>
<td>Lax-a-day®/Golytely®</td>
<td>Constipation: 17 g powder dissolved in 4-8 oz liquid PO OD</td>
<td>Constipation: 17 g powder dissolved in 4-8 oz liquid PO OD</td>
<td>Constipation: 17 g powder dissolved in 4-8 oz liquid PO OD</td>
<td>Constipation: 17 g powder dissolved in 4-8 oz liquid PO OD</td>
<td>Relief of constipation</td>
<td>Hypersensitivity to drug</td>
</tr>
<tr>
<td><strong>Prokinetic Laxatives</strong></td>
<td>senna</td>
<td>Senokot®</td>
<td>Tablets: 1-4 PO qhs, Syrup: 10-15 mL PO qhs</td>
<td>Induce peristalsis in lower colon</td>
<td>Constipation</td>
<td>Patients with acute abdomen</td>
<td>Abdominal cramps, discoloration of breast milk, urine, feces, melanosis coli and atomic colon from prolonged use (controversial)</td>
</tr>
<tr>
<td>bisacodyl</td>
<td>Bisacodyl®</td>
<td></td>
<td>5-30 mg PO OD (start at 10 mg for bowel preparation)</td>
<td>Enteric nerve stimulation and local contact-induced secretory effects. Colonic movements</td>
<td>Constipation: Preparation of bowel for procedure</td>
<td>GI obstruction, Gastroenteritis</td>
<td>Abdominal colic, abdominal discomfort, proctitis (with suppository use), diarrhea</td>
</tr>
<tr>
<td>metoclopramide</td>
<td>Maxeran®</td>
<td></td>
<td>See anti-emetics</td>
<td>See anti-emetics</td>
<td>See anti-emetics</td>
<td>See anti-emetics</td>
<td>See anti-emetics</td>
</tr>
<tr>
<td><strong>Bulk Laxatives</strong></td>
<td>psyllium</td>
<td>Metamucil®</td>
<td>2-4 tabs (1 tab = 0.52 g) PO qd-tid pm</td>
<td>Increases stool bulk → water retention in stool</td>
<td>Constipation</td>
<td>Hypersensitivity to drug, GI obstruction</td>
<td>GI obstruction, diarrhea, constipation, abdominal cramps</td>
</tr>
<tr>
<td>Class</td>
<td>Generic Drug Name</td>
<td>Trade Name</td>
<td>Dosing</td>
<td>Mechanism of Action</td>
<td>Indications</td>
<td>Contraindications</td>
<td>Side Effects</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------</td>
<td>------------</td>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Antidiarrheal Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>loperamide</td>
<td>Imodium®</td>
<td></td>
<td>25-50 mg PO/N/IM q4-8h pm</td>
<td>Competitive H₁, receptor antagonist in GI tract, blood vessels, and respiratory tract</td>
<td>Motion sickness, radiation sickness, postoperative vomiting, and drug-induced nausea and vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diphenoxylate/ atropine</td>
<td>Lomotil®</td>
<td></td>
<td>5 mg PO tid to qid</td>
<td>Inhibits GI propulsion via direct action on smooth muscle, resulting in a decrease in peristaltic action and increase in transit time</td>
<td>Adjunctive therapy for diarrhea, as above</td>
<td>Hypersensitivity to diphenoxylate or atropine, jaundice, pseudomembranous enterocolitis, diarrhoea caused by enterotoxin producing bacteria</td>
<td>Dizziness, drowsiness, insomnia, headache, nausea, vomiting, cramps, allergic reaction</td>
</tr>
<tr>
<td><strong>Anti-emetics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>metoclopramide</td>
<td>Maxeran®</td>
<td></td>
<td>10 mg IV/IM q2-3h pm, 10-15 mg PO qid (30 min before meals and qhs)</td>
<td>Dopamine and HT receptor antagonist in chemoreceptor trigger zone. Enhances response to Ach in upper GI tract, enhancing motility and gastric emptying. Increases LES tone</td>
<td>Post op nausea and vomiting, antipsychotic, anxiety</td>
<td>Hypersensitivity to drug</td>
<td>Dystonia, EPS, seizure, neuroleptic malignant syndrome (MMS) (rarely)</td>
</tr>
<tr>
<td>ondansetron</td>
<td>Zofran®</td>
<td></td>
<td>Depends on procedure, generally 8-16 mg PO</td>
<td>Selective 5HT3 receptor antagonist in central chemoreceptor trigger zone and peripherally on vagus nerve</td>
<td>Nausea and vomiting caused by cancer chemotherapy and radiation therapy. Multiple off label uses, including gastroenteritis nausea and vomiting</td>
<td>Morphine, hypersensitivity to drug</td>
<td>Constipation, diarea, increased liver enzymes, headache, fatigue, malaise, cardiac dysrhythmia</td>
</tr>
<tr>
<td>granisetron</td>
<td>Kytril®</td>
<td></td>
<td>1 mg PO bid (for nausea from chemotherapy/ radiation)</td>
<td>Same as above</td>
<td>Nausea and vomiting caused by cancer chemotherapy and radiation therapy</td>
<td>Same as above</td>
<td>Constipation, prolonged QT interval (rarely)</td>
</tr>
<tr>
<td><strong>IBD Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mesalamine</td>
<td>Pentasa®</td>
<td>Safalfax®</td>
<td>CD: 1g tid/qd Active UC: 1g tid Maintenance UC: 1.6 g divided doses daily also as suppositories and enemas</td>
<td>5-ASA: blocks arachidonic acid metabolism to prostaglandins and leukotrienes</td>
<td>IBD</td>
<td>Hyperosensitivity to mesalamine salicylates</td>
<td>Abdominal pain, constipation, arthralgia, headache</td>
</tr>
<tr>
<td>sulfasalazine</td>
<td>Salazopyrin®</td>
<td>Asacol®</td>
<td>3-4 g/d in divided doses</td>
<td>Compound composed of 5-ASA bound to sulfapyridine, hydrolysis by intestinal bacteria releases 5-ASA, the active component</td>
<td>Colonic disease</td>
<td>Hyperosensitivity to sulfasalazine, sulfapyridine, salicylates, intestinal or urinary obstruction, porphyria</td>
<td>Rash, loss of appetite, nausea, vomiting, headache, oligospermia (reversible)</td>
</tr>
<tr>
<td>prednisone</td>
<td></td>
<td>Mesasa®</td>
<td>20-40 mg PO OD for acute exacerbation</td>
<td>Anti-inflammatory</td>
<td>Colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immunosuppressive Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-mercaptopurine (6-MP)</td>
<td>Purinethol®</td>
<td></td>
<td>CD: 1.5 mg/kg/d</td>
<td>Immunosuppressive</td>
<td>IBD: active inflammation and to maintain remission</td>
<td>Hyperosensitivity to mercaptopurine, prior resistance to mercaptopurine or thioguanine, history of treatment with alkylating agents, hyperosensitivity to acitretin, pregnancy</td>
<td>Pancreatitis, bone marrow suppression, increased risk of cancer</td>
</tr>
<tr>
<td><strong>Immunomodulators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infliximab</td>
<td>Remicade®</td>
<td></td>
<td>5-10 mg/kg IV over 2 h</td>
<td>Antibody to TNFα</td>
<td>Medically refractory CD</td>
<td>Heart failure, moderate to severe, doses &gt;5 mg/kg</td>
<td>Reported cases of reactivated TB, PCP, lymphoma, other infections</td>
</tr>
</tbody>
</table>
Landmark Gastroenterology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALF</td>
<td>Gastroenterology 2009; 137:856-64</td>
<td>IV NAC was shown to improve transplant-free survival in patients with early non-acetaminophen related acute liver failure. Later stage disease did not improve with IV NAC</td>
</tr>
<tr>
<td>BISAP</td>
<td>Am J Gastro 2009; 104:966</td>
<td>Five point scoring system for patients with acute pancreatitis to identify those at increased risk for mortality</td>
</tr>
<tr>
<td>Early combined vs. conventional management in Crohn’s</td>
<td>Lancet 2008; 371:660-7</td>
<td>Initiation of more intensive therapy early in Crohn’s disease may be more likely to result in corticosteroid-free remission than conventional therapy</td>
</tr>
<tr>
<td>FAMOUS</td>
<td>Lancet 2009; 374:119-25</td>
<td>Famotidine was effective in preventing gastric and duodenal ulcers, and erosive esophagitis in patients receiving low-dose ASA therapy</td>
</tr>
<tr>
<td>Glucocorticoids and NAC in Alcoholic Hepatitis</td>
<td>NEJM 2011; 365:1781-9</td>
<td>Combination therapy improved 1 mo survival, but not 6 mo survival compared to prednisolone monotherapy</td>
</tr>
<tr>
<td>MELD</td>
<td>Gastroenterology 2003; 124:91-6</td>
<td>MELD score can be applied for allocation of donor livers as it accurately predicts 3 mo mortality in patients with chronic liver failure</td>
</tr>
<tr>
<td>SONIC</td>
<td>NEJM 2010; 362:1383-95</td>
<td>In moderate-severe Crohn’s disease, infliximab + azathioprine was more likely to result in corticosteroid-free remission than infliximab monotherapy. Infliximab monotherapy was more effective than azathioprine monotherapy</td>
</tr>
</tbody>
</table>

References

Atlas
Kandel G. Division of gastroenterology, St. Michael’s Hospital, Toronto.
Olscamp G. Division of gastroenterology, St. Michael’s Hospital, Toronto.
Saibil F. Division of gastroenterology, SWCHSC.
Haber G. Division of gastroenterology, Lennox Hall Hospital, New York.

Esophageal and Gastric Disease

Stomach and Duodenum

Small and Large Bowel
Hatchette TF, Farina D. Infectious diarrhea: when to test and when to treat. CMAJ 2011;183:339-344.
Liver and Biliary Tract
Williams JV and Simel DL. Does this patient have ascites? JAMA 1992;267:2645-2646.

Pancreas

Rational Clinical Examination
Grover SA, Barkun AN, and Sackett DL. Does this patient have splenomegaly? JAMA 1993;270:2218-2221.
Williams JV and Simel DL. Does this patient have ascites? How to divine fluid in the abdomen. JAMA 1992;267:2645-2646.
Acronyms ........................................... 2
Basic Anatomy Review ............................. 2
Differential Diagnoses of Common Presentations ................................. 4
Acute Abdominal Pain
Abdominal Mass
GI Bleeding
Jaundice
Preoperative Preparations ......................... 6
Surgical Complications ............................. 7
Postoperative Fever
Wound/Incisional Complications
Urinary and Renal Complications
Postoperative Dyspnea
Respiratory Complications
Cardiac Complications
Intra-abdominal Abscess
Paralytic Ileus
Delirium
Thoracic Surgery ................................. 12
Hiatus Hernia
Esophageal Perforation
Esophageal Carcinoma
Chest Wall
Pleura, Lung, and Mediastinum
Tube Thoracostomy
Lung Transplantation
Chronic Obstructive Pulmonary Disease
Stomach and Duodenum ........................ 17
Peptic Ulcer Disease
Gastric Carcinoma
Gastrointestinal Stromal Tumour (GIST)
Bariatric Surgery
Complications of Gastric Surgery
Small Intestine .................................... 21
Tumours of Small Intestine
Hernia .................................................. 22
Groin Hernias
Bowel Obstruction ................................ 24
Small Bowel Obstruction (SBO)
Large Bowel Obstruction (LBO)
Colonic Pseudo-Obstruction ....................... 26
Toxic Megacolon
Paralytic Ileus
Ogilvie’s Syndrome
Intestinal Ischemia ................................ 28
Appendix .............................................. 28
Appendicitis
Tumours of the Appendix
Inflammatory Bowel Disease (IBD) ............... 29
Crohn’s Disease
Ulcerative Colitis
Diverticular Disease ............................... 31
Diverticulosis
Diverticulitis
Colorectal Neoplasms ............................. 33
Colorectal Polyps
Familial Colon Cancer Syndromes
Colorectal Carcinoma (CRC)
Other Conditions of the Large Intestine ........ 36
Angiodysplasia
Volvulus
Fistula
Stomas
Anorectum ........................................... 38
Hemorrhoids
Anal Fissures
Anorectal Abscess
Fistula-In-Ano
Pilonidal Disease
Rectal Prolapse
Anal Neoplasms
Liver ................................................. 41
Liver Cysts
Liver Abscesses
Neoplasms
Liver Transplantation
Biliary Tract ......................................... 45
Cholelithiasis
Biliary Colic
Acute Cholecystitis
Acalculous Cholecystitis
Choledocholithiasis
Acute Cholangitis
Gallstone ileus
Carcinoma of the Gallbladder
Cholangiocarcinoma
Pancreas .............................................. 50
Acute Pancreatitis
Chronic Pancreatitis
Pancreatic Cancer
Spleen ................................................. 53
Splenic Trauma
Splenectomy
Breast .................................................. 54
Benign Breast Lesions
Breast Cancer
Surgical Endocrinology ........................... 59
Thyroid and Parathyroid
Adrenal Gland
Pancreas
Pediatric Surgery ................................ 61
Skin Lesions ......................................... 64
Common Medications ............................ 65
References .......................................... 65
Acronyms

AAA: abdominal aortic aneurysm
ABG: arterial blood gas
ABI: ankle brachial index
APR: abdomino-perineal resection
BRBPR: bright red blood per rectum
CBD: common bile duct
CVA: costovertebral angle
CVP: central venous pressure
DIC: disseminated intravascular coagulation
DPL: diagnostic peritoneal lavage
EBL: estimated blood loss
EGD/EGD: esophagogastro-duodenoscopy
EUA: examination under anesthesia
ERCP: endoscopic retrograde cholangiopancreatography
ERCP: endoscopic ultrasound
FAST: focused abdominal sonogram for trauma
FNA: fine needle aspiration
FOBT: fecal occult blood test
Gastroesophageal reflux disease
Gerard’s syndrome
HNPCC: hereditary non-polyposis colorectal cancer
HDGC: hereditary diffuse gastric carcinoma
I&D: incision and drainage
IAR: low anterior resection
I&D: incision and drainage
MRCP: magnetic resonance cholangiography
NGT: nasogastric tube
OBJ: oesophageo-gastro-duodenoscopy
POD: postoperative day
PTC: percutaneous transhepatic cholangiography
SBO: small bowel obstruction
SIADH: syndrome of inappropriate anti-diuretic hormone
TED: thromboembolic deterrent
TEE: transesophageal echocardiogram
TEE: thoracic echocardiogram
UGIB: upper GI bleed
VATS: video-assisted thoracic surgery

Layers from Superficial to Deep

- skin (epidermis, dermis, subcutaneous fat)
- superficial fascia
  - Camper’s fascia (fatty) → Dartos
  - Scarpa’s fascia (membranous) → Colles’ superficial perineal fascia
- muscle (see Figure 2 and Figure 3)
  - external oblique → inguinal ligament → external spermatic fascia → fascia lata
  - internal oblique → cremasteric muscle/fascia
  - transversus abdominis → posterior inguinal wall
  - transversalis fascia → internal spermatic fascia
  - preperitoneal fat
  - peritoneum → tunica vaginalis
- at midline
  - rectus abdominus muscle: in rectus sheath, divided by linea alba
- above arcuate line (semicircular line of Douglas), which is midway between symphysis pubis and umbilicus
  - anterior rectus sheath = external oblique aponeurosis and anterior leaf of internal oblique aponeurosis
  - posterior rectus sheath = posterior leaf of internal oblique aponeurosis and transversus muscle aponeurosis
- below arcuate line
  - anterior rectus sheath = aponeurosis of external, internal oblique, transversus muscles
  - posterior rectus sheath = transversalis fascia
- arteries: superior epigastric (branch of internal thoracic), inferior epigastric (branch of external iliac); both arteries Anastomose and lie behind the rectus muscle

Basic Anatomy Review

Figure 1. Abdominal incisions

- Paramedian
- McBurney’s
- Pfannenstiel
- Lower midline
- Access to pelvic organs, sigmoid colon, and rectum

Figure 2. Continuity of the abdominal wall with layers of the scrotum and spermatic cord
Figure 3. Midline cross-section of abdominal wall

Figure 4. Blood supply to the GI tract

Venous Flow

Porto-systemic anastomoses:
1. Esophageal branches of left gastric vein with esophageal veins
2. Paraumbilical veins with subcutaneous veins of anterior abdominal wall
3. Superior rectal vein with middle and inferior rectal veins

Figure 5. Venous drainage of the GI tract
# Differential Diagnoses of Common Presentations

## Acute Abdominal Pain

### Table 1. Differential Diagnosis of Acute Abdominal Pain

<table>
<thead>
<tr>
<th>RUQ</th>
<th>EPIGASTRIC</th>
<th>LUQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatobiliary</td>
<td>Cardiac</td>
<td>Pancreatic (acute vs. chronic)</td>
</tr>
<tr>
<td>Biliary colic</td>
<td>Aortic dissection/ruptured AAA</td>
<td>Pancreatic pseudocyst</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>MI</td>
<td>Pancreatic tumours</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>Pericarditis</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>CBD obstruction (stone, tumour)</td>
<td>Gastrointestinal</td>
<td>Gastritis</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Gastritis</td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td>Budd-Chiari</td>
<td>GERD/esophagitis</td>
<td>Splenic flexure pathology (e.g. CRC, ischemia)</td>
</tr>
<tr>
<td>Hepatic abscess/mass</td>
<td>Peptic ulcer disease</td>
<td>Splenic</td>
</tr>
<tr>
<td>Right subphrenic abscess</td>
<td>Pancreatitis</td>
<td>Splenic infarct/abscess</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Mallory-Weiss tear</td>
<td>Splenomegaly</td>
</tr>
</tbody>
</table>

### DIFFUSE

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Peritonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early appendicitis, perforated appendix</td>
<td>Early appendicitis, perforated appendix</td>
</tr>
<tr>
<td>Mesenteric ischemia</td>
<td>Mesenteric ischemia</td>
</tr>
<tr>
<td>Gastroenteritis/colitis</td>
<td>Gastroenteritis/colitis</td>
</tr>
<tr>
<td>Constipation</td>
<td>Constipation</td>
</tr>
<tr>
<td>Bowel obstruction</td>
<td>Bowel obstruction</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>Ogilvie’s syndrome</td>
<td>Ogilvie’s syndrome</td>
</tr>
<tr>
<td>Cardiovascular/Hematological</td>
<td>Aortic dissection/ruptured AAA</td>
</tr>
<tr>
<td>Aortic dissection/ruptured AAA</td>
<td>Sickle cell crisis</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Renal failure</td>
</tr>
</tbody>
</table>

### Gastroenteritis/colitis

<table>
<thead>
<tr>
<th>Constipation</th>
<th>Bowel obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>Ogilvie’s syndrome</td>
<td>Ogilvie’s syndrome</td>
</tr>
<tr>
<td>Cardiovascular/Hematological</td>
<td>Aortic dissection/ruptured AAA</td>
</tr>
<tr>
<td>Aortic dissection/ruptured AAA</td>
<td>Sickle cell crisis</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Renal failure</td>
</tr>
</tbody>
</table>

### Genitourinary / Gynecological

| Perforated ectopic pregnancy | Perforated ectopic pregnancy |
| PID | PID |
| Acute urinary retention | Acute urinary retention |
| Gastrointestinal | Gastrointestinal |
| Diverticulitis | Diverticulitis |
| Colonic/rectal cancer | Colonic/rectal cancer |
| Fecal impaction | Fecal impaction |
| Praxis (ulcerative colitis, infectious; i.e. gonococcus or chlamydia) | Praxis (ulcerative colitis, infectious; i.e. gonococcus or chlamydia) |
| Sigmoid volvulus | Sigmoid volvulus |
| Hernia | Hernia |

### Gynecological

<table>
<thead>
<tr>
<th>See ‘suprapubic’</th>
</tr>
</thead>
<tbody>
<tr>
<td>See ‘suprapubic’</td>
</tr>
</tbody>
</table>

### Genitourinary

| Abdominal wall hernoma/abscess |
| Psoas abscess |

### Extraperitoneal

| Abdominal wall hernoma/abscess |
| Psoas abscess |

### Referred Pain

- Biliary colic: to right shoulder or scalpula
- Renal colic: to groin
- Appendicitis: periumbilical to right lower quadrant (RLQ)
- Pancreatitis: to back
- Ruptured aortic aneurysm: to back or flank
- Perforated ulcer: to RLQ (right paracolic gutter)

### Localization of Pain

- Most digestive tract pain is perceived in the midline because of bilaterally symmetric innervation. Kidney, ureter, ovary, or somatically innervated structures are more likely to cause lateralized pain.

### Types of Peritonitis

- Primary peritonitis: spontaneous without clear etiology
- Secondary peritonitis: due to a perforated viscus
- Tertiary peritonitis: recurrent secondary peritonitis more often with resistant organisms

### Key Tests for Specific Diagnosis

- ALP, ALT, AST, bilirubin
- Amylase/lipase
- Urinalysis
- t-HCG (in women of childbearing age)
- Troponins
- Lactate

### Key Tests for OR Preparation

- CBC, electrolytes, BUN, creatinine, glucose
- CXR + ECG

### Pancreatitis can look like a surgical abdomen, but is rarely an indication for immediate laparotomy.
## Abdominal Mass

### Table 2. Differential Diagnosis of Abdominal Mass

<table>
<thead>
<tr>
<th>Right Upper Quadrant (RUQ)</th>
<th>Upper Midline</th>
<th>Left Upper Quadrant (LUQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallbladder: cholecystitis, cholangiocarcinoma, peri-ampullary malignancy, cholelithiasis</td>
<td>Pancreas: pancreatic adenocarcinoma, other pancreatic neoplasm, pseudocyst</td>
<td>Abdominal aorta: AAA (pulsatile)</td>
</tr>
<tr>
<td>Biliary tract: Klatskin tumour</td>
<td></td>
<td>Gastric tumour (adenocarcinoma, gastrointestinal stromal tumour, carcinoid tumour), MALT lymphoma</td>
</tr>
<tr>
<td>Liver: hepatomegaly, hepatitis, abscess, tumour (hepatocellular carcinoma, metastatic tumour, etc.)</td>
<td></td>
<td>Spleen: splenomegaly, tumour, abscess, subcapsular splenic hemorrhage, can also present as RLQ mass if extreme splenomegaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stomach: tumour</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Right Lower Quadrant (RLQ)</th>
<th>Lower Midline</th>
<th>Left Lower Quadrant (LLQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestine: stool, tumour (CRC), mesenteric adenitis, appendicitis, appendiceal phlegmon or other abscess, typhilitis, intussusception, Crohn's inflammation</td>
<td>Uterus: pregnancy, leiomyoma (fibroid), uterine cancer, pyometra, hematometra</td>
<td>Intestine: stool, tumour, abscess (see RLQ)</td>
</tr>
<tr>
<td>Ovary: ectopic pregnancy, cyst (physiological vs. pathological), tumour (serous, mucinous, struma ovarii, germ cell, Krukenberg)</td>
<td>GU: bladder distention, tumour</td>
<td>Ovary: ectopic pregnancy, cyst, tumour (see RLQ)</td>
</tr>
<tr>
<td>Fallopian tube: ectopic pregnancy, tubo-ovarian abscess, hydrosalpinx, tumour</td>
<td></td>
<td>Fallopian tube: ectopic pregnancy, tubo-ovarian abscess, hydrosalpinx, tumour</td>
</tr>
</tbody>
</table>

## GI Bleeding

- see Gastroenterology, G25

### Indications for Surgery

- failure of medical management
- hemodynamic instability despite vigorous resuscitation
- recurrent hemorrhage after initial stabilization procedures with up to two attempts of endoscopic hemostasis
- hypovolemic shock
- prolonged bleeding with transfusion requirement >3 units/d

### Surgical Management of GI Bleeding

- upper GI bleeding:
  - bleeding from a source proximal to the ligament of Treitz
  - often presents with hematemesis and melena unless very brisk (then can present with hematochezia, hypotension, tachycardia)
  - initial management with endoscopy; if fails, then consider surgery
  - note: PUD accounts for approximately 55% of severe UGI bleeding
- lower GI bleeding:
  - bleeding from a source distal to the ligament of Treitz
  - often presents with BRBPR unless proximal to transverse colon
  - may occasionally present with melena
  - initial management with colonoscopy to detect and potentially stop source of bleeding
  - angiography, RBC scan to determine source as indicated
  - surgical intervention if no source found – obscure bleed

### Table 3. Differential Diagnosis of GI Bleeding

<table>
<thead>
<tr>
<th>Anatomical Source</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td>Excess anticoagulation (coumadin, heparin, etc.)</td>
</tr>
<tr>
<td></td>
<td>Excess antplatelet (clopidogrel, ASA)</td>
</tr>
<tr>
<td></td>
<td>Disseminated intravascular coagulation (DIC)</td>
</tr>
<tr>
<td></td>
<td>Congenital bleeding disorders</td>
</tr>
<tr>
<td>Nose</td>
<td>Epistaxis</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Esophageal varices</td>
</tr>
<tr>
<td></td>
<td>Mallory-Weiss tear</td>
</tr>
<tr>
<td></td>
<td>Esophagitis</td>
</tr>
<tr>
<td>Stomach</td>
<td>Gastritis</td>
</tr>
<tr>
<td></td>
<td>Gastric varices</td>
</tr>
<tr>
<td></td>
<td>Dieulafoy’s lesion</td>
</tr>
<tr>
<td>Duodenum</td>
<td>Duodenal ulcer</td>
</tr>
<tr>
<td></td>
<td>Perforated duodenal ulcer*</td>
</tr>
<tr>
<td>Jejunum</td>
<td>Tumours*</td>
</tr>
<tr>
<td></td>
<td>Polyps</td>
</tr>
<tr>
<td></td>
<td>Ulcers</td>
</tr>
<tr>
<td></td>
<td>Aorto-esophageal fistula (generally post endovascular aortic repair)*</td>
</tr>
<tr>
<td></td>
<td>Esophageal cancer</td>
</tr>
<tr>
<td></td>
<td>Gastric ulcer</td>
</tr>
<tr>
<td></td>
<td>Gastric cancer*</td>
</tr>
<tr>
<td></td>
<td>Duodenal cancer*</td>
</tr>
</tbody>
</table>

### Indications for Urgent Operation

- IHOP: Ischemia, Hemorrhage, Obstruction, Perforation

### Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

*NEJM 2013;368:11-21*

Recent study by Villanueva et. al, demonstrates that a restrictive transfusion strategy significantly improves outcomes in patients with acute upper GI bleeding, compared to a liberal transfusion strategy. Refer to study for details.
Table 3. Differential Diagnosis of GI Bleeding (continued)

<table>
<thead>
<tr>
<th>Anatomical Source</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileum and Ileocecal Junction</td>
<td>Meckel’s diverticulum (rare surgical management) Small bowel obstruction</td>
</tr>
<tr>
<td>Large Intestine</td>
<td>Colorectal cancer* Mesenteric thrombosis/ischemic bowel* Ulcerative colitis* (subtotal colectomy if failure of medical management) Angiodysplasia Diverticula</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>Diverticulosis* Sigmoid cancer* Bleeding post-polypectomy</td>
</tr>
<tr>
<td>Rectum and Anus</td>
<td>Hemorrhoids Fissures Rectal cancer* Anal varices</td>
</tr>
</tbody>
</table>

*Managed surgically in most cases

Jaundice

- see Gastroenterology, G40

Table 4. Differential Diagnosis of Jaundice

<table>
<thead>
<tr>
<th>Pre-hepatic: Pathology prior to the level of the liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolysis</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Portal systemic shunts</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Large heme load (e.g. large hematoma reabsorption)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatic: Pathology at the level of the liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral hepatitis</td>
</tr>
<tr>
<td>Alcohol related hepatitis</td>
</tr>
<tr>
<td>Non-alcohol related steatohepatitis</td>
</tr>
<tr>
<td>Drug-induced hepatitis</td>
</tr>
<tr>
<td>Dubin-Johnson syndrome</td>
</tr>
<tr>
<td>Sepsis and hyperperfusion states</td>
</tr>
<tr>
<td>TPN</td>
</tr>
<tr>
<td>Infiltrative diseases (e.g. amyloidosis, lymphoma, sarcoidosis, tuberculosis)</td>
</tr>
<tr>
<td>Hepatic crisis in sickle cell disease</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Cirrhosis</td>
</tr>
<tr>
<td>End-stage liver disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-hepatic (obstructive): Pathology after the conjugation of bilirubin in the liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct</td>
</tr>
<tr>
<td>Intraductal</td>
</tr>
</tbody>
</table>

| Cholangiitis |
| Sclerosing cholangitis |
| Choledochal cyst |
| Biliary obstruction |
| Cholangiocarcinoma |
| Autoimmune cholangiopathy |
| Certain parasitic infections (e.g. Ascaris lumbricoides, liver flukes) |

| Extrahepatic |
| Carcinoma: head of pancreas, ampulla of Vater, duodenum |
| Lymphoma |
| Metastases in peri-portal nodes |
| Acute/chronic pancreatitis |

Biochemical Signs for Differentiating Jaundice

Hepatocellular: Elevated bilirubin + elevated ALT/AST
Cholestatic: Elevated bilirubin + elevated ALP/GGT + duct dilatation upon biliary U/S
Hemolysis: ↓ haptoglobin ↑ LDH

Note: cholestatic jaundice is usually surgical.

Bilirubin Levels

<table>
<thead>
<tr>
<th>Prehepatic</th>
<th>Intrahepatic</th>
<th>Posthepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin</td>
<td>↑ ↑ N</td>
<td>↑</td>
</tr>
<tr>
<td>Direct</td>
<td>N</td>
<td>↑</td>
</tr>
<tr>
<td>Urate</td>
<td>↑ ↑ –</td>
<td>↑</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>– ↑ ▼</td>
<td>–</td>
</tr>
<tr>
<td>Fecal</td>
<td>↑ ↑ –</td>
<td>–</td>
</tr>
</tbody>
</table>

In patients with liver disease and an acute abdomen, spontaneous bacterial peritonitis must be ruled out.

Preoperative Preparations

Considerations
- informed consent (see Ethical, Legal and Organizational Aspects of Medicine, ELOAM5)
- screening questionnaire to assess important potential risk factors such as age, exercise capacity, and medication use
- consults: anesthesia, medicine, cardiology as indicated
- NPO ≥ 6 h prior, AAT (activity as tolerated), VSR (vital signs routine)
- IV – balanced crystalloid at maintenance rate (4:2:1 rule → roughly 100-125 cc/h): normal saline or Ringer’s lactate; bolus to catch up on estimated losses including losses from bowel prep
- appropriate use of fluids perioperatively decreases risk of cardiorespiratory complications
- patient’s regular medications including prednisone: consider pre-op stress dose if prednisone with β-blocker used in past year
- prophylactic antibiotics depending on wound class (within 1 h prior to incision): usually cefazolin (Ancef®) ± metronidazole (Flagyl®)
- bowel prep: cleans out bowel and decreases bacterial population
- oral cathartic (e.g. fleet Phosphosoda®) starting previous day
- in selected cases; current evidence does not support routine use
- consider DVT prophylaxis for all inpatient surgery (heparin)

Best Practice in General Surgery (BPIGS)
http://www.bpigs.ca/
BPIGS is a University of Toronto initiative with the goal of standardizing care in general surgery. This link contains EBM based guidelines which have been implemented by consensus within all Toronto teaching hospitals. This is a highly recommended source for the most up to date pre-operative and general treatment guidelines.
preoperative preperations/surgical complications

- do not hold heparin prior to surgery unless epidural is expected
- hold ASA x 1 wk pre-op
- smoking cessation x 6 wk pre-op can significantly decrease post-op complications

investigations

- blood components: group and screen or cross and type depending on procedure
- CBC, electrolytes, BUN, creatinine
- INR/PT, PTT
- ABGs if predisposed to respiratory insufficiency
- CXR (PA and lateral) if >50 yr old or previously abnormal within past 6 mo
- ECG if >50 yr old or as indicated by history
- β-HCG testing in all women of reproductive age

drains

- nasogastric (NG) tube:
  - indications: gastric decompression, analysis of gastric contents, irrigation/dilution of gastric contents, feeding (only if necessary due to risk of aspiration → naso-jejunal tube preferable)
  - contraindications: suspected basal skull fracture, obstruction of nasal passages due to trauma
- Foley catheter with urometer:
  - indications: to accurately monitor urine output, decompression of bladder, relieve obstruction, rapidly expanding suprapubic mass
  - contraindications: suspected urethral injury, difficult insertion of catheter

surgical complications

postoperative fever

- fever does not necessarily imply infection particularly in the first 24-48 h post-op
- fever may not be present or is blunted if patient is receiving chemotherapy, glucocorticoids or immunosuppression
- timing of fever may help identify cause
  - hours after surgery – POD #1 (immediate):
    - inflammatory reaction in response to trauma from surgery
    - reaction to blood products received during surgery
    - malignant hyperthermia
  - POD #1-2 (acute):
    - atelectasis (most common cause of fever on POD #1)
    - early wound infection (especially Clostridium, Group A Streptococcus – feel for crepitus and look for “dishwater” drainage)
    - aspiration pneumonitis
    - other: Addisonian crisis, thyroid storm, transfusion reaction
  - POD #3-7 (subacute): infections more likely
    - UTI, surgical site infection, IV site/line infection, septic thrombophlebitis, leakage at bowel anastomosis (tachycardia, hypotension, oliguria, abdominal pain)
  - POD #8+ (delayed):
    - intra-abdominal abscess, DVT/PE (can be anytime post-op, most commonly POD #8-10), drug fever
    - other: cholecystitis, peri-rectal abscess, URTI, infected seroma/biloma/hematoma, parotitis, C. difficile colitis, endocarditis

Treatment

- treat primary cause
- antipyrexia (e.g. acetaminophen)

wound/incisional complications

wound care

- can shower POD #2-3 after epithelialization of wound
- dressings can be removed POD #2 and left uncovered if dry
- examine wound if wet dressing, signs of infection (fever, tachycardia, pain)
- skin sutures and staples can be removed POD #7-10:
  - exceptions: incision crosses crease (groin), closed under tension, in extremities (hand) or patient factors (elderly, corticosteroid use, immunosuppressed) removed POD #14, earlier if signs of infection
- negative pressure dressings consist of foam and suction, promote granulation
  - ideal for large (grafted sites) or non-healing wounds (irradiated skin, ulcer)
DRAINS
- sometimes placed intra-operatively to prevent fluid accumulation (blood, pus, serum, bile, urine)
- can be used to assess quantity of third space fluid accumulation post-operatively
- potential route of infection, bring out through separate incision (vs. operative wound) to decrease risk of wound infection and remove as soon as possible
- types of drains
  - open (Penrose), higher risk of infection
  - closed (Jackson-Pratt, hemovac) connected to suction
  - pump (Davol) suction with airflow system to prevent obstruction
- monitor drain outputs daily
- drains should be removed once drainage is minimal (usually less than 30-50 cc/24 h)
- evidence does not support routine post-operative drainage of abdominal cavity

SURGICAL SITE INFECTION

Etiology
- S. aureus, E. coli, Enterococcus, Streptococcus spp., Clostridium spp.

Risk Factors
- type of procedure:
  - clean (elective, not emergent, not traumatic, no acute inflammation, resp/GI/biliary/GU tracts not entered): <1.5%
  - clean-contaminated (elective entering of resp/GI/biliary/GU tracts): <3%
  - contaminated (nonpurulent inflammation, gross spillage from GI, entry into biliary or GU tracts with infected bile/urine, penetrating trauma <4 h old): 5%
  - dirty (purulent inflammation, pre-op perforation of resp/GI/biliary/GU tracts, penetrating trauma >4 h old): ~33-50%
  - increased risk with procedures >2 h long, use of drains
- patient characteristics:
  - age, DM, steroids, immunosuppression, obesity, burn, malnutrition, patient with other infections, traumatic wound, radiation, chemotherapy
- other factors:
  - prolonged preoperative hospitalization, reduced blood flow, break in sterile technique, multiple antibiotics, hematoma, seroma, foreign bodies (drains, sutures, grafts), skin preparation, hypoxemia, hypothermia

Clinical Presentation
- typically fever POD #3-6 (Streptococcus and Clostridium can present in 24 h)
- pain, blanchable wound erythema, induration, frank pus or purulosanguinous discharge, warmth
- complications: fistula, sinus tracts, sepsis, abscess, suppressed wound healing, superinfection, spreading infection to myonecrosis or fascial necrosis (necrotizing fasciitis), wound dehiscence, evisceration, hernia

Prophylaxis
- used to reduce the chance of surgical site infections
- pre-op antibiotics for most surgeries (cefazolin ± metronidazole or if β-lactam allergy, clindamycin ± gentamycin):
  - within 1 h pre-incision; can re-dose at 1-2 half lives (~q4-8h) in the OR
  - not required for low risk elective cholecystectomy, hemorrhoidectomy, fistulotomy, sphincterotomy for fissure
- generally no need to continue prophylactic antibiotics postoperatively, reserve post-operative antibiotics for treatment of suspected or documented intra-abdominal infection
- normothermia (maintain patient temperature 36-38°C during OR)
- hyperoxygenation (consider FiO₂ of 80% in OR)
- chlorhexidine-alcohol wash of surgical site
- hair removal should not be performed unless necessary; if so, clipping superior to shaving
- consider delayed primary closure of incision for contaminated wounds

Treatment
- examination of the wound: inspect, compress adjacent areas, swab drainage for C&S and Gram stain
- re-open affected part of incision, pack, heal by secondary intention
- antibiotics and débridement of erythema only if cellulitis or immunodeficiency
- debride necrotic and non-viable tissue
WOUND HEMORRHAGE/HEMATOMA
• secondary to inadequate surgical control of hemostasis

Risk Factors
• anticoagulant therapy, coagulopathies, thrombocytopenia, DIC, severe liver disease, myeloproliferative disorders, severe arterial hypertension, severe cough
• more common with transverse incisions through muscle

Clinical Features
• pain, swelling, discolouration of wound edges, leakage
• rapidly expanding neck hematoma can compromise airway and is a surgical emergency

Treatment
• pressure dressing
• open drainage ± wound packing (large hematoma only)
• if significant bleeding, may need to re-operate to find source (often do not find a discrete vessel)

SEROMA
• fluid collection other than pus or blood
• secondary to transection of lymph vessels
• delays healing
• increased infection risk

Treatment
• pressure dressing ± needle drainage
• if significant may need to re-operate

WOUND DEHISCENCE
• disruption of fascial layer, abdominal contents contained by skin only
• 95% caused by intact suture tearing through fascia

Clinical Features
• typically POD #1-3, most common presentation sign is serosanguinous drainage from wound, ± evisceration (disruption of all abdominal layers and extrusion of abdominal contents – mortality of 15%)
• palpation of wound edge: should normally feel a “healing ridge” from abdominal wall closure (raised area of tissue under incision)

Risk Factors
• local: technical failure of closure, increased intra-abdominal pressure (e.g. COPD, ileus, bowel obstruction), hematoma, infection, poor blood supply, radiation, patient not fully paralyzed while closing
• systemic: smoking, malnutrition (hypalbuminemia, vitamin C deficiency), connective tissue diseases, immunosuppression, pulmonary disease, ascites, poor nutrition, steroids, chemotherapy, obesity, other (e.g. age, sepsis, uremia)
• diabetes mellitus alone is not a risk factor

Treatment
• place moist dressing over wound with binder around abdomen and transfer to OR
• may consider conservative management with debridement of facial and/or skin margins
• evisceration is a surgical emergency: take patient for operative closure, use slowly absorbable suture ± retention sutures

URINARY RETENTION
• may occur after any operation with general anesthesia or spinal anesthesia
• more likely in older males with history of benign prostatic hyperplasia, patients on anticholinergics

Clinical Presentation
• abdominal discomfort, palpable bladder, overflow incontinence, post-void residual urine volume >100 mL

Treatment
• Foley catheter to rest bladder, then trial of voiding
OLIGURIA/ANURIA (see Nephrology, NP33)

**Etiology**
- pre-renal vs. renal vs. post-renal:
  - most common post-op cause is pre-renal ± ischemic ATN
  - external fluid loss: hemorrhage, dehydration, diarrhea
  - internal fluid loss: third-spacing due to bowel obstruction, pancreatitis

**Clinical Presentation**
- urine output <0.5 cc/kg/h, increasing Cr, increasing BUN

**Treatment**
- according to underlying cause; fluid deficit is treated with crystalloid (NS or RL)

---

### Postoperative Dyspnea

- see Respiratory Complications below and Cardiac Complications, GS11

**Etiology**
- respiratory: atelectasis, pneumonia, pulmonary embolus (PE), acute respiratory distress syndrome (ARDS), asthma, pleural effusion
- cardiac: MI, arrhythmia, CHF
- inadequate pain control

---

### Respiratory Complications

#### ATELECTASIS
- comprises 90% of post-op pulmonary complications

**Clinical Features**
- low-grade fever on POD #1, tachycardia, crackles, decreased breath sounds, bronchial breathing, tachypnea

**Risk Factors**
- COPD, smoking, obesity, elderly persons
- upper abdominal/thoracic surgery, oversedation, significant post-op pain, poor inspiratory effort

**Treatment**
- pre-operative prophylaxis
  - smoking cessation (best if >8 wk pre-op)
- postoperative prophylaxis
  - incentive spirometry, deep breathing exercise, chest physiotherapy, intermittent positive-pressure breathing
  - selective nasogastric tube decompression after abdominal surgery
  - short-acting neuromuscular blocking agents
  - minimize use of respiratory depressive drug, good pain control, early ambulation

---

#### PNEUMONIA/PNEUMONITIS
- may be secondary to aspiration of gastric contents during anesthetic induction or extubation, causing a chemical pneumonitis

**Risk Factors**
- aspiration: general anesthetic, decreased LOC, GERD, full stomach, bowel/gastric outlet obstruction + non-functioning NG tube, pregnancy, seizure disorder
- non-aspiration: atelectasis, immobility, pre-existing respiratory disease

**Clinical Features**
- productive cough, fever
- tachycardia, cyanosis, respiratory failure, decreased LOC
- CXR: pulmonary infiltrate

**Treatment**
- prophylaxis: see atelectasis prophylaxis, pre-op NPO/NG tube, rapid sequence anesthetic induction
- immediate removal of debris and fluid from airway
- consider endotracheal intubation and flexible bronchoscopic aspiration
- IV antibiotics to cover oral nosocomial aerobes and anaerobes (e.g. ceftriaxone, metronidazole)
PULMONARY EMBOLUS (see Respirology, R17)

Clinical Features
- unilateral leg swelling and pain (DVT as a source of PE), sudden onset SOB, tachycardia, fever
- most commonly POD #8-10, but can occur anytime post-op

Treatment
- IV heparin, long term warfarin (INR = 2-3) for 3 mo
- Greenfield (IVC) filter if contraindications to anticoagulation
- prophylaxis: subcutaneous heparin (3000 units bid) or LMWH, compression stockings (T.E.D. Hose)

PULMONARY EDEMA

Etiology
- cardiogenic vs. noncardiogenic
- circulatory overload: excess volume replacement, LV failure, shift of fluid from peripheral to pulmonary vascular bed, negative airway pressure, alveolar injury due to toxins (e.g. ARDS)
- more common with pre-existing cardiac disease
- negative pressure pulmonary edema due to inspiratory efforts against a closed glottis upon awakening from general anaesthesia

Clinical Features
- shortness of breath, crackles at lung bases, CXR abnormal

Treatment (LMNOP)
- L
  - Lasix
- M
  - Morphine (decreases symptoms of dyspnea, venodilator and afterload reduction)
- N
  - Nitrates (venodilator)
- O
  - Oxygen + non-invasive ventilation
- P
  - Position (sit patient up)

RESPIRATORY FAILURE

Clinical Features
- dyspnea, cyanosis, evidence of obstructive lung disease
- earliest manifestations – tachypnea and hypoxemia (RR >25, pO\textsubscript{2} <60)
- pulmonary edema, unexplained decrease in SaO\textsubscript{2}

Treatment
- ABCs, O\textsubscript{2}, ± intubation
- bronchodilators, diuretics to treat CHF
- adequate blood pressure to maintain pulmonary perfusion
- if these measures fail to keep PaO\textsubscript{2} >60, consider acute respiratory distress syndrome (ARDS)

Cardiac Complications

- abnormal ECGs common in post-op period (compare to pre-op ECG)
- common arrhythmias: supraventricular tachycardia (SVT), atrial fibrillation (secondary to fluid overload, PE, MI)

MYOCARDIAL INFARCTION (MI)

- see Cardiology and Cardiovascular Surgery, C24
- surgery increases risk of MI
- incidence:
  - 0.5% in previously asymptomatic men >50 yr old
  - 40-fold increase in men >50 yr old with previous MI

Risk Factors
- pre-op hypertension, CHF
- previous MI (highest risk ≤6 mo, but risk never returns to baseline)
- increased age
- intra-operative hypotension
- operations >3 h
- angina

Clinical Features
- majority of cases on day of operation or POD #3-4 (shifting of third space fluid back into intravascular compartment)
- often silent without chest pain, may only present with new-onset CHF (dyspnea), arrhythmias, hypotension
Intra-abdominal Abscess

Definition
- collection of pus walled-off from rest of peritoneal cavity by inflammatory adhesions and viscera

Etiology
- usually polymicrobial: Gram-negative bacteria, anaerobes
  - consider Gram-positives if coexisting cellulitis

Risk Factors
- emergency, contaminated OR
- GI surgery with anastomoses
- poor healing risk factors (DM, poor nutrition, etc.)
- may occur POD #3 after laparotomy when third space fluid re-distribution occurs

Clinical Features
- persistent spiking fever, dull pain, weight loss
- mass difficult to palpate
- peritoneal signs if abscess perforation and secondary peritonitis
- leukocytosis or leukopenia (immunocompromised, elderly)
- co-existing effusion (pleural effusion with subphrenic abscess)
- common sites: pelvis, Morrison's pouch (space between kidney and liver), subphrenic, paracolic gutters, lesser sac, peri-appendiceal, post-surgical anastomosis, diverticular, psoas

Investigations
- CBC, blood cultures x2
- CT ± water-soluble contrast
- DRE (pelvic abscess)

Treatment
- eradication (preferred), laparoscopy, open drainage
- subsequent antibiotic coverage, ciprofloxacin (Cipro®) + metronidazole (Flagyl®)

Paralytic Ileus
- see Bowel Obstruction, GS24

Delirium
- see Psychiatry, PS19 and Neurology, N17

Thoracic Surgery

Hiatus Hernia

![Types of hiatus hernia](image)

Figure 6. Types of hiatus hernia
SLIDING HIATUS HERNIA (Type I) (see Figure 6)
• herniation of both the stomach and the gastroesophageal (GE) junction into thorax
• 90% of esophageal hernias

Risk Factors
• age
• increased intra-abdominal pressure (e.g. obesity, pregnancy, coughing, heavy lifting)
• smoking

Clinical Features
• majority are asymptomatic
• larger hernias frequently associated with GERD due to decreased competence of GE junction

Complications
• most common complication is GERD
• other complications are rare and are related to reflux:
  • esophagitis (dysphagia, heartburn)
  • consequences of esophagitis (peptic stricture, Barrett’s esophagus, esophageal carcinoma)
  • extra-esophageal complications (pneumonitis/pneumonia, asthma, cough, laryngitis)

Investigations
• CXR, barium swallow, endoscopy, or esophageal manometry (technique for measuring LES pressure)
• 24-h esophageal pH monitoring to quantify reflux
• gastroscopy with biopsy to document type and extent of tissue damage and rule out esophagitis, Barrett’s esophagus and cancer

Treatment
• lifestyle modification:
  • stop smoking, weight loss, elevate head of bed, no meals <3 h prior to sleeping, smaller and more frequent meals, avoid alcohol, coffee, mint and fat
• medical:
  • antacid, H2-antagonist, proton pump inhibitor, prokinetic agent
• surgical (<15%):
  • if failure of medical therapy, esophageal stricture, severe nocturnal aspiration, Barrett’s esophagus
  • anti-reflux procedure (usually laparoscopic) e.g. Nissen fundoplication
    • fundus of stomach is wrapped around the lower esophagus and sutured in place
    • 90% success rate

PARAESOPHAGEAL HIATUS HERNIA (Type II) (see Figure 6)
• herniation of all or part of the stomach through the esophageal hiatus into the thorax with an undisplaced GE junction
• least common esophageal hernia (<10%)

Clinical Features
• usually asymptomatic due to normal GE junction
• pressure sensation in lower chest, dysphagia

Complications
• hemorrhage, incarceration, strangulation, obstruction, gastric stasis ulcer

Treatment
• surgery to prevent severe complications:
  • reduce hernia and excise hernia sac, repair defect at hiatus, and anti-reflux procedure (e.g. Nissen fundoplication)
  • may consider suturing stomach to anterior abdominal wall (gastropexy)
  • in very elderly patients at high surgical risk consider PEG (percutaneous endoscopic gastrostomy)

MIXED HIATUS HERNIA (Type III)
• combination of Types I and II

TYPE IV HERNIA
• herniation of other abdominal organs into thorax: colon, spleen, small bowel

Differential Diagnosis of Hiatus Hernia

<table>
<thead>
<tr>
<th>GI Causes</th>
<th>Non-GI Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholelithiasis</td>
<td>MI</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>Angina</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Achalasia</td>
<td>GERD</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Gastritis</td>
</tr>
<tr>
<td>GERD</td>
<td>MI</td>
</tr>
<tr>
<td>Gastritis</td>
<td>Angina</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Pancreatitis</td>
</tr>
</tbody>
</table>
Esophageal Perforation

Etiology
• iatrogenic (most common):
  ▪ endoscopic, dilatation, biopsy, intubation, operative, NG tube placement
• barogenic:
  ▪ trauma
  ▪ repeated, forceful vomiting (Boerhaave’s syndrome)
  ▪ other: convulsions, defecation, labour (rare)
• ingestion injury:
  ▪ foreign body, corrosive substance
  ▪ carcinoma

Clinical Features
• neck or chest pain
• fever, tachycardia, hypotension, dyspnea, respiratory compromise
• subcutaneous emphysema, pneumothorax, hematemesis

Investigations
• CXR: pneumothorax, pneumomediastinum, pleural effusion, subdiaphragmatic air
• CT chest: widened mediastinum, pneumomediastinum
• contrast swallow (water-soluble then thin barium): contrast extravasation

Treatment
• supportive if rupture is contained:
  ▪ NPO, vigorous fluid resuscitation, broad-spectrum antibiotics, possible percutaneous drainage
• surgical:
  ▪ <24 h
    ▪ primary closure of a healthy esophagus or resection of diseased esophagus
  ▪ >24 h or non-viable wound edges
    ▪ diversion and exclusion followed by delayed reconstruction (i.e. esophagostomy proximally, close esophagus distally, gastrostomy/jejunostomy for decompression/feeding)

Complications
• sepsis, abscess, fistula, empyema, mediastinitis, death
• post-op esophageal leak
• mortality 10-50% dependent on timing of diagnosis

Esophageal Carcinoma

Epidemiology
• M:F = 3:1
• onset 50-60 yr of age
• upper (20-33%), middle (33%), lower (33-50%)
• main types:
  ▪ most common worldwide: squamous cell carcinoma (SCC) in upper 2/3 of esophagus
  ▪ most common in western countries: adenocarcinoma in distal 1/3 of esophagus

Risk Factors
• geographic variation in incidence
• SCC:
  ▪ underlying esophageal disease such as strictures, diverticula, achalasia
  ▪ more common in patients from Asia
• adenocarcinoma:
  ▪ Barrett’s esophagus (most important), smoking, obesity (increased reflux), GERD

Clinical Features
• frequently asymptomatic: late presentation
• progressive dysphagia (mechanical): first solids then liquids
• odynophagia then constant pain
• constitutional symptoms
• regurgitation and aspiration (aspiration pneumonia)
• hematemesis, anemia
• tracheoesophageal or bronchoesophageal fistula
• direct, hematogenous or lymphatic spread:
  ▪ trachea (coughing), recurrent laryngeal nerves (hoarseness, vocal paralysis), aortic, liver, lung, bone, celiac and mediastinal nodes
Investigations
- barium swallow: shows narrowing – suggestive but not diagnostic
- esophagoscopy: biopsy and assess resectability
- endoscopic ultrasound (EUS):
  - visualize local disease
  - regional nodal involvement (most accurate way to stage the cancer)
- bronchoscopy ± thoracoscopy:
  - rule out airway invasion in tumours of the upper and mid esophagus
- CT chest/abdomen
- full metastatic workup (CXR, bone scan, CT-head/CAP, LTFs, etc.)

Treatment
- if present with distant metastatic disease
  - treat with systemic therapy and treat symptoms (esophageal stent)
- if locally advanced (locally invasive disease or nodal disease on CT or EUS):
  - multimodal therapy:
    - concurrent external beam radiation and chemotherapy (cisplatin and 5-FU)
    - possibility of curative esophagectomy after chemoradiation if disease responds well
    - if unable to tolerate multimodal therapy or if highly advanced disease, consider palliative resection, brachytherapy, or endoscopic dilatation/stenting/laser ablation for palliation
- if early stage (non-transmural and without evidence of nodal disease):
  - esophagectomy (transhiatal or trans-hiatal approach) and lymphadenectomy
  - anastomosis in chest or neck
  - stomach most often used for reconstruction; may also use colon
  - neoadjuvant chemotherapy and radiation are controversial
  - adjuvant chemotherapy ± radiation usually recommended for post-op node-positive disease

Prognosis
- prognosis usually poor because presentation is usually at advanced stage

OTHER DISORDERS
- esophageal varices (see Gastroenterology, G26)
- Mallory-Weiss tear (see Gastroenterology, G27)

Chest Wall

CONGENITAL ABNORMALITIES
- pectus excavatum, pectus carinatum, sternal fissures
- surgery for cosmesis, psychosocial factors, respiratory or cardiovascular insufficiency (uncommon)

THORACIC OUTLET SYNDROME
- impingement of subclavian vessels and brachial plexus nerve trunk

Etiology
- congenital: cervical rib
- trauma
- degenerative: osteoporosis, arthritis

Clinical Features
- neurogenic: ulnar and median nerve motor and sensory deficit
- arterial: fatigue, weakness, coldness, ischemic pain, paresthesia
- venous: edema, venous distention, collateral formation, cyanosis

Treatment
- conservative (50-90%)
  - physiotherapy, posture and behaviour modification
- surgical: if conservative treatment fails, removal of first or cervical rib (if applicable)

TUMOURS
- benign: fibrous dysplasia, eosinophilic granuloma, osteochondroma
- malignant: fibrosarcoma, chondrosarcoma, osteogenic sarcoma, Ewing's sarcoma, myeloma
**Pleura, Lung, and Mediastinum**

- see *Respirology*, R20

**Tube Thoracostomy**

**Indications**
- to drain abnormal large-volume air or fluid collections in the pleural space
  - hemothorax, chylothorax, empyema
  - pneumothorax, if:
    - large or progressive
    - patient is on mechanical ventilation
    - bronchopleural fistula
    - tension pneumothorax
- to facilitate pleurodesis:
  - i.e. obliteration of the pleural space by instilling talc or doxycycline to cause fibrosis and adherence of parietal and visceral pleura
  - indicated for recurrent pleural effusions (often malignant)
- for long-term drainage of malignant effusions

**Complications**
- overall complications are rare (1-3%)
- malposition (most common complication), especially by inexperienced operators:
  - tubes may dissect along the external chest wall, or may be placed below the diaphragm
- bleeding (anticoagulation is a relative contraindication)
- local infection, empyema
- perforation of lung parenchyma
- risk of re-expansion pulmonary edema when large volumes of air or fluid are drawn off quickly (>1.0-1.5 L)

**Lung Transplantation**

**Conditions Leading to Transplantation**
- chronic obstructive pulmonary disease (COPD), emphysema due to α-1 antitrypsin deficiency
- cystic fibrosis (CF)
- idiopathic interstitial pneumonias: idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonitis
- idiopathic pulmonary arterial hypertension (IPAH), secondary pulmonary hypertension
- Eisenmenger’s syndrome
- sarcoidosis, lymphangioleiomyomatosis, pulmonary Langerhan’s cell histiocytosis

**Clinical Indications**
- transplantation should be considered for patients with advanced lung disease refractory to maximal medical or surgical therapy
- patients who are symptomatic during activities of daily living and limited expected survival over the next 2 yr

**Criteria for Transplantation**
- lung allocation score based on: 1) post-transplant survival measure, and 2) waiting list urgency measure
- transplant benefit = post-transplant survival (days) – waitlist survival (days)

**Contraindications**
- uncontrolled or untreatable pulmonary or extrapulmonary infection
- malignancy in the last 2 yr
- advanced cardiopulmonary disease
- significant chest wall/spinal deformity
- active cigarette smoking
- HIV infection, ongoing HBV or HCV infections

**Post-op Complications**
- primary graft dysfunction: main cause is ischemia-reperfusion injury, graded by PaO2/FiO2 ratio and CXR findings
- airway anastomotic complications (focal infection, bronchial necrosis and dehiscence, excess granulation tissue, tracheobronchomalacia, stenosis, fistula)
- chronic graft dysfunction: bronchiolitis obliterans syndrome
• infectious complications (bacterial, fungal, CMV, community-acquired respiratory viruses, mycobacteria)
• malignancy (non-melanoma skin cancer, post-transplant lymphoproliferative disease, colon, breast, Kaposis sarcoma, bladder)

Prognosis
• median survival for all adult recipients: 5.4 yr
• 1 yr survival: COPD > IPF > IPAH
• 10 yr survival: CF, α-1 antitrypsin deficiency > IPAH > COPD, IPF

Chronic Obstructive Pulmonary Disease

• see Respirology, R8

Treatment
• indications for surgical management:
  ▪ dyspnea despite maximal medical therapy and pulmonary rehabilitation
  ▪ CT showing hyperinflation and heterogeneously distributed emphysema predominant in the upper lung zone
  ▪ may be used as a bridging procedure to lung transplantation
• contraindications:
  ▪ age >75, cigarette smoking within the prior 6 mo, higher risk of surgical mortality
  ▪ homogeneously distributed emphysematous changes without areas of preserved lung tissue
  ▪ DLCO <20% of predicted, PaCO2 >60 mm Hg, PaO2 <45 mmHg
• surgical procedures:
  ▪ lung volume reduction surgery (LVRS): wedge excision of emphysematous tissue
  ▪ bilateral or unilateral, thoracotomy or VATS

Complications of Treatment
• air leak: may require reintubation and mechanical ventilation
• arrhythmias, pneumonia

Prognosis
• total mortality at 2 yr same as with maximal medical therapy, but better exercise capacity and quality of life with LVRS

Stomach and Duodenum

Peptic Ulcer Disease

GASTRIC ULCERS
• see Gastroenterology, G12

Indications for Surgery
• unresponsive to medical treatment (intractability):
  ▪ always operate if fails to heal completely, even if biopsy negative: could be primary gastric lymphoma or adenocarcinoma
  ▪ dysplasia or carcinoma:
    ▪ always biopsy ulcer for malignancy
  ▪ hemorrhage: 3x greater risk of bleeding compared to duodenal ulcers
  ▪ complications: obstruction, perforation, bleeding
  ▪ surgical treatment is increasingly rare due to H. pylori eradication and medical treatment

Procedures
• distal gastrectomy with ulcer excision: Billroth I or Billroth II (see Figure 9)
• vagotomy and pyloroplasty only if acid hypersecretion (rare)
• wedge resection if possible or biopsy with primary repair

DUODENAL ULCERS
• see Gastroenterology, Bleeding Peptic Ulcer, G13 and Peptic Ulcer Disease, G12
• most within 2 cm of pylorus (duodenal bulb)

Indications for Surgery
• hemorrhage, rebleed in hospital, perforation, gastric outlet obstruction
  ▪ decision to operate based on amount of blood loss (usually >8 units), rate of bleeding and hemodynamic stability
  ▪ intractable despite medical management (endoscopy)
Procedures
- Graham patch of perforated ulcer – plication of ulcer and omental patch
- oversewing of bleeding ulcer ± pyloroplasty
- pyloroplasty, gastroduodenostomy or gastrojejunostomy (improved drainage)
- antrectomy (eliminate hormonal stimulation from the antrum)
- gastric resection (decrease the number of parietal cells)
- vagotomy
  - rarely done now due to H. pylori eradication and proton pump inhibitors

Complications of Surgery
- retained antrum
- fistula (gastrocolic/gastrojejunal)
- dumping syndrome, postvagotomy diarrhea, afferent loop syndrome (see Complications of Gastric Surgery, GS20)

Table 5. Complications of Duodenal Ulceration

<table>
<thead>
<tr>
<th>Complication</th>
<th>Clinical Features</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perforated ulcer (typically on anterior surface)</td>
<td>Sudden onset of pain (possibly in RLQ due to track down right paracolic gutter) Acute abdomen: rigid, diffuse guarding Ileus Initial chemical peritonitis followed by bacterial peritonitis</td>
<td>Investigation: CXR – free air under diaphragm (70% of patients) Treatment: Oversew ulcer (plication) and omental (Graham) patch – most common treatment</td>
</tr>
<tr>
<td>Posterior penetration</td>
<td>Elevated amylase/lipase if penetration into pancreas Constant mid-epigastric pain burrowing into back, unrelated to meals</td>
<td>Resuscitation initially with crystalloids; blood transfusion if necessary Diagnostic and/or therapeutic endoscopy (laser, cautery or injection); if recurs, may have second scope Consider interventional radiology: angiography with embolization/coiling Surgery if severe or recurrent bleeding, hemodynamically unstable, or failure of endoscopy and IR: oversewing of ulcer, pyloroplasty</td>
</tr>
<tr>
<td>Hemorrhage (typically on posterior surface)</td>
<td>Gastroduodenal artery involvement</td>
<td>NG decompression and correction of hypochloremic, hypokalemic metabolic alkalosis Medical management initially: high dose PPI therapy Surgical resection if obstruction does not resolve: either Billroth I, pyloroplasty or gastrojejunostomy</td>
</tr>
<tr>
<td>Gastric outlet obstruction</td>
<td>Ulcer can lead to edema, fibrosis of pyloric channel, neoplasm Nausea and vomiting (undigested food, non-bilious), dilated stomach, crampy abdominal pain Succussion splash (splashing noise heard with stethoscope over the stomach when patient is shaken) Auscultate gas and fluid movement in obstructed organ</td>
<td>NG decompression and correction of hypochloremic, hypokalemic metabolic alkalosis Medical management initially: high dose PPI therapy Surgical resection if obstruction does not resolve: either Billroth I, pyloroplasty or gastrojejunostomy</td>
</tr>
</tbody>
</table>

Gastric Carcinoma

Epidemiology
- male:female = 3:2
- incidence of adenocarcinoma <10 (U.S.) vs. 60 (Japan, Korea) per 100,000 (incidence highest in Asia and Latin America)
- most common age group = 50-59 yr
- incidence has decreased by 2/3 in past 50 yr

Risk Factors
- H. pylori, causing chronic atrophic gastritis
- hereditary nonpolyposis colorectal cancer (HNPPC), hereditary diffuse gastric carcinoma (HDGC)
- smoking, alcohol, smoked food, nitrosamines
- pernicious anemia associated with achlorhydria and chronic atrophic gastritis
- gastric adenomatous polyps
- previous partial gastrectomy (>10 yr post-gastrectomy)
- hypertrophic gastropathy
- blood type A
Clinical Features
- clinical suspicion:
  - ulcer fails to heal
  - lesion on greater curvature of stomach or cardia
- asymptomatic, insidious or late onset of symptoms:
  - postprandial abdominal fullness, vague epigastric pain
  - anorexia, weight loss
  - burping, nausea, vomiting, dyspepsia, dysphagia
  - hepatomegaly, epigastric mass (25%)
  - hematemesis, fecal occult blood, melena, iron-deficiency anemia
- metastasis:
  - peritoneum, liver, lung, brain

Investigations
- OGD and biopsy; EUS to assess preoperative T-stage and N-stage
- chest/abdo/pelvis CT (for metastatic work-up see Table 7)

Table 6. TNM Classification System for Staging of Gastric Carcinoma (AJCC/IUCC 2010)

<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>NX</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>N0</td>
<td>No regional node metastasis</td>
</tr>
<tr>
<td>T3</td>
<td>N1</td>
<td>Metastasis in 1-2 regional nodes</td>
</tr>
<tr>
<td>T2</td>
<td>N2</td>
<td>Metastasis in 3-6 regional nodes</td>
</tr>
<tr>
<td>T3</td>
<td>N3a</td>
<td>Metastasis in 7-15 regional nodes</td>
</tr>
<tr>
<td>T4a</td>
<td>N3b</td>
<td>Metastasis in &gt;16 regional nodes</td>
</tr>
<tr>
<td>T4b</td>
<td></td>
<td>No distant metastasis</td>
</tr>
</tbody>
</table>

Staging and 5-year Survival Rates for Gastric Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1N0M0</td>
<td>71%</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0M0</td>
<td>57%</td>
</tr>
<tr>
<td>IIA</td>
<td>T3N0M0</td>
<td>45%</td>
</tr>
<tr>
<td>IIIA</td>
<td>T4aN0M0</td>
<td>33%</td>
</tr>
<tr>
<td>IIIIB</td>
<td>T4bN0M0</td>
<td>14%</td>
</tr>
<tr>
<td>IIC</td>
<td>T4bN2M0</td>
<td>9%</td>
</tr>
<tr>
<td>IV</td>
<td>TwNxM1</td>
<td>4%</td>
</tr>
</tbody>
</table>

Treatment
- adenocarcinoma:
  - proximal lesions:
    - total gastrectomy and esophagojejunostomy – Roux-en-Y (see Figure 9)
  - distal lesions:
    - distal gastrectomy: wide margins, en bloc removal of omentum and lymph nodes
    - palliation:
      - gastric resection to decrease bleeding and relieve obstruction, enables the patient to eat
      - radiation therapy
      - studies are showing larger role for chemotherapy
  - lymphoma:
    - H. pylori eradication, chemotherapy ± radiation, surgery in limited cases (perforation, bleeding, obstruction)

Gastrointestinal Stromal Tumour (GIST)

Epidemiology
- most common mesenchymal neoplasm of GI tract
- derived from interstitial cells of Cajal (cells associated with Auerbach’s plexus that have autonomous pacemaker function which coordinate peristalsis throughout the GI tract)
- 75-80% associated with tyrosine kinase (c-KIT) mutations
- most common in stomach (50%) and proximal small intestine (25%), but can occur anywhere along GI tract
- typically present with vague abdominal mass, feeling of abdominal fullness, or with secondary symptoms of bleeding and anemia
- often discovered incidentally on CT, laparotomy or endoscopy

Risk Factors
- Carney’s triad: GISTs, paraganglioma, and pulmonary chondroma
- Type IA neurofibromatosis
Investigations

- pre-operative biopsy: controversial, but useful for indeterminate lesions:
  - not recommended if index of suspicion for GIST is high
  - percutaneous biopsy is NOT recommended due to high friability and risk of peritoneal spread

Treatment

- surgical resection if >2 cm; follow with serial endoscopy if <2 cm and resect if growing or symptomatic
- localized GIST
  - surgical resection with preservation of intact pseudocapsule
  - lymphadenectomy NOT recommended, as GISTs rarely metastasize to lymph nodes
  - consider imatinib postop for high-risk GIST (large, >4 cm with significant mitotic activity)
- advanced disease (i.e. metastases to liver and/or peritoneal cavity)
  - chemotherapy with imatinib

Prognosis

- risk of metastatic potential depends on:
  - tumour size (worse if >10 cm)
  - mitotic activity (worse if >5 mitotic figures or 50/hpf)
  - degree of nuclear pleomorphism
  - location: with identical sizes, extra-gastric location has a higher risk of progression than GISTs in the stomach
- mets to liver, omentum, peritoneum; nodal mets rare

Bariatric Surgery

- weight reduction surgery for morbid obesity
- indications: BMI >40 or BMI >35 with related comorbidity (e.g. DM, CAD, sleep apnea, severe joint disease)
- requires multidisciplinary evaluation and follow-up

Surgical Options

- malabsorptive/restrictive:
  - laparoscopic Roux-en-Y gastric bypass (most common – see Figure 9)
  - staple off small gastric pouch (restrictive) with Roux-en-Y limb to pouch (malabsorptive) with dumping syndrome physiology
  - most effective, higher complication rates
- restrictive:
  - laparoscopic adjustable gastric banding
  - silicone band around fundus creates pouch, adjustable through port under skin
  - laparoscopic vertical banded gastroplasty
  - vertical staple small gastric pouch with placement of silastic ring band
- malabsorptive:
  - biliopancreatic diversion with duodenal switch
  - gastrectomy, enterointerostomy, duodenal division closure and duodenoenterostomy

Complications

- perioperative mortality ~1% (anastomotic leak with peritoneal signs, PE)
- obstruction at enterointerostomy (see Complications of Gastric Surgery, below)
- staple line dehiscence
- dumping syndrome
- cholelithiasis due to rapid weight loss (20-30%)
- band abscess (if long-term)

Complications of Gastric Surgery

- most resolve within 1 yr (see Figure 10)

Alkaline Reflux Gastritis (see Figure 10A)
- duodenal contents (bilious) reflux into stomach causing gastritis ± esophagitis
- treatment:
  - medical: H2-blocker, metoclopramide, cholestyramine (bile acid sequestrant)
  - surgical: conversion of Billroth I or II to Roux-en-Y
Afferent Loop Syndrome (see Figure 10B)
- accumulation of bile and pancreatic secretions causes intermittent mechanical obstruction and distention of afferent limb
- clinical features:
  - early postprandial distention, RUQ pain, nausea, bilious vomiting, anemia
  - treatment: surgery (conversion to Roux-en-Y increases afferent loop drainage)

Dumping Syndrome (see Figure 10C)
- early – 15 min post-prandial:
  - etiology:
    - hyperosmotic chyme released into small bowel (fluid accumulation and jejunal distention)
  - clinical features:
    - post-prandial symptoms
    - epigastric fullness or pain, emesis, nausea, diarrhea, palpitations, dizziness, tachycardia, diaphoresis
  - treatment:
    - small multiple low carbohydrate, low fat and high protein meals and avoidance of liquids with meals
    - last resort is interposition of antiperistaltic jejunal loop between stomach and small bowel to delay gastric emptying
- late – 3 h post-prandial:
  - etiology: large glucose load leads to large insulin release and hypoglycemia
  - treatment: small snack 2 h after meals

Blind-Loop Syndrome (see Figure 10D)
- bacterial overgrowth of colonic Gram-negative bacteria in afferent limb
- clinical features:
  - anemia/weakness, diarrhea, malnutrition, abdominal pain and hypocalcemia
- treatment: broad-spectrum antibiotics, surgery (conversion to Billroth I)

Postvagotomy Diarrhea (see Figure 10E)
- up to 25%
- bile salts in colon inhibit water resorption
- treatment: medical (cholestyramine), surgical (reversed interposition jejunal segment)

Small Intestine

Tumours of Small Intestine

BENIGN TUMOURS
- 10x more common than malignant
- usually asymptomatic until large
- most common sites: terminal ileum, proximal jejunum
- polyps:
  - adenomas
  - hamartomas
  - familial adenomatous polyposis (FAP) (see Familial Colon Cancer Syndromes, GS33)
  - juvenile polyps
- other: leiomyomas, lipomas, hemangiomas

Table 7. Malignant Tumours of the Small Intestine

<table>
<thead>
<tr>
<th>Epidemiology</th>
<th>Adenocarcinoma</th>
<th>Carcinoid</th>
<th>Lymphoma</th>
<th>Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>Usually 50-70 yr old M&gt;F</td>
<td>Increased incidence 50-80 yr old</td>
<td>Highest incidence in 70s M&gt;F Usually non-Hodgkin’s lymphoma</td>
<td>Most common site of GI metastases in patients with metastatic melanoma</td>
</tr>
<tr>
<td>Carcinoid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk Factors
- FAP, history of colorectal cancer (CRC), HNPCC
- Crohn’s, celiac disease, autoimmune disease, immunosuppression, radiation therapy, nodular lymphoid hyperplasia
- Melanoma, breast, lung, ovary, colon, cervical cancer
Table 7. Malignant Tumours of the Small Intestine (continued)

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Adenocarcinoma</th>
<th>Carcinoid</th>
<th>Lymphoma</th>
<th>Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Features</td>
<td>Early metastasis to LNs 80% metastatic at time of operation Abdo pain (common)</td>
<td>Nausea, vomiting, anemia, GI bleeding, jaundice, weight loss (less common) Often slow-growing Usually asymptomatic, incidental finding Obstruction, bleeding, crampy abdominal pain, intussusception Carcinoid syndrome (&lt;10%): • Hot flashes, hypotension, diarrhea, bronchoconstriction, right heart failure • Requires liver involvement: lesion secretes serotonin, kinins and vasoactive peptides directly to systemic circulation (normally inactivated by liver)</td>
<td>Fatigue, weight loss, fever malabsorption, abdo pain, anorexia, vomiting, constipation, mass Rarely – perforation, obstruction, bleeding, intussusception</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>CT abdo/pelvis Endoscopy</td>
<td>Most found incidentally at surgery for obstruction or appendectomy Chest thorax/abdo/pelvis Consider small bowel enteroclysis to look for primary Elevated 5-HIAA (breakdown product of serotonin) in urine or increased 5-HT in blood Radiolabelled octreotide or MIBG scans to locate tumour</td>
<td>CT abdo/pelvis</td>
<td>CT abdo/pelvis</td>
</tr>
<tr>
<td>Treatment</td>
<td>Surgical resection ± chemotherapy</td>
<td>Surgical resection ± chemotherapy Carcinoid syndrome treated with steroids, histamine, octreotide Metastatic risk 2% if size &lt; 1 cm, 90% if &gt; 2 cm</td>
<td>Low grade: chemotherapy with cyclophosphamide High grade: surgical resection, radiation Palliative: somatostatin, doxorubicin</td>
<td>Palliation</td>
</tr>
<tr>
<td>Prognosis</td>
<td>5-yr survival 25% (if node positive)</td>
<td>5 yr survival 70%; 20% with liver metastases</td>
<td>5-yr survival 40%</td>
<td>Poor</td>
</tr>
<tr>
<td>Origin/Location</td>
<td>Usually in proximal small bowel, incidence decreases distally</td>
<td>Classified based on embryological origin (foregut, midgut, hindgut) Originate from gut enterochromaffin cell Appendix 46%, distal ileum 28%, rectum 17%</td>
<td>Usually distal ileum Proximal jejunum in patients with celiac disease</td>
<td>Hematogenous spread from breast, lung, kidney Direct extension from cervix, ovaries, colon</td>
</tr>
<tr>
<td>Staging System</td>
<td>TNM</td>
<td>TNM</td>
<td>Ann Arbor</td>
<td></td>
</tr>
</tbody>
</table>

Hernia

**Definition**
- fascial defect → protrusion of a viscus into an area in which it is not normally contained

**Epidemiology**
- M:F = 9:1
- lifetime risk of developing a hernia: males 20-25%, females 2%
- 50% are indirect inguinal hernia, 25% are direct inguinal hernia, 5% are femoral
- most common surgical disease of males

**Risk Factors**
- activities which increase intra-abdominal pressure:
  - obesity, chronic cough, pregnancy, constipation, straining on urination or defecation, ascites, heavy lifting
  - congenital abnormality (e.g. patent processus vaginalis)
  - previous hernia repair

**Clinical Features**
- mass of variable size
- tenderness worse at end of day, relieved with supine position or with reduction
- abdominal fullness, vomiting, constipation
- transmits palpable impulse with coughing or straining

**Investigations**
- physical examination usually sufficient
- ultrasound ± CT (CT required for obturator hernias, internal abdominal hernias and Spigelian femoral hernias in obese patients)
Classification
- complete: hernia sac and contents protrude through defect
- incomplete: partial protrusion through the defect
- internal hernia: sac herniating into or involving intra-abdominal structure
- external hernia: sac protrudes completely through abdominal wall
- strangulated hernia: vascular supply of protruded viscus is compromised (ischemia)
  - requires emergency repair
- incarcerated hernia: irreducible hernia, not necessarily strangulated
- Richter’s hernia: only part of bowel circumference (usually anti-mesenteric border) is incarcerated or strangulated so may not be obstructed
  - a strangulated Richter’s hernia may self-reduce and thus be overlooked, leaving a gangrenous segment at risk of perforation
- sliding hernia: part of wall of hernia formed by protruding viscus (usually cecum)

Anatomical Types
- groin (see Tables 8 and 9)
  - indirect and direct inguinal, femoral (see Figure 13)
  - pantoloan: combined direct and indirect hernias, peritoneum draped over inferior epigastric vessels
- epigastric: defect in linea alba above umbilicus
- incisional: ventral hernia at site of wound closure, may be secondary to wound infection
- other: Littre’s (involving Meckel’s), Amyand’s (containing appendix), lumbar, obturator, parastomal, umbilical, Spigelian (ventral hernia through linea semilunaris)

Complications
- incarceration: irreducible
- strangulation: irreducible with resulting ischemia
  - small, new hernias more likely to strangulate
  - femoral >> indirect inguinal > direct inguinal
- intense pain followed by tenderness
- intestinal obstruction, gangrenous bowel, sepsis
- surgical emergency
- DO NOT attempt to manually reduce hernia if septic or if contents of hernial sac gangrenous
  - will cause closed loop SBO – and EMERGENCY

Treatment
- surgical treatment (herniorrhaphy) is only to prevent strangulation and evisceration, for symptomatic relief, for cosmesis; if asymptomatic can delay surgery
- repair may be done open or laparoscopic and may use mesh for tension-free closure
- most repairs are now done using tension free techniques – a plug in the hernial defect and a patch over it or patch alone
- observation is acceptable for small asymptomatic inguinal hernias

Postoperative Complications
- recurrence (15-20%):
  - risk factors: recurrent hernia, age >50, smoking, BMI ≥25, poor pre-op functional status (ASA ≥3 – see Anesthesia, A3), associated medical conditions: type II DM, hyperlipidemia, immunosuppression, any comorbid conditions increasing intra-abdominal pressure
  - less common with mesh/”tension-free” repair
- scrotal hematoma (3%):
  - painful scrotal swelling from compromised venous return of testes
  - deep bleeding: may enter retroperitoneal space and not be initially apparent
  - difficulty voiding
- nerve entrapment:
  - ilioinguinal (causes numbness of inner thigh or lateral scrotum)
  - genital branch of genitofemoral (in spermatic cord)
- stenosis/occlusion of femoral vein:
  - acute leg swelling
- ischemic colitis

Anatomical Types
- Spermatic Cord
  - vas deferens, testicular artery/veins, genital branch of genitofemoral nerve, lymphatics, cremaster muscle, hernia sac

Inguinal canal walls = MALT x 2
- Roof 2M 2 muscles
- Ant. wall 2A 2 aponesineus
- Floor 2L 2 ligaments
- Post. wall 2T 2 tendons

Cooper’s Ligament, which runs on the pectineal line of the pubic bone, is often exploited in hernia repair.

Contents of Spermatic Cord
- vas deferens, testicular artery/veins, genital branch of genitofemoral nerve, lymphatics, cremaster muscle, hernia sac

Watchful Waiting vs. Repair of Inguinal Hernia in Minimally Symptomatic Men: A Randomized Clinical Trial
JAMA 2008;299:235-239

**Purpose:** To compare pain and the physical component score (PCS) of the Short Form-36 (SF-36) Version 2 survey at 2 yr in men with minimally symptomatic inguinal hernias treated with watchful waiting or surgical repair.

**Methods:** RCT of 720 men (n=364 watchful waiting, n=356 surgical repair) followed up for 2-4.5 yr. Watchful waiting patients were followed up at 6 mo and annually and watched for hernia symptoms; repair patients received standard open tension-free repair and were followed up at 3 and 6 mo and annually. The main outcome was pain and discomfort interfering with usual activities at 2 yr and change in PCS from baseline to 2 yr. Secondary outcomes were complications, patient-reported pain, functional status, activity levels, and satisfaction with care.

**Results:** Primary intention-to-treat outcomes were similar at 2 yr for watchful waiting vs. surgical repair: pain limiting activities (5.1% vs. 2.2%, respectively; P = .18 [convergent]; PCS improvement over baseline, 0.29 points vs. 0.13 points; P = .78). Twenty-three percent of patients assigned to watchful waiting crossed over to receive surgical repair (increase in hernia-related pain was the most common reason offered); 1% assigned to receive repair crossed over to watchful waiting. Self-reported pain in watchful-waiting patients crossing over improved after repair. Occurrence of postoperative hernia-related complications was similar in patients who received repair as assigned and in watchful-waiting patients who crossed over. One watchful-waiting patient (0.3%) experienced acute hernia incarceration without strangulation within 2 yr; a second had acute incarceration with bowel obstruction at 4 yr, with a frequency of 1.8/100 patient/yr inclusive of patients followed up for as long as 4.5 yr.

**Conclusion:**Watchful waiting is an acceptable option for men with minimally symptomatic inguinal hernias. Delaying surgical repair until symptoms increase is safe because acute hernia incarcerations occur rarely.
### Groin Hernias

#### Table 8. Groin Hernias

<table>
<thead>
<tr>
<th></th>
<th>Direct Inguinal</th>
<th>Indirect Inguinal</th>
<th>Femoral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>1% of all men</td>
<td>Most common hernia in men and women</td>
<td>Affects mostly females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males &gt; females</td>
<td></td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Acquired weakness of transversalis fascia</td>
<td>Congenital persistence of processus vaginalis in 20% of adults</td>
<td>Pregnancy – weakness of pelvic floor musculature</td>
</tr>
<tr>
<td></td>
<td>“Wear and tear”</td>
<td>Increased intra-abdominal pressure</td>
<td>Increased intra-abdominal pressure</td>
</tr>
<tr>
<td><strong>Anatomy</strong></td>
<td>Through Hesselbach’s triangle</td>
<td>Originates in deep inguinal ring</td>
<td>Into femoral canal, below inguinal ligament but may override it</td>
</tr>
<tr>
<td></td>
<td>Medial to inferior epigastric artery</td>
<td>Lateral to inferior epigastric artery</td>
<td>Medial to femoral vein within femoral canal</td>
</tr>
<tr>
<td></td>
<td>Usually does not descend into scrotal sac</td>
<td>Often descends into scrotal sac (or labia majora)</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Surgical repair</td>
<td>Surgical repair</td>
<td>Surgical repair</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>3-4% risk of recurrence</td>
<td>&lt;1% risk of recurrence</td>
<td></td>
</tr>
</tbody>
</table>

#### Bowel Obstruction

**Definition**
- partial or complete blockage of the bowel resulting in failure of intestinal contents to pass through lumen

**Pathogenesis**
- disruption of the normal flow of intestinal contents $\rightarrow$ proximal dilatation + distal decompression
- may take 12-24 h to decompress, therefore passage of feces and flatus may occur after the onset of obstruction
- bowel ischemia may occur if blood supply is strangulated or bowel wall inflammation leads to venous congestion
- bowel wall edema and disruption of normal bowel absorptive function $\rightarrow$ increased intraluminal fluid $\rightarrow$ transudative fluid loss into peritoneal cavity, electrolyte disturbances

**Differential Diagnosis**
- small bowel obstruction (SBO), large bowel obstruction (LBO), pseudo-obstruction

**Clinical Features**
- must differentiate between obstruction and ileus, and characterize obstruction as acute vs. chronic, partial vs. complete (constipation vs. obstipation), small vs. large bowel, strangulating vs. non-strangulating, and with vs. without perforation

#### Table 10. Bowel Obstruction vs. Paralytic Ileus

<table>
<thead>
<tr>
<th></th>
<th>SBO</th>
<th>LBO</th>
<th>Paralytic Ileus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nausea, Vomiting</strong></td>
<td>Early, may be bilious</td>
<td>Late, may be feculent</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Abdominal Pain</strong></td>
<td>Colicky</td>
<td>Colicky</td>
<td>Minimal or absent</td>
</tr>
<tr>
<td><strong>Abdominal Distention</strong></td>
<td>+ (prox SBO), + + (distal SBO)</td>
<td>+ +</td>
<td>+</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>± visible peristalsis</td>
<td>± visible peristalsis</td>
<td></td>
</tr>
<tr>
<td><strong>Bowel Sounds</strong></td>
<td>Normal, increased</td>
<td>Normal, increased (borborygmi)</td>
<td>Decreased, absent</td>
</tr>
<tr>
<td></td>
<td>Absent if secondary ileus</td>
<td>Absent if secondary ileus</td>
<td></td>
</tr>
<tr>
<td><strong>AXR Findings</strong></td>
<td>Air-fluid levels</td>
<td>Air-fluid levels</td>
<td>Air throughout small bowel and colon</td>
</tr>
<tr>
<td></td>
<td>“Ladder” pattern (plicae circularis)</td>
<td>“Picture frame” appearance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proximal distention (&gt;3 cm)</td>
<td>Proximal distention + distal decompression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ no colonic gas</td>
<td>No small bowel air if competent ileocecal valve</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coffee bean sign</td>
<td></td>
</tr>
</tbody>
</table>
Complications (of total obstruction)
• strangulating obstruction (10% of bowel obstructions) = surgical emergency:
  ▪ cramping pain turns to continuous ache, hematemesis, melena (if infarction)
  ▪ fever, leukocytosis, tachycardia
  ▪ peritoneal signs, early shock
  ▪ see Intestinal Ischemia, GS28
• other:
  ▪ perforation: secondary to ischemia and luminal distention
  ▪ septicemia
  ▪ hypovolemia (due to third spacing)

Investigations
• radiological:
  ▪ upright CXR or left lateral decubitus (LLD) to rule out free air, usually seen under the right hemidiaphragm
  ▪ abdominal x-ray (3 views) to determine SBO vs. LBO vs. ileus (see Table 10)
  ▪ if ischemic bowel look for: free air, pneumatosis, thickened bowel wall, air in portal vein, dilated small and large bowels, thickened or hose-like haustra (normally finger-like projections)
• other:
  ▪ most used: CT provides information on level of obstruction, severity, cause
    – important to r/o closed loop obstruction, especially in the elderly
  ▪ less used: upper GI series/small bowel series for SBO (if no cause apparent, i.e. no hernias, no previous surgeries)
  ▪ if suspect LBO, consider a rectal water-soluble (Gastrografin® for PO/PR; Hypaque® for IV) enema rather than barium enema (can thicken and cause complete obstruction)
  ▪ may consider ultrasound or MRI in pregnant patients
• laboratory:
  ▪ may be normal early in disease course
  ▪ BUN, creatinine, hematocrit (hemoconcentration) to assess degree of dehydration
  ▪ fluid, electrolyte abnormalities
  ▪ amylase elevated
  ▪ metabolic alkalosis due to frequent emesis
  ▪ if strangulation: leukocytosis with left shift, lactic acidosis, elevated LDH (late signs)

Treatment
• stabilize vitals, fluid and electrolyte resuscitation (with normal saline/Ringer’s first, then with added potassium after fluid deficits are corrected)
• NG tube to relieve vomiting, prevent aspiration and decompress small bowel by prevention of further distention by swallowed air
• Foley catheter to monitor in/outs

Small Bowel Obstruction (SBO)

Etiology

Table 11. Common Causes of SBO

<table>
<thead>
<tr>
<th>Intraluminal</th>
<th>Intramural</th>
<th>Extramural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intussusception Gallstones</td>
<td>Crohn’s Disease</td>
<td>Radiation stricture</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment
• consider whether complete or partial obstruction, ongoing or impending strangulation, location and cause:
  ▪ SBO with history of abdo/pelvic surgery → conservative management (likely to resolve) → surgery if no resolution in 48-72 h or complications
  ▪ complete SBO, strangulation → urgent surgery after stabilizing patient with fluid resuscitation
  ▪ SBO with no previous surgery and no evidence of carcinomatosis → operate
  ▪ trial of medical management may be indicated in Crohn’s, recurrent SBO, carcinomatosis
  ▪ NGT decompression, GI rest, serial abdominal exams
  ▪ special case: early postoperative SBO (within 30 d of abdominal surgery) – prolonged trial of conservative therapy may be appropriate, surgery is reserved for complications such as strangulation

Prognosis
• mortality: non-strangulating <1%, strangulating 8% (25% if >36 h), ischemic = up to 50%
Large Bowel Obstruction (LBO)

Etiology

Table 12. Common Causes of LBO

<table>
<thead>
<tr>
<th>Intraluminal</th>
<th>Intramural</th>
<th>Extramural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Adenocarcinoma</td>
<td>Volvulus</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Diverticulitis</td>
<td>Adhesions</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>IBD stricture</td>
<td></td>
</tr>
<tr>
<td>IBD stricture</td>
<td>Radiation stricture</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features (unique to LBO)

• open loop (10-20%) (safer):
  - incompetent ileocecal valve allows relief of colonic pressure as contents reflux into ileum, therefore clinical presentation similar to SBO

• closed loop (80-90%) (dangerous):
  - competent ileocecal valve, resulting in proximal and distal occlusions
  - massive colonic distention → increased pressure in cecum → bowel wall ischemia → necrosis → perforation

Treatment

• surgical correction of obstruction (usually requires resection + temporary diverting colostomy)
• volvulus requires sigmoidoscopic or endoscopic decompression followed by operative reduction if unsuccessful
  - if successful, consider sigmoid resection on same admission
• cecal volvulus can be a true volvulus or a cecal ‘bascul’ – both need surgical treatment

Prognosis

• overall mortality: 10%
• cecal perforation + feculent peritonitis: 20% mortality

Colonic Pseudo-Obstruction

• aka paralytic ileus of large bowel

Definition

• condition with symptoms of intestinal blockage without any physical signs of blockage

Differential Diagnosis

• acute: toxic megacolon, trauma, postoperative (especially post orthopedic procedures with prolonged immobilization), neurologic disease, retroperitoneal disease, medications (narcotics, psychiatric)
• chronic: neurologic disease (enteric, central, peripheral nervous system), scleroderma

Toxic Megacolon

Pathogenesis

• extension of inflammation into smooth muscle layer causing paralysis
• damage to myenteric plexus and electrolyte abnormalities are not consistently found

Etiology

• inflammatory bowel disease (ulcerative colitis > Crohn’s disease)
• infectious colitis: bacterial (C. difficile, Salmonella, Shigella, Campylobacter), viral (cytomegalovirus), parasitic (E. histolytica)
• volvulus, diverticulitis, ischemic colitis, obstructing colon cancer are rare causes

Clinical Features

• infectious colitis usually present for >1 wk before colonic dilatation
• improvement of diarrhea may portend onset of megacolon
• abdominal distention, tenderness, ± local/general peritoneal signs (suggest perforation)
• triggers: hypokalemia, constipating agents (opioids, antidepressants, loperamide, anticholinergics), barium enema, colonoscopy

In a patient with clinical LBO consider impending perforation when:
- Cecum ≥12 cm in diameter
- Tenderness present over cecum

Colon is MEGA and patient is TOXIC.
Diagnostic Criteria
• must have both colitis and systemic manifestations for diagnosis
• radiologic evidence of dilated colon
• three of: fever, HR >120, WBC >10.5, anemia
• one of: fluid and electrolyte disturbances, hypotension, altered LOC

Investigations
• CBC (leukocytosis with left shift, anemia from bloody diarrhea), electrolytes, elevated CRP, ESR
• metabolic alkalosis (volume contraction and hypokalemia) and hypoalbuminemia are late findings
• AXR: dilated colon >6 cm (right > transverse > left), loss of haustra
• CT: useful to assess underlying disease

Treatment
• NPO, NG tube, stop constipating agents, correct fluid and electrolyte abnormalities, transfusion
• serial AXRs
• broad-spectrum antibiotics (reduce sepsis, anticipate perforation)
• aggressive treatment of underlying disease (e.g. steroids in IBD, metronidazole for C. difficile)
• indications for surgery (50% improve on medical management):
  ▪ worsening or persisting toxicity or dilation after 48-72 h
  ▪ severe hemorrhage, perforation
  ▪ high lactate and WBC especially for C. difficile
• procedure: subtotal colectomy + end ileostomy (may be temporary, with second operation for re-anastomosis later)

Prognosis
• average 25-30% mortality

Paralytic Ileus

Pathogenesis
• temporary paralysis of the myenteric plexus

Associations
• postoperative, intra-abdominal sepsis, medications (opiates, anesthetics, psychotropics), electrolyte disturbances (Na⁺, K⁺, Ca²⁺), C. difficile, inactivity

Treatment
• NG decompression, NPO, fluid resuscitation, correct causative abnormalities (e.g. sepsis, medications, electrolytes), consider TPN for prolonged ileus
• post-op: gastric and small bowel motility returns by 24-48 h, colonic motility by 3-5 d
• current interest in novel therapies such as gum chewing and pharmacologic therapy (opioid antagonists)

Ogilvie’s Syndrome

• acute pseudo-obstruction
• distention of colon without mechanical obstruction in distal colon
• arises in bedridden patients with serious extraintestinal illness or trauma
• exact mechanism unknown, likely autonomic motor dysregulation → possibly sympathetic deprivation to colon, unopposed parasympathetic tone, and interruption of sacral parasympathetic tone to distal bowel
• first presents with abdominal distention (>90%) ± tenderness
• later symptoms mimic true obstruction

Associations
• most common: trauma, infection, cardiac (MI, CHF)
• disability (long term debilitation, chronic disease, bed-bound nursing home patients, paraplegia), drugs (narcotic use, laxative abuse, polypharmacy), other (recent orthopedic or neurosurgery, post-partum, electrolyte abnormalities including hypokalemia, retroperitoneal hematoma, diffuse carcinomatosis)

Investigations
• AXR: cecal dilatation – if diameter ≥12 cm, increased risk of perforation

Treatment
• treat underlying cause
• NPO, NG tube
• decompression: rectal tube, colonoscopy, neostigmine (cholinergic drug), surgical decompression (ostomy/resection) uncommon
• surgery (extremely rare): if perforation, ischemia or failure of conservative management

Prognosis
• most resolve with conservative management
Intestinal Ischemia

Etiology
• acute:
  ▪ arterio-occlusive mesenteric ischemia (AOMI)
  ▪ thrombotic, embolic, extrinsic compression (e.g. strangulating hernia)
  ▪ non-occlusive mesenteric ischemia (NOMI)
  ▪ mesenteric vasoconstriction secondary to systemic hypoperfusion (preserves supply to vital organs)
  ▪ mesenteric venous thrombosis (MVT)
  ▪ consider hypercoagulable state (i.e. rule out malignancy), DVT (prevents venous outflow)
• chronic: usually due to atherosclerotic disease – look for CVD risk factors

Clinical Features
• acute: severe abdominal pain out of proportion to physical findings, vomiting, bloody diarrhea, bloating, minimal peritoneal signs early in course, hypotension, shock, sepsis
• chronic: postprandial pain, fear of eating, weight loss
• common sites: superior mesenteric artery (SMA) supplied territory, “watershed” areas of colon – splenic flexure, left colon, sigmoid colon

Investigations
• laboratory: leukocytosis (non-specific), lactic acidosis (late finding)
  ▪ amylase, LDH, CK, ALP can be used to observe progress
  ▪ hypercoagulability workup if suspect venous thrombosis
• AXR: portal venous gas, intestinal dilatation, SMA or SMV thrombus, mesenteric/portal venous gas, pneumatosis
• CT angiography is the gold standard for acute arterial ischemia

Treatment
• fluid resuscitation, correct metabolic acidosis, NPO, NG decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, exploratory laparotomy
• prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• fluid resuscitation, correct metabolic acidosis, NPO, NG decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, exploratory laparotomy
• prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• fluid resuscitation, correct metabolic acidosis, NPO, NG decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, exploratory laparotomy
• prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• fluid resuscitation, correct metabolic acidosis, NPO, NG decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, exploratory laparotomy
• prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• fluid resuscitation, correct metabolic acidosis, NPO, NG decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, exploratory laparotomy
• prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• fluid resuscitation, correct metabolic acidosis, NPO, NG decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, exploratory laparotomy
• prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• fluid resuscitation, correct metabolic acidosis, NPO, NG decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, exploratory laparotomy
• prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• fluid resuscitation, correct metabolic acidosis, NPO, NG decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, exploratory laparotomy
• prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• fluid resuscitation, correct metabolic acidosis, NPO, NG decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, exploratory laparotomy
• prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• fluid resuscitation, correct metabolic acidosis, NPO, NG decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, exploratory laparotomy
• prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• fluid resuscitation, correct metabolic acidosis, NPO, NG decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, exploratory laparotomy
• prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• fluid resuscitation, correct metabolic acidosis, NPO, NG decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, exploratory laparotomy
• prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• fluid resuscitation, correct metabolic acidosis, NPO, NG decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
• angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, exploratory laparotomy
• prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis

Appendix

Appendicitis

Epidemiology
• 6% of population, M>F
• 80% between 5-35 yr of age

Pathogenesis
• luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess (walled off by omentum) or peritonitis
• etiology:
  ▪ children or young adult: hyperplasia of lymphoid follicles, initiated by infection
  ▪ adult: fibrosis/stricture, fecolith, obstructing neoplasm
  ▪ other causes: parasites, foreign body

Clinical Features
• most reliable feature is progression of signs and symptoms
• low grade fever (38°C), rises if perforation
• abdominal pain then anorexia, nausea and vomiting
• classic pattern: pain initially periumbilical; constant, dull, poorly localized, then well localized pain over McBurney’s point
• due to progression of disease from visceral irritation (causing referred pain from structures of the embryonic midgut, including the appendix) to irritation of parietal structures
• McBurney’s sign

Modified Alvarado Score for Acute Appendicitis
• 1 point per:
  ▪ Migratory right iliac fossa pain (1 point)
  ▪ Anorexia (1 point)
  ▪ Nausea/vomiting (1 point)
  ▪ Tenderness in right iliac fossa (2 points)
  ▪ Fever >37.5°C (1 point)
  ▪ Leukocytosis (2 points)
• 0-3 = low risk, discharge to return if no improvement
• 4-6 = moderate risk, admit, observe, repeat examinations
• Male 7-9 = appendectomy
• Female (not pregnant) 7-9 = diagnostic laparoscopy ± appendectomy

Laparoscopic vs. Open Appendectomy
• Wound infection less likely
• Intra-abdominal abscesses 2 times more likely
• Reduced pain on POD #1
• Reduced hospital stay by 1.1 d
• Sooner return to normal activity, work and sport
• Costs outside hospital are reduced

Laparoscopic Surgery
• Wound infection less likely
• Intra-abdominal abscesses 2 times more likely
• Reduced pain on POD #1
• Reduced hospital stay by 1.1 d
• Sooner return to normal activity, work and sport
• Costs outside hospital are reduced

Open Surgery
• Shorter duration of surgery
• Lower operation costs

Cochrane DB Syst Rev 2010;10:CD001546

Figure 14. Appendix anatomy
• signs:
  ▪ inferior appendix: McBurney’s sign (see GS28), Rovsing’s sign (palpation pressure to left abdomen causes McBurney’s point tenderness)
  ▪ retrocecal appendix: psoas sign (pain on flexion of hip against resistance or passive hyperelevation of hip)
  ▪ pelvic appendix: obturator sign (flexion then external or internal rotation about right hip causes pain)
• complications:
  ▪ perforation (especially if >24 h duration)
  ▪ abscess, phlegmon

Investigations
• laboratory:
  ▪ mild leukocytosis with left shift (may have normal WBC counts)
  ▪ higher leukocyte count with perforation
  ▪ β-hCG to rule out ectopic pregnancy
  ▪ urinalysis
• imaging:
  ▪ upright CXR, AXR: usually nonspecific – free air if perforated (rarely), calcified fecolith, loss of psoas shadow, RLQ ileus
  ▪ ultrasound: may visualize appendix, but also helps rule out gynecological causes – overall accuracy 90-94%, can rule in but CANNOT rule out appendicitis (if >6 mm, SENS/SPEC/NPV/PPV 98%)
  ▪ CT scan: thick wall, appendicolith, inflammatory changes – overall accuracy 94-100%, optimal investigation

Treatment
• hydrate, correct electrolyte abnormalities
• surgery (gold standard, 20% mortality with perforation especially in elderly) + antibiotic coverage
  ▪ if localized abscess (palpable mass or large phlegmon on imaging and often pain >4-5 d), consider radiologic drainage + antibiotics x 14 d ± interval appendectomy in 6 wk (controversial)
  ▪ appendectomy:
    ▪ laparoscopic vs. open (see sidebar)
    ▪ complications: spillage of bowel contents, pelvic abscess, enterocutaneous fistula
    ▪ perioperative antibiotics:
      ▪ cefazolin + metronidazole (no post-op antibiotic unless perforated)
      ▪ other choices: 2nd/3rd generation cephalosporin for aerobic gut organisms
    ▪ colonoscopy in the elderly to rule out other etiology (neoplasm)
• prophylactic antibiotics against postoperative infections after appendectomy.
  ▪ Various prophylactic antibiotic regimens are effective in preventing postoperative infection and abscess rates.
  ▪ Treatment with antibiotics decreased wound infection, intra abdominal abscess, length of hospital stay, and mortality.
  ▪ The main outcomes of interest were patients undergoing appendectomy for suspected appendicitis. The main outcomes of interest were wound infection, intra abdominal abscess, length of hospital stay, and mortality.
  ▪ Results: 45 studies (n = 9576) were included.
  ▪ Conclusion: Various prophylactic antibiotic regimens are effective in preventing postoperative complications after appendectomy.

Prognosis
• mortality rate: 0.08% (non-perforated), 0.5% (perforated appendicitis)

Tumours of the Appendix
CARCINOID TUMOURS (most common type)
• see Tumours of Small Intestines: Carcinoid section, GS21

ADENOCARCINOMA
• 50% present as acute appendicitis
• spreads rapidly to lymph nodes, ovaries, and peritoneal surfaces
• treatment: right hemicolectomy

OTHER
• malignant mucinous cystadenocarcinoma

Inflammatory Bowel Disease (IBD)
• see Gastroenterology, G19

Principles of Surgical Management
• can alleviate symptoms, address complications, improve quality of life
• conserve bowel: resect as little as possible to avoid short gut syndrome
• perioperative management:
  ▪ optimize medical status: may require TPN (especially if >7 d NPO) and bowel rest
  ▪ hold immunosuppressive therapy pre-op, provide pre-op stress dose of corticosteroid if patient had recent steroid therapy, taper steroids post-op
  ▪ DVT prophylaxis: heparin (IBD patients at increased risk of thromboembolic events)
Crohn’s Disease

- see Gastroenterology, G20

Treatment
- surgery is NOT curative, but over lifetime ~70% of Crohn's patients will have surgery
- indications for surgical management:
  - failure of medical management
  - SBO (due to stricturing/inflammation): indication in 50% of surgical cases
  - abscess, fistula (enterocolic, vesicular, vaginal, cutaneous abscess), quality of life, perforation, hemorrhage, chronic disability, failure to thrive (children), perianal disease
- surgical procedures:
  - resection and anastomosis/stoma if active or subacute inflammation, perforation, fistula
  - resection margin only has to be free of gross disease (microscopic disease irrelevant to prognosis)
  - stricturoplasty – widens lumen in chronically scarred bowel: relieves obstruction without resecting bowel (contraindicated in acute inflammation)

Complications of Treatment
- short gut syndrome (diarrhea, steatorrhea, malnutrition)
- fistulas
- gallstones (if terminal ileum resected, decreased bile salt resorption → increased cholesterol precipitation)
- kidney stones (loss of calcium in diarrhea → increased oxalate absorption and hyperoxaluria → stones)

Prognosis
- recurrence rate at 10 yr: ileocolic (25-50%), small bowel (50%), colonic (40-50%)
- re-operation at 5 yr: primary resection (20%), bypass (50%), stricturoplasty (10% at 1 yr)
- 80-85% of patients who need surgery lead normal lives
- mortality: 15% at 30 yr

Ulcerative Colitis

- see Gastroenterology, G22

Treatment
- indications for surgical management:
  - failure of medical management (including inability to taper steroids)
  - complications: hemorrhage, obstruction, perforation, toxic megacolon (emergency), failure to thrive (children)
  - reduce cancer risk (1-2% risk per year after 10 yr of disease)
- surgical procedures:
  - proctocolectomy and ileal pouch-anal anastomosis (IPAA) ± rectal mucosectomy (operation of choice)
  - proctocolectomy with permanent end ileostomy (if not a candidate for ileoanal procedures)
  - colectomy and IPAA ± rectal mucosectomy
  - in emergency: total colectomy and ileostomy with Hartmann closure of the rectum, rectal preservation

Complications of Treatment
- early: bowel obstruction, transient urinary dysfunction, dehydration (high stoma output), anastomotic leak
- late: stricture, anal fistula/abscess, pouchitis, poor anorectal function, reduced fertility

Prognosis
- mortality: 5% over 10 yr
- total proctocolectomy will completely eliminate risk of cancer
- perforation of the colon is the leading cause of death from ulcerative colitis
Diverticular Disease

Definitions
- diverticulum: abnormal sac-like protrusion from the wall of a hollow organ
- diverticulosis: presence of multiple diverticula
- diverticulitis: inflammation of diverticula
- true (congenital) diverticuli: contain all layers of colonic wall, often right-sided
- false (acquired) diverticuli: contain mucosa and submucosa, often left-sided

Diverticulosis

Epidemiology
- 5-50% of Western population, lower incidence in non-Western countries, M=F
- prevalence is age dependent: <5% by age 40, 30% by age 60, 65% by age 85
- 95% involve sigmoid colon (site of highest pressure)

Pathogenesis
- risk factors:
  - lifestyle: low-fibre diet (predispose to motility abnormalities and higher intraluminal pressure) inactivity, obesity
  - muscle wall weakness from aging and illness (e.g. Ehler-Danlos, Marfan’s)
  - high intraluminal pressures cause outpouching to occur at point of greatest weakness, most commonly where vasa recta penetrate the circular muscle layer, therefore increased risk of hemorrhage

Clinical Features
- uncomplicated diverticulosis: asymptomatic (70-80%)
- episodic abdominal pain (often LLQ), bloating, flatulence, constipation, diarrhea
- absence of fever/leukocytosis
- no physical exam findings or poorly localized LLQ tenderness
- complications:
  - diverticulitis (15-25%): 25% of which are complicated (i.e. abscess, obstruction, perforation, fistula)
  - bleeding (5-15%): PAINLESS rectal bleeding, 30-50% of massive lower GI bleeds
  - diverticular colitis (rare): diarrhea, hematochezia, tenesmus, abdominal pain

Treatment
- uncomplicated diverticulosis: high fibre, education
- diverticular bleed:
  - initially work up and treat as any lower GI bleed
  - if hemorrhage does not stop, resect involved region

Diverticulitis

Epidemiology
- 95% left-sided in patients of Western countries, 75% right-sided in Asian populations

Pathogenesis
- erosion of the wall by increased intraluminal pressure or inspissated food particles → inflammation and focal necrosis → micro or macroscopic perforation
- usually mild inflammation with perforation walled off by pericolic fat and mesentery; abscess, fistula or obstruction can ensue
- poor containment results in free perforation and peritonitis
Clinical Features
- depend on severity of inflammation and whether or not complications are present; hence ranges from asymptomatic to generalized peritonitis
- LLQ pain/tenderness (2/3 of patients) often for several days before admission
- constipation, diarrhea, nausea, vomiting, urinary symptoms (with adjacent inflammation)
- complications (25% of cases):
  - abscess: palpable tender abdominal mass
  - fistula: colovesical (most common), coloenteric, colovaginal, colocutaneous
  - colonic obstruction: due to scarring from repeated inflammation
  - perforation: generalized peritonitis (feculent vs. purulent)
    - recurrent attacks rarely lead to peritonitis
- low-grade fever, mild leukocytosis common,
- occult or gross blood in stool rarely coexist with acute diverticulitis

Investigations
- AXR, upright CXR:
  - localized diverticulitis (ileus, thickened wall, SBO, partial colonic obstruction)
  - free air may be seen in 30% with perforation and generalized peritonitis
- CT scan (test of choice): very useful for assessment of severity and prognosis
  - 97% sensitive, 99% specific
  - increased soft tissue density within pericolonic fat secondary to inflammation, diverticula secondary to inflammation, bowel wall thickening, soft tissue mass (pericolic fluid, abscesses), fistula
  - 10% of diverticulitis cannot be distinguished from carcinoma
- Hypaque® (water soluble) enema – safe (under low pressure):
  - saw-tooth pattern (colonic spasm)
  - may show site of perforation, abscess cavities or sinus tracts, fistulas
- elective evaluations: establish extent of disease and rule out other diagnoses (polyps, malignancy) after resolution of acute episode
  - colonoscopy or barium enema and flexible sigmoidoscopy

Treatment
- uncomplicated: conservative management
- outpatient: clear fluids only until improvement and antibiotics (e.g. ciprofloxacin and metronidazole) 7-10 d to cover gram negative rods and anaerobes (e.g. B. fragilis)
- hospitalize: if severe presentation, inability to tolerate oral intake, significant comorbidities, fail to improve outpatient management
- treat with NPO, IVF, IV antibiotics (e.g. IV ceftriaxone + metronidazole, ampicillin, gentamicin)
- indications for surgery:
  - unstable patient with peritonitis
  - Hinchey stage 3-4 (see Table 13)
  - after 1 attack if: (a) immunosuppressed, (b) abscess needing percutaneous drainage
  - consider after 2 or more attacks, recent trend is toward conservative management of recurrent mild/moderate attacks
  - complications: generalized peritonitis, free air, abscess, fistula, obstruction, hemorrhage, inability to rule out colon cancer on endoscopy, or failure of medical management
- surgical procedures:
  - for emergency or complex cases: Hartmann procedure: colon resection + colostomy and rectal stump → colostomy reversal in 3-6 mo (see Figure 16)
  - elective cases or minimal contamination of the abdominal cavity: consider colon resection + primary anastomosis

Prognosis
- mortality rates: 6% for purulent peritonitis, 35% for fecal peritonitis
- recurrence rates: 13-30% after first attack, 30-50% after second attack

<table>
<thead>
<tr>
<th>Hinchey Stage</th>
<th>Description</th>
<th>Acute treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phlegmon/small pericolic abscess</td>
<td>Medical</td>
</tr>
<tr>
<td>2</td>
<td>Large abscess/fistula</td>
<td>Abscess drainage, resection ± primary anastomosis</td>
</tr>
<tr>
<td>3</td>
<td>Purulent peritonitis (ruptured abscess)</td>
<td>Hartmann procedure</td>
</tr>
<tr>
<td>4</td>
<td>Feculent peritonitis</td>
<td>Hartmann procedure</td>
</tr>
</tbody>
</table>
**Colorectal Neoplasms**

**Colorectal Polyps**

**Definition**
- polyp: protuberance into the lumen of normally flat colonic mucosa
- sessile (flat) or pedunculated (on a stalk) (see Figure 17)

**Epidemiology**
- 30% of the population have polyps by age 50, 40% by age 60, 50% by age 70

**Clinical Features**
- 50% in the rectosigmoid region, 50% are multiple
- usually asymptomatic, do not typically bleed, tenesmus, intestinal obstruction, mucus
- usually detected during routine endoscopy or familial/high risk screening

**Pathology**
- non-neoplastic:
  - hyperplastic: most common non-neoplastic polyp
  - mucosal polyps: small <5 mm, no clinical significance
  - inflammatory pseudopolyps: associated with IBD, no malignant potential
  - submucosal polyps: lymphoid aggregates, lipomas, leiomyomas, carcinoids
- neoplastic:
  - hamartomas: juvenile polyps (large bowel), Peutz-Jegher syndrome (small bowel)
  - low malignant potential: most spontaneously regress or autoamputate
  - adenomas: premalignant, often carcinoma in situ:
    - some may contain invasive carcinoma (“malignant polyp” – 3-9%): invasion into muscularis
    - malignant potential: villous > tubulovillous > tubular (see Table 14)

**Table 14. Characteristics of Tubular vs. Villous Polyps**

<table>
<thead>
<tr>
<th>Type</th>
<th>Tubular</th>
<th>Villous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Common (60% to 80%)</td>
<td>Less common (10%)</td>
</tr>
<tr>
<td>Size</td>
<td>Small (&lt;2 cm)</td>
<td>Large (usually &gt;2 cm)</td>
</tr>
<tr>
<td>Attachment</td>
<td>Pedunculated</td>
<td>Sessile</td>
</tr>
<tr>
<td>Malignant Potential</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Distribution</td>
<td>Even</td>
<td>Left-sided predominance</td>
</tr>
</tbody>
</table>

**Investigations**
- colonoscopy is the gold standard for diagnosis and treatment of colonic polyps
- CT colonography: increasing in availability; patients still require bowel prep and will require colonoscopy if polyps are identified
- other: flexible sigmoidoscope if polyps are detected, proceed to colonoscopy for examination of entire bowel and biopsy

**Treatment**
- indications: symptoms, malignancy or risk of malignancy (i.e. adenomatous polyps)
- endoscopic removal of entire growth
- surgical resection for those invading into muscularis (high risk of malignancy) and those too large to remove endoscopically
- follow-up endoscopy 1 yr later, then every 3-5 yr

**Familial Colon Cancer Syndromes**

**FAMILIAL ADENOMATOUS POLYPOSIS (FAP)**

**Pathogenesis**
- autosomal dominant (AD) inheritance, mutation in adenomatous polyposis coli (APC) gene on chromosome 5q21

**Clinical Features**
- hundreds to thousands of colorectal adenomas usually by age 20 (by 40s in attenuated FAP)
- extracolonic manifestations:
  - carcinoma of small bowel (i.e. polyps in colon), bile duct, pancreas, stomach, thyroid, adrenal, small bowel
  - congenital hypertrophy of retinal pigment epithelium presents early in life in 2/3 of patients; 97% sensitivity
  - virtually 100% lifetime risk of colon cancer (because of number of polyps)
variants:
- Gardner’s syndrome: FAP + extraintestinal lesions (sebaceous cysts, osteomas, desmoid tumours)
- Turcot syndrome: FAP + CNS tumours (childhood cerebellar medulloblastoma)

Investigations
- genetic testing (80-95% sensitive, 99-100% specific) (see sidebar)
- if no polyposis found: annual flexible sigmoidoscopy from puberty to age 50, then routine screening
- if polyposis or APC gene mutation found: annual colonoscopy and consider surgery (see Figure 16); consider upper endoscopy to evaluate for periampullary tumours

Treatment
- surgery indicated by age 17-20
- total proctocolectomy with ileostomy or total colectomy with ileorectal anastomosis
- doxorubicin-based chemotherapy
- NSAIDs for intra-abdominal desmoids

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC) – LYNCH SYNDROME

Pathogenesis
- AD inheritance, mutation in a DNA mismatch repair gene (MSH2, MSH6, MLH1) resulting in microsatellite genomic instability and subsequent mutations
- microsatellite instability account for approximately 15% of all colorectal cancers

Clinical Features
- early age of onset, right > left colon, synchronous and metachronous lesions
- mean age of cancer presentation is 44 yr, lifetime risk 70-80% (M>F)
- HNPCC I: hereditary site-specific colon cancer
- HNPCC II: cancer family syndrome – high rates of extracolonic tumours (endometrial, ovarian, hepatobiliary, small bowel)

Diagnosis
- Amsterdam Criteria:
  - 3 or more relatives with verified Lynch syndrome associated cancers, and 1 must be 1st degree relative of the other 2
  - 2 or more generations involved
  - 1 case must be diagnosed before 50 yr old
  - FAP is excluded
- genetic testing (80% sensitive) – colonoscopy mandatory even if negative
  - refer for genetic screening individuals who fulfill EITHER the Amsterdam Criteria (as above) OR the revised Bethesda Criteria (see sidebar)
- colonoscopy (starting age 20) annually
- surveillance for extracolonic lesions

Treatment
- total colectomy and ileorectal anastomosis with annual proctoscopy

Colorectal Carcinoma (CRC)

Epidemiology
- 4th most common cancer (after lung, prostate and breast), 2nd most common cause of cancer death

Risk Factors
- most patients have no specific risk factors
- age >50 (dominant risk factor in sporadic cases), mean age is 70
- genetic: FAP, HNPCC, family history of CRC
- colonic conditions:
  - adenomatous polyps (especially if >1 cm, villous, multiple)
  - IBD (especially UC: risk is 1-2%/yr if UC >10 yr)
  - previous colorectal cancer (also gonadal or breast)
- diet (increased fat, red meat, decreased fibre) and smoking
- diabetes mellitus and acromegaly (insulin and IGF-1 are growth factors for colonic mucosal cells)

Pathogenesis
- adenoma-carcinoma sequence; rarely arise de novo

Staging for CRC
<table>
<thead>
<tr>
<th>Stage</th>
<th>Colon</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1,N0,M0</td>
<td>T1,N0,M0</td>
</tr>
<tr>
<td>II</td>
<td>T2,N0,M0</td>
<td>T2,N0,M0</td>
</tr>
<tr>
<td>III</td>
<td>T3,N+M0</td>
<td>T3,N+M0</td>
</tr>
<tr>
<td>IV</td>
<td>T4,N+M1</td>
<td>T4,N+M1</td>
</tr>
</tbody>
</table>

5-year Survival Rates for CRC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Colon</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>74%</td>
<td>74%</td>
</tr>
<tr>
<td>IIA</td>
<td>67%</td>
<td>64%</td>
</tr>
<tr>
<td>IIB</td>
<td>59%</td>
<td>52%</td>
</tr>
<tr>
<td>IIC</td>
<td>37%</td>
<td>32%</td>
</tr>
<tr>
<td>IIA</td>
<td>73%</td>
<td>74%</td>
</tr>
<tr>
<td>IIB</td>
<td>66%</td>
<td>45%</td>
</tr>
<tr>
<td>IIC</td>
<td>28%</td>
<td>33%</td>
</tr>
<tr>
<td>IV</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Clinical Features (see Table 15)
- often asymptomatic
- haemachorea/melena, abdominal pain, change in bowel habits
- others: weakness, anemia, weight loss, palpable mass, obstruction
- 20% patients have distant metastatic disease at time of presentation
- spread:
  - direct extension, lymphatic, hematogenous (liver most common, lung, bone, brain; tumour of distal rectum → IVC → lungs)
  - peritoneal seeding: ovari, Blumer’s shelf (pelvic cul-de-sac)

<table>
<thead>
<tr>
<th>Table 15. Clinical Presentation of CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Colon</td>
</tr>
<tr>
<td>Frequency</td>
</tr>
<tr>
<td>Pathology</td>
</tr>
<tr>
<td>Signs</td>
</tr>
</tbody>
</table>

Investigations
- colonoscopy (best), look for synchronous lesions (3-5% of patients); alternative: air contrast barium enema (“apple core” lesion) + sigmoidoscopy
- if a patient is FOBT +ve, or has microcytic anemia or has a change in bowel habits, do colonoscopy
- laboratory: CBC, urinalysis, liver enzymes, liver function test, carcinoembryonic antigen (CEA) (preoperative for baseline, >5 ng/mL have worse prognosis)

Pathology
- staging (see Table 16 and sidebar): chest, abdominal and pelvis CT; bone scan, CT head only if lesions suspected
- rectal cancer: pelvic MRI or endorectal ultrasound to determine T and N stage

Pathology
- signs
- weight loss, weakness, rarely
- exophytic lesions with occult bleeding
- annular, invasive lesions
- ulcerating
- pathologic
- 25% 35% 30%
- frequency
- T4
- T3
- T1
- T0
- primary tumour (T)
- regional lymph nodes (N)
- distant metastasis (M)

Treatment
- colon cancer
  - wide surgical resection of lesion and regional lymphatic drainage; usually colectomy with primary anastomosis
  - curative: wide resection of lesion (5 cm margins) with nodes and mesentery
  - palliative: if distant spread, local control for hemorrhage or obstruction
  - care is taken to not spread tumour by unnecessary palpation
  - cancer-bearing portion of colon is removed according to vascular distribution of segment
  - adjuvant chemotherapy (5-FU or oral capecitabine with oxaliplatin) can be considered for stage II or III

- rectal cancer
  - choice of operation depends on individual case. Types of operations (see Figure 18):
    - low anterior resection of rectum (LAR): curative procedure of choice if adequate distal margins; uses technique of total mesorectal excision
    - abdominoperineal resection of rectum (APR): if adequate distal margins cannot be obtained; involves the removal of distal sigmoid colon, rectum, and anus – permanent end colostomy required
    - local excision: for select T1 lesions only
    - palliative procedures: electrocoagulation or laser photocoagulation for unresectable cancers for symptom relief
    - adjuvant therapy:
      - combined neoadjuvant chemoradiation therapy followed by postoperative adjuvant chemotherapy for stage II and III

Follow-Up
- currently there are no data suggesting optimal follow-up
- combination of periodic CT chest/abdo/pelvis, CEA and colonoscopy is recommended
- CEA to monitor for initial response to treatment, and to assess for recurrence q3mo (not a screening test)
- intensive follow-up improves overall survival in low risk patients

Table 16. TNM Classification System for Staging of Colorectal Carcinoma (AJCC/IUCC 2010)

<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No regional node involvement</td>
<td>N0</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
<td>N1</td>
</tr>
<tr>
<td>T1</td>
<td>Invasion into submucosa</td>
<td>N2</td>
</tr>
<tr>
<td>T2</td>
<td>Invasion into muscularis propria</td>
<td>N2</td>
</tr>
<tr>
<td>T3</td>
<td>Invasion through muscularis propria and into serosa</td>
<td>N2</td>
</tr>
<tr>
<td>T4</td>
<td>Invasion into adjacent structures or organs</td>
<td>N2</td>
</tr>
</tbody>
</table>

Figure 18. APR vs LAR

Table 16. TNM Classification System for Staging of Colorectal Carcinoma (AJCC/IUCC 2010)

<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No primary tumour found</td>
<td>N0</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
<td>N1</td>
</tr>
<tr>
<td>T1</td>
<td>Invasion into submucosa</td>
<td>N2</td>
</tr>
<tr>
<td>T2</td>
<td>Invasion into muscularis propria</td>
<td>N2</td>
</tr>
<tr>
<td>T3</td>
<td>Invasion through muscularis propria and into serosa</td>
<td>N2</td>
</tr>
<tr>
<td>T4</td>
<td>Invasion into adjacent structures or organs</td>
<td>N2</td>
</tr>
</tbody>
</table>

Follow-Up
- currently there are no data suggesting optimal follow-up
- combination of periodic CT chest/abdo/pelvis, CEA and colonoscopy is recommended
- CEA to monitor for initial response to treatment, and to assess for recurrence q3mo (not a screening test)
- intensive follow-up improves overall survival in low risk patients

Table 16. TNM Classification System for Staging of Colorectal Carcinoma (AJCC/IUCC 2010)

<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No primary tumour found</td>
<td>N0</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
<td>N1</td>
</tr>
<tr>
<td>T1</td>
<td>Invasion into submucosa</td>
<td>N2</td>
</tr>
<tr>
<td>T2</td>
<td>Invasion into muscularis propria</td>
<td>N2</td>
</tr>
<tr>
<td>T3</td>
<td>Invasion through muscularis propria and into serosa</td>
<td>N2</td>
</tr>
<tr>
<td>T4</td>
<td>Invasion into adjacent structures or organs</td>
<td>N2</td>
</tr>
</tbody>
</table>
**Angiodysplasia**

**Definition**
- vascular anomaly: focal submucosal venous dilatation and tortuosity

**Clinical Features**
- most frequently in right colon of patients >60 yr old
- bleeding typically intermittent, rarely massive, not usually hypotensive (melena, anemia, guaiac positive stools)

**Investigations**
- colonoscopy: cherry red spots, branching pattern from central vessel
- angiography: early-filling vein, vascular tuft, delayed emptying vein; rarely active bleeding
- RBC technetium-99 scan
- barium enema is contraindicated (obscures other x-rays, i.e. angiogram)

**Treatment**
- none if asymptomatic
cautery, right hemicolectomy, embolization, vasopressin infusion, sclerotherapy, band ligation, laser, octreotide, and rarely segmental resection if other treatments fail

**Volvulus**

**Definition**
- rotation of segment of bowel about its mesenteric axis
- sigmoid (65%), cecum (30%), transverse colon (3%), splenic flexure (2%)
- 5-10% of large bowel obstruction; 25% of intestinal obstruction during pregnancy

**Risk Factors**
- age (50% of patients >70 yr: stretching/elongation of bowel with age is a predisposing factor)
- high fibre diet (can cause elongated/redundant colon), chronic constipation, laxative abuse, pregnancy, bedridden, institutionalization (less frequent evacuation of bowels)
- congenital hypermobile cecum

**Clinical Features**
- symptoms due to bowel obstruction (see GS24) or intestinal ischemia (see GS28)
colic abdominal pain, persistence of pain between spasms, abdominal distention, vomiting

**Investigations**
- AXR (classic findings): "omega", "bent inner-tube", "coffee-bean" signs
- barium/Gastrografin® enema: "ace of spades" (or "bird's beak") appearance due to funnel-like luminal tapering of lower segment towards volvulus
- sigmoidoscopy or colonoscopy as appropriate
- CT

**Treatment**
- initial supportive management(same as initial management for bowel obstruction (see GS24)
cecum:
  - nonsurgical:
    - may attempt colonoscopic detorsion and decompression
  - surgical:
    - right colectomy + ileotransverse colonic anastomosis
sigmoid:
  - nonsurgical:
    - decompression by flexible sigmoidoscopy and insertion of rectal tube past obstruction
    - subsequent elective surgery recommended (50-70% recurrence)
  - surgical: Hartmann procedure (if urgent)
    - indications: strangulation, perforation or unsuccessful endoscopic decompression
Fistula

Definition
- abnormal communication between two epithelialized surfaces (e.g. enterocutaneous, colovesical, aortoenteric, entero-enteric)

Etiology
- foreign object erosion (e.g. gallstone, graft)
- inflammatory states (e.g. infection, IBD (especially Crohn’s), diverticular disease)
- iatrogenic/surgery (e.g. postoperative anastomotic leak, radiation)
- congenital, trauma
- neoplastic

Investigations
- ultrasound, CT scan, fistulogram
- measure amount of drainage from fistula

Treatment
- decrease secretion: octreotide/somatostatin/omeprazole
- surgical intervention: dependent upon etiology (for non-closing fistulas); uncertainty of diagnosis

Stomas

Definition
- an opening of the GI tract onto the surface of the abdomen wall

Ileostomy
- usually positioned in RLQ; ileum is brought through rectus abdominus muscles
- indications: after proctocolectomy for ulcerative colitis, in some cases of Crohn’s disease or familial polyposis
- conventional ileostomy: discharges small quantities of liquid material continuously, appliance (plastic bag attached to a sheet of protective material) required at all times
- continent ileostomy: reservoir is constructed from distal ileum, emptied by inserting catheter into stoma several times a day; rarely used, has mostly been replaced by ileal pouch anal anastomosis

Colostomy
- indications: to decompress an obstructed colon, to protect a distal anastomosis after resection, or to evacuate stool after distal colon or rectum is removed
- colostomies can be done by making an opening in a loop of colon (loop colostomy) or by dividing the colon and bringing out one end (end colostomy)
- most common permanent colostomy is a sigmoid colostomy – expels stool once per day, no appliance required
- chronic paracolostomy hernia is a common complication

Complications (10%)
- obstruction: herniation, stenosis (skin and abdominal wall), adhesive bands, volvulus
- peri-ileostomy abscess and fistula
- skin irritation
- prolapse or retraction
- diarrhea (excessive output)

Figure 19. Ostoimes

Why Fistulae Stay Open
FRIENDO
- Foreign body
- Radiation
- Infection
- Epithelialization
- Neoplasim
- Distal obstruction (most common)
- Others: increased flow; steroids (may inhibit closure, usually will not maintain fistula)

Colostomy/Ileostomy
- Connection of proximal limb of colon or ileum to abdominal wall skin
- Mucous Fistula
- Connection of distal limb of colon to abdominal wall skin
- Ileal Conduit
- Connection of bowel to ureter proximally and abdominal wall distally to drain urine

Figure 20. End vs. loop colostomy

© Geoffrey Cheung 2010

© Jean Yi-Chun Lin 2014
**Anorectum**

## Hemorrhoids

### Etiology
- Vascular and connective tissue complexes form a plexus of dilated veins (cushion)
  - Internal: Superior hemorrhoidal veins, above dentate line, portal circulation
  - External: Inferior hemorrhoidal veins, below dentate line, systemic circulation

### Risk Factors
- Increased intra-abdominal pressure: chronic constipation, pregnancy, obesity, portal hypertension, heavy lifting

### Clinical Features and Treatment
- **Internal Hemorrhoids:**
  - Engorged vascular cushions usually at 3, 7, 11 o'clock positions (patient in lithotomy position)
  - Painless rectal bleeding, anemia, prolapse, mucus discharge, pruritus, burning pain, rectal fullness:
    - **1st degree:** bleed but do not prolapse through the anus
      - Treatment: high fiber/bulk diet, sitz baths, steroid cream, paresol (Anusol®), rubber band ligation, sclerotherapy, photocoagulation
    - **2nd degree:** bleed, prolapse with straining, spontaneous reduction
      - Treatment: same as 2nd degree, but may require closed hemorrhoidectomy
    - **3rd degree:** bleed, prolapse, requires manual reduction
      - Treatment: closed hemorrhoidectomy
    - **4th degree:** bleed, permanently prolapsed, cannot be manually reduced
      - Treatment: closed hemorrhoidectomy
- **External Hemorrhoids:**
  - Dilated venules usually mildly symptomatic
  - Pain after bowel movement, associated with poor hygiene
  - Medical treatment: dietary fiber, stool softeners, steroid cream (short course), paresol (Anusol®), avoid prolonged straining
  - Thrombosed hemorrhoids are very painful:
    - Resolve within 2 wk, may leave excess skin = perianal skin tag
    - Treatment: consider surgical decompression within first 48 h of thrombosis, otherwise medical treatment

### Table 17. Signs and Symptoms of Internal vs. External Hemorrhoids

<table>
<thead>
<tr>
<th>Internal Hemorrhoids</th>
<th>External Hemorrhoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painless bright red blood per rectum</td>
<td>Sudden severe perianal pain</td>
</tr>
<tr>
<td>Rectal fullness or discomfort</td>
<td>Perianal mass</td>
</tr>
<tr>
<td>Mucus discharge</td>
<td></td>
</tr>
</tbody>
</table>

## Anal Fissures

### Definition
- Tear of anal canal below dentate line (very sensitive squamous epithelium)
- 90% posterior midline, 10% anterior midline
- If off midline: consider other possible causes such as IBD, STIs, TB, leukemia or anal carcinoma
- Repetitive injury cycle after first tear:
  - Sphincter spasm occurs preventing edges from healing and leads to further tearing
  - Ischemia may ensue and contribute to chronicity

### Etiology
- Forceful dilation of anal canal: large, hard stools and irritant diarrheal stools
- Tightening of anal canal secondary to nervousness/pain leads to further tearing
- Others: habitual use of cathartics, childbirth

### Clinical Features
- Acute fissure:
  - Very painful bright red bleeding especially after bowel movement, sphincter spasm on limited DRE
  - Treatment is conservative: stool softeners, bulking agent, sitz baths (heals 90%)
- Chronic fissure (anal ulcer):
  - Triad: fissure, sentinel skin tags, hypertrophied papillae
• treatment:
  • stool softeners, bulking agents, sitz baths
  • topical nitroglycerin or nifedipine: increases local blood flow, promoting healing and relieves sphincter spasm
  • lateral internal anal sphincterotomy (most effective): objective is to relieve sphincter spasm → increases blood flow and promotes healing; but 5% chance of fecal incontinence therefore not commonly done
  • alternative treatment:
    • botulinum toxin: inhibits release of acetylcholine (ACh), reducing sphincter spasm

### Anorectal Abscess

**Definition**
- infection in one or more of the anal spaces
- usually bacterial infection of blocked anal gland at the dentate line
  - *E. coli, Proteus, Streptococci, Staphylococci, Bacteroides, anaerobes*

**Clinical Features**
- throbbing pain that may worsen with straining and ambulation
- abscess can spread vertically downward (perianal), vertically upward (supralevator) or horizontally (ischiorectal)
- tender perianal/rectal mass on exam

**Treatment**
- incision and drainage
  - curative in 50% of cases
  - 50% develop anorectal fistulas
  - may require antibiotics if diabetic, heart murmur or cellulitis

### Fistula-In-Ano

**Definition**
- anal fistula from rectum to perianal skin
- an inflammatory tract with internal os at dentate line, external os on skin

**Etiology**
- see *Fistula, GS37*
- same perirectal process as an anal abscess, therefore usually associated with an abscess
- other causes: post-op, trauma, anal fissure, malignancy, radiation proctitis

**Clinical Features**
- intermittent or constant purulent discharge from perianal opening
- pain
- palpable cord-like tract
**Pilonidal Disease**

**Definition**
- chronic recurring abscess or chronic draining sinus in sacrococcygeal area

**Epidemiology**
- occurs most frequently in young men age 15–40 yr; rare in >50 yr

**Etiology**
- obstruction of the hair follicles in this area → formation of cysts, sinuses or abscesses

**Clinical Features**
- asymptomatic until acutely infected, then pain/tenderness, purulent discharge, ininspissated hair

**Treatment**
- acute abscess:
  - I&D (often performed by primary care doctors)
  - wound packed open
  - 40% develop chronic pilonidal sinuses
- surgery:
  - indication: failure of healing after I&D, recurrent disease, complex disease
  - pilonidal cystotomy: excision of sinus tract and cyst; wound closed by secondary intention, primary closure with tissue flap, or marsupialization (cyst edge sewn to surrounding tissue to leave sinus tract open)

**Rectal Prolapse**

**Definition**
- protrusion of some or all of rectal mucosa through external anal sphincter

**Epidemiology**
- extremes of ages: <5 yr old and >5th decade
- 85% women

**Etiology**
- lengthened attachment of rectum secondary to constant straining
- 2 types:
  1. false/partial/mucosal: protrusion of mucosa only, radial furrows at junction with anal skin; most common type of rectal prolapse in childhood
  2. true/complete (most common); full thickness extrusion of rectal wall, concentric folds in:
     - first degree: prolapse includes mucocutaneous junction
     - second degree: without involvement of mucocutaneous junction
     - third degree (internal intussusception): prolapse is internal, concealed, or occult
Risk Factors
- gynecological surgery
- chronic neurologic/psychiatric disorders affecting motility

Clinical Features
- extrusion of mass with increased intra-abdominal pressure:
  - straining, coughing, laughing, Valsalva
- difficulty in bowel regulation:
  - tenesmus, constipation, fecal incontinence
- permanently extruded rectum with excoriation, ulceration and constant soiling
- may be associated with urinary incontinence or uterine prolapse

Treatment
- Type I:
  - conservative: gentle manual reduction of prolapsed area, especially in children
  - mucosectomy with excision of redundant mucosa, mostly in adults
- Type II:
  - conservative: reduce if possible
  - surgery: abdominal, perineal, transsacral approaches

Anal Neoplasms

ANAL CANAL

Squamous Cell Carcinoma (SCC) of Anal Canal (above dentate line)
- most common tumour of anal canal (75%)
- anus prone to human papilloma virus (HPV) infection, therefore at risk for anal squamous intraepithelial lesions (ASIL)
  - high grade squamous intraepithelial lesion (HSIL) and low grade squamous intraepithelial lesion (LSIL) terminology used
- clinical features: anal bleeding, pain, mass, ulceration, pruritus; 25% asymptomatic
- treatment: chemotherapy ± radiation ± surgery
- prognosis: 80% 5-yr survival

Malignant Melanoma of Anal Canal
- 3rd most common site for primary malignant melanoma after skin, eyes
- aggressive, distant metastases common at time of diagnosis
- treatment: wide excision or APR ± chemoradiation
- prognosis: <5% 5-yr survival

ANAL MARGIN
- clinical features and treatment as for skin tumours elsewhere
- squamous and basal cell carcinoma, Bowen's disease (SCC in situ) and Paget's disease

Liver

Figure 26. Anatomy of liver
Liver Cysts

SIMPLE CYSTS
- most common type of liver cyst, may have multiple simple cysts
- clinical features: usually asymptomatic, if large may present with pain or mass; diagnose with U/S
- treatment: generally not required for simple cysts unless very large
- complications: intracystic hemorrhage (may be confused with complex cysts)

POLYCYSTIC LIVER DISEASE
- progressive condition where cysts replace much of the liver
- 50% associated with polycystic kidney disease
- treatment: if symptomatic treat by partial liver resection or by creating drainage for cysts

CHOLEDOCHAL CYSTS
- congenital malformations of pancreaticobiliary tree; majority present before age 10 yr
- 5 types, most extreme form called Caroli’s disease (multiple cystic dilations in intrahepatic ducts)
- clinical features: recurrent abdominal pain, intermittent jaundice, RUQ mass, cholangitis, pancreatitis
- diagnosis: U/S, CT, transhepatic cholangiography, LFTs
- treatment:
  - high risk of malignancy, current treatment is complete excision of cysts
  - abnormal pancreaticobiliary junction is associated with increased risk of malignancy
  - liver transplant indicated if cyst involves intrahepatic bile ducts (Caroli’s disease)
- complications of choledochal cysts: biliary cirrhosis, portal hypertension, rupture, cholangiocarcinoma

HYDATID LIVER CYSTS (CYSTIC ECHINOCOCCOSIS)
- etiology:
  - infection with parasite Echinococcus granulosus commonly found in Southern Europe, Middle East, Australasia, South America
  - associated with exposure to dogs, sheep and cattle
- clinical features:
  - asymptomatic mass (most often) or chronic pain, hepatomegaly; if large may compress inferior vena cava
  - rupture can cause biliary colic, jaundice, cholangitis, pancreatitis, or anaphylactic reaction
- investigations:
  - detection of anti-Echinococcus Ab (IgG) using ELISA
  - U/S, CT: presence of mass, often calcified
  - needle biopsy
- treatment:
  - medical: albendazole (anti-helminthic) – cure up to 30%
  - surgical (risk of spillage into abdomen):
    - conservative: open endocystectomy or PAIR (Percutaneous Aspiration, Injection of protoscolicidal agent, Re-aspiration)
    - radical: partial hepatectomy or total pericystectomy

CYSTADENOMA (PREMALIGNANT)/CYSTADENOCARCINOMA
- clinical features:
  - appear as complex cysts on imaging: internal septae, papillary projections, irregular lining
- all complex, multiloculated cysts (except echinococcal) should be excised because of malignancy risk

Liver Abscesses

Etiology
- types:
  - pyogenic (bacterial): most common etiology; most often polymicrobial – E. coli, Klebsiella, Proteus, Strep. milleri
  - parasitic (amoebic): Entamoeba histolytica
  - fungal: Candida
- sources: direct spread from biliary tract infection, portal spread from GI infection, systemic infection (e.g. endocarditis)

Clinical Features
- fever, malaise, chills, anorexia, weight loss, abdominal pain, nausea
- RUQ tenderness, hepatomegaly, jaundice
Investigations
- leukocytosis, anemia, elevated liver enzymes, hemagglutination titres for *Entamoeba* antibodies
- U/S, CXR (right basal atelectasis/effusion), CT, cyst aspiration with C&S

Treatment
- treat underlying cause
- generally will treat initially with antibiotics alone and add surgical or percutaneous drainage and IV antibiotics for larger abscesses (initially ceftriaxone + metronidazole or piperacillin/tazobactam)

Prognosis
- overall mortality 15% – higher rate if delay in diagnosis, multiple abscesses, malnutrition

Neoplasms

**BENIGN LIVER NEOPLASMS**

**Hemangioma (cavernous)**
- pathogenesis: most common benign hepatic tumour; results from malformation of angioblastic fetal tissue
- risk factors: F:M = 3:1, steroid therapy, estrogen (exogenous, pregnancy)
- clinical features:
  - usually small and asymptomatic, larger tumours may produce pain or compress nearby structures
  - shock if ruptured (very rare), consumptive coagulopathy if giant (in children)
- investigations:
  - contrast CT (well-demarcated hypodense mass with peripheral enhancement and delayed venous emptying), U/S (homogenous hyperechoic mass), arteriography (rarely used; "cotton wool" appearance), RBC scan
  - biopsy may result in hemorrhage
- treatment:
  - usually none unless tumour bleeds or is symptomatic, then excision by lobectomy or enucleation

**Focal Nodular Hyperplasia**
- pathogenesis: unclear, may be regenerative response to hyperperfusion from anomalous arteries at centre of nodule
- risk factors: female, age 20-50
- clinical features: asymptomatic, rarely grows or bleeds, no malignant potential
- investigations: central stellate scar on CT scan; technetium-99 scan is helpful
- treatment: may be difficult to distinguish from adenoma/fibrolamellar HCC (malignant potential) → often resected

**Adenoma**
- definition: benign glandular epithelial tumour
- risk factors: female, age 20-50, estrogen (OCP, pregnancy)
- clinical features: asymptomatic, 25% present with RUQ pain or mass
- investigations: CT (well-demarcated masses, often heterogeneous, isodense on non-contrast CT, peripheral enhancement/isodense/hypodense on contrast CT), U/S, biopsy (tendency to bleed following biopsy)
- treatment:
  - stop anabolic steroids or OCP
  - excise, especially if large (>5 cm), due to risk of transformation to hepatocellular carcinoma and spontaneous rupture/hemorrhage
  - smaller lesions can be effectively treated with embolization

**MALIGNANT LIVER NEOPLASMS**

**Primary**
- usually hepatocellular carcinoma (HCC)/hepatoma
- others include angiosarcoma, hepatoblastoma, hemangioendothelioma
- epidemiology: 3rd leading cause of cancer death worldwide, 9th in United States; highest in Africa, China, Taiwan
- risk factors:
  - chronic liver inflammation: chronic hepatitis B (inherently oncogenic) and C, cirrhosis (especially macronodular), hemochromatosis, α1-anti-trypsin deficiency
  - medications: OCPs (3x increased risk), steroids
  - smoking, alcohol, Betel nuts
  - chemical carcinogens (aflatoxin, microcystin, vinyl chloride – associated with angiosarcoma)
- clinical features:
  - RUQ discomfort, right shoulder pain
  - jaundice, weakness, weight loss, ± fever (if central tumour necrosis)
  - hepatomegaly, bruist, hepatic friction rub

Secondary liver metastases are common in many cancers, with some studies showing a prevalence of 40-50% amongst patients with extrahepatic cancers. They commonly arise from breast, lung and colorectal cancers. For metastases secondary to colorectal cancer, surgical resection offers the greatest likelihood of cure.
Liver Transplantation

Table 18. Conditions Leading to Transplantation

<table>
<thead>
<tr>
<th>Parenchymal Disease</th>
<th>Cholestatic Disease</th>
<th>Inborn Errors</th>
<th>Tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis B or C*</td>
<td>Biliary atresia**</td>
<td>α1-antitrypsin deficiency</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>Primary biliary cirrhosis</td>
<td>Wilson’s disease</td>
<td></td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>Sclerosing cholangitis</td>
<td>Hemochromatosis</td>
<td></td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital hepatic fibrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis (CF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune Hepatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptogenic Cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilsons disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Leading cause in adults; **leading cause in children

Clinical Indications
- early referral for transplant should be considered for all patients with progressive liver disease not responsive to medical therapy, especially decompensated cirrhosis, unresectable primary liver cancers and fulminant hepatic failure
- end-stage liver disease with life expectancy <1 yr and if no other therapy is appropriate
- progressive jaundice, refractory ascites, spontaneous hepatic encephalopathy, recurrent sepsis, fulminant hepatic failure
- recurrent variceal hemorrhage, coagulopathy, severe fatigue

Criteria for Transplantation
- Model for End-Stage Liver Disease (MELD): considers probability of death within 3 mo if patient does not receive transplant; based on creatinine, bilirubin, INR; MELD scores from 6-40 used to prioritize liver allocation
- Child-Turcotte-Pugh Score: patient must have ≥7 points (Class B)

Contraindications
- active alcohol/substance abuse
- extrahepatic malignancy within 5 yr
- advanced cardiopulmonary disease

Liver Mass

**Differential Diagnosis of Metastatic Liver Mass**
- Some GU Cancers Produce Bumpy Lumps:
  - Stomach
  - Genitourinary cancers
  - Kidney, ovary, uterus
- Colon
- Pancreas
- Breast
- Lung

**Characteristics of Metastatic Liver Mass**
- Not poorly differentiated
- No systemic symptoms
- No extrahepatic or extrapulmonary metastases
- If the possibility of “curative” resection

**Staging Criteria for Hepatocellular Carcinoma**
- Milan Criteria
  - 1 tumour ≤5 cm
  - Up to 3 tumours each ≤3 cm
- UCSF Criteria
  - 1 tumour ≤5 cm
  - Up to 3 tumours each ≤4.5 cm, total diameter ≤8 cm
- Toronto Criteria
  - No tumour size of number restrictions
  - Not poorly differentiated

*Each criteria assumes no extrahepatic and no macrovascular invasion.

**Liver Mass**

- Liver metastases: GI (colorectal most common), lung, breast, pancreas, ovary, uterus, kidney, gallbladder
- Prognosis:
  - 5-yr survival: all patients – 5%; patients undergoing complete resection – 11-40%

**Clinical Indications**
- early referral for transplant should be considered for all patients with progressive liver disease not responsive to medical therapy, especially decompensated cirrhosis, unresectable primary liver cancers and fulminant hepatic failure
- end-stage liver disease with life expectancy <1 yr and if no other therapy is appropriate
- progressive jaundice, refractory ascites, spontaneous hepatic encephalopathy, recurrent sepsis, fulminant hepatic failure
- recurrent variceal hemorrhage, coagulopathy, severe fatigue

**Criteria for Transplantation**
- Model for End-Stage Liver Disease (MELD): considers probability of death within 3 mo if patient does not receive transplant; based on creatinine, bilirubin, INR; MELD scores from 6-40 used to prioritize liver allocation
- Child-Turcotte-Pugh Score: patient must have ≥7 points (Class B)

**Contraindications**
- active alcohol/substance abuse
- extrahepatic malignancy within 5 yr
- advanced cardiopulmonary disease

**Staging Criteria for Hepatocellular Carcinoma**

<table>
<thead>
<tr>
<th>Milan Criteria</th>
<th>UCSF Criteria</th>
<th>Toronto Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 tumour ≤5 cm</td>
<td>1 tumour ≤5 cm</td>
<td>No tumour size of number restrictions</td>
</tr>
<tr>
<td>Up to 3 tumours each ≤3 cm</td>
<td>Up to 3 tumours each ≤4.5 cm, total diameter ≤8 cm</td>
<td>Not poorly differentiated</td>
</tr>
</tbody>
</table>

**Child-Turcotte-Pugh Score (Prognosis of Chronic Liver Disease/Cirrhosis, Including Postoperatively)**

<table>
<thead>
<tr>
<th>Points</th>
<th>Class</th>
<th>One Year Survival</th>
<th>Two Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>A</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>7-9</td>
<td>B</td>
<td>81%</td>
<td>57%</td>
</tr>
<tr>
<td>10-11</td>
<td>C</td>
<td>43%</td>
<td>35%</td>
</tr>
</tbody>
</table>
Clinical Features
- asymptomatic (80%):
  - most do NOT require treatment
  - consider cholecystectomy if: increased risk of malignancy (choledochal cysts, Caroli’s disease, porcelain or calcified gallbladder), sickle cell disease, pediatric patient, bariatric surgery, diabetes, immunosuppression

cholelithiasis

Definition
- the formation of gallstones

Pathogenesis
- imbalance of cholesterol and its solubilizing agents (bile salts and lecithin)
- excessive hepatic cholesterol secretion → bile salts and lecithin are “overloaded” → supersaturated cholesterol can precipitate and form gallstones
- North America: cholesterol stones (80%), pigment stones (20%)

Risk Factors
- cholesterol stones:
  - obesity, age <50
  - estrogens: female, multiparity, OCPs
  - ethnicity: First Nations heritage (especially Pima Indians) > Caucasian > Black
  - terminal ileal resection or disease (e.g. Crohn’s disease)
  - impaired gallbladder emptying: starvation, TPN, DM
  - rapid weight loss: rapid cholesterol mobilization and biliary stasis
- pigment stones (contain calcium bilirubinate):
  - cirrhosis
  - chronic hemolysis
  - biliary stasis (strictures, dilation, biliary infection)
  - protective factors: statins, vitamin C, coffee

Post-op Complications
- primary non-function (graft failure): urgent re-transplantation is indicated
- acute and chronic rejection, ischemia-reperfusion injury
- vascular: hepatic artery or portal vein thrombosis, IVC obstruction
- biliary complications: fever, increasing bilirubin and ALP
- complications related to immunosuppression: hypertension, renal disease, diabetes, obesity, hyperlipidemia, osteoporosis, malignancy, neurologic complications, infection (leading cause of mortality following transplant)

Prognosis
- patient survival at 1 yr: 85%
- graft survival at 1 yr: >80%, at 5 yr: 60-70%

Biliary Tract

Cholelithiasis

Figure 27. Gallstone disease

1. Common hepatic duct
2. Cystic duct
3. Gallbladder
4. Common bile duct
5. Sphincter of Oddi
6. Ampulla of Vater
7. Pancreas
8. Pancreatic duct
9. Duodenum

© Merry Shiyu Wang 2012
• biliary colic (10-25%)
• cholecystitis
• cholelithiasis (8-15%)
• cholangitis
• gallstone pancreatitis (see Acute Pancreatitis, GS50)
• gallstone ileus

Investigations
• U/S – diagnostic procedure of choice:
  ▪ image for signs of inflammation, obstruction, localization of stones
• ERCP (endoscopic retrograde cholangiopancreatography):
  ▪ visualization of upper GI tract, ampullary region, biliary and pancreatic ducts
  ▪ method for treatment of CBD stones in periampullary region
  ▪ complications: traumatic pancreatitis (1-2%), pancreatic or biliary sepsis
• MRCP (magnetic resonance cholangiopancreatography):
  ▪ same information gained as ERCP but non-invasive
  ▪ cannot be used for therapeutic purposes
• PTC (percutaneous transhepatic cholangiography):
  ▪ injection of contrast via needle passed through hepatic parenchyma
  ▪ useful for proximal bile duct lesions or when ERCP fails or not available
  ▪ requires prophylactic antibiotics
  ▪ contraindications: coagulopathy, ascites, peri/intrahepatic sepsis, disease of right lower lung or pleura
  ▪ complications: bile peritonitis, chylothorax, pneumothorax, sepsis, hemobilia
• HIDA scan (hepatobiliary imino-diacetic acid scan):
  ▪ used less commonly
  ▪ radioisotope technetium-99 injected into a vein is excreted in high concentrations into bile, allowing visualization of the biliary tree
  ▪ does not visualize stones; diagnosis by seeing occluded cystic duct or CBD

Pathogenesis

Clinical Features
• steady, severe dull pain in epigastrium or RUQ for minutes to hours, crescendo-decrescendo pattern
• may present with chest pain
• frequently occurs at night or after fatty meal, not after fasting
• can radiate to right shoulder or scapula
• patients often restless
• no peritoneal findings, no systemic signs

Investigations
• normal blood work: CBC, electrolytes, LFTs, bilirubin, amylase
• U/S shows cholelithiasis, may show stone in cystic duct

Treatment
• analgesia, rehydration during colic episode
• elective cholecystectomy (95% success):
  ▪ complications: CBD injury (0.3-0.5%), hollow viscus injury, bile peritonitis, vessel injury
  ▪ laparoscopic cholecystectomy is the standard of care, no benefit to delaying surgery
  ▪ risk of open cholecystectomy higher in emergency situations

Acute Cholecystitis

Pathogenesis
• inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or Hartmann’s pouch
• no cholelithiasis in 5-10% (see Acalculous Cholecystitis, GS47)

Clinical Features
• often have history of biliary colic
• severe constant (hours to days) epigastric or RUQ pain, anorexia, nausea, vomiting, low grade fever (<38.5°C)
• focal peritoneal findings: Murphy’s sign, palpable, tender gallbladder (in 33%)
• Boas’ sign: right subscapular pain

Investigation
• bloodwork: elevated WBC and left shift, mildly elevated bilirubin, AST, ALT and ALP
• U/S: 98% sensitive, consider HIDA scan if U/S negative

Acalculous Cholecystitis
• Acute or chronic cholecystitis in the absence of stones, typically due to gallbladder ischemia, stasis
• Risk factors: DM, immunosuppression, ICU admission, trauma patient, TPN, sepsis
• Clinical features same as Acute cholecystitis, occurs in 20% of cases of acute cholecystitis
• Investigations: U/S shows sludge in gallbladder, other U/S features of cholecystitis (see above), CT or HIDA scan
• Treatment: broad-spectrum antibiotics, cholecystectomy, if patient unstable → cholecystostomy

Rouviere’s Sulcus
Fissure between right lobe and caudate process of liver. Keeping dissection anterior to this landmark prevents bile duct injury.

Critical View of Safety
Space between the gallbladder and liver clear of any structures other than the cystic artery.
Complications
- gallbladder mucocele (hydrops): long term cystic duct obstruction results in mucous accumulation in gallbladder (clear fluid)
- gangrene (20%), perforation (2%): result in abscess formation or peritonitis
- empyema of gallbladder: suppurative cholecystitis, pus in gallbladder + sick patient
- cholecystoenteric fistula, from repeated attacks of cholecystitis, can lead to gallstone ileus
- emphysematous cholecystitis: bacterial gas present in gallbladder lumen, wall or pericholecystic space (risk in diabetic patient)
- Mirizzi syndrome: extra-luminal compression of CBD/CHD due to large stone in cystic duct

Treatment
- admit, hydrate, NPO, NG tube (if persistent vomiting from associated ileus), analgesics once diagnosis is made
- antibiotics:
  - cefazolin if uncomplicated cholecystitis
- cholecystectomy:
  - early (within 72 h) vs. delayed (after 6 wk)
    - equal morbidity and mortality
    - early cholecystectomy preferred: shorter hospitalization and recovery time, no benefit to delaying surgery
    - emergent OR indicated if high risk, e.g. emphysematous
- laparoscopic is standard of care (convert to open for complications or difficult case)
- laparoscopic: reduced risk of wound infections, shorter hospital stay, reduced post-op pain, increased risk of bile duct injury
- intra-operative cholangiography (IOC):
  - indications: clarify bile duct anatomy, obstructive jaundice, history of biliary pancreatitis, small stones in gallbladder with a wide cystic duct (>15 mm), single faceted stone in gallbladder, bilirubin >137 µmol/L
  - percutaneous cholecystostomy tube: critically ill or if general anesthetic contraindicated

Acalculous Cholecystitis

Definition
- acute or chronic cholecystitis in the absence of stones

Pathogenesis
- typically due to gallbladder ischemia, stasis

Risk Factors
- DM, immunosuppression, ICU admission, trauma patient, TPN, sepsis

Clinical Features
- see Acute Cholecystitis, GS46
- occurs in 20% of cases of acute cholecystitis

Investigations
- U/S: shows sludge in gallbladder, other U/S features of cholecystitis (see Acute Cholecystitis, GS46)
- CT or HIDA scan

Treatment
- broad-spectrum antibiotics, cholecystectomy
- if patient unstable → cholecystostomy

Choledocholithiasis

Definition
- stones in common bile duct (CBD)

Clinical Features
- 50% asymptomatic
- often have history of biliary colic
- tenderness in RUQ or epigastrum
- acholic stool, dark urine, fluctuating jaundice
- primary vs. secondary stones:
  - primary: formed in bile duct, indicates bile duct pathology (e.g. benign biliary stricture, sclerosing cholangitis, choledochal cyst, cystic fibrosis)
  - secondary: formed in gallbladder (85% of cases in U.S.)
Investigations
• CBC: usually normal; leukocytosis suggests cholangitis
• LFTs: increased AST, ALT early in disease, increased bilirubin (more sensitive), ALP, GGT later
• amylase/lipase: to rule out gallstone pancreatitis
• U/S: intra-extra-hepatic duct dilatation; differential diagnosis is choledochal cyst
• ERCP, PTC
• MRCP (90% sensitive, almost 100% specific, not therapeutic)

Complications
• cholangitis, pancreatitis, biliary stricture and biliary cirrhosis

Treatment
• if no evidence of cholangitis: treat with ERCP for CBD stone extraction possibly followed by elective cholecystectomy in 25% of patients

Acute Cholangitis

Pathogenesis
• obstruction of CBD leading to biliary stasis, bacterial overgrowth, suppuration and biliary sepsis – may be life-threatening, especially in elderly

Etiology
• choledocholithiasis (60%), stricture, neoplasm (pancreatic or biliary), extrinsic compression (pancreatic pseudocyst or pancreatitis), instrumentation of bile ducts (PTC, ERCP), biliary stent
• organisms: E. coli, Klebsiella, Pseudomonas, Enterococcus, B. fragilis, Proteus

Clinical Features
• Charcot's triad: fever, RUQ pain, jaundice
• Reynold's pentad: fever, RUQ pain, jaundice, shock, confusion
• may have nausea, vomiting, abdominal distention, ileus, acholic stools, tea-coloured urine (elevated direct bilirubin)

Investigations
• CBC: elevated WBC + left shift
• may have positive blood cultures
• LFTs: obstructive picture (elevated ALP, GGT and conjugated bilirubin, mild increase in AST, ALT)
• amylase/lipase: rule out pancreatitis
• U/S: intra-extra-hepatic duct dilatation

Treatment
• initial: NPO, fluid and electrolyte resuscitation, ± NG tube, IV antibiotics (treats 80%)
• decompression:
  ▪ ERCP + sphincterotomy: diagnostic and therapeutic
  ▪ PTC with catheter drainage: if ERCP not available or unsuccessful
  ▪ laparotomy with CBD exploration and T-tube placement if above fails
• all patients should also have a cholecystectomy, unless contraindicated

Prognosis
• suppurative cholangitis mortality rate: 50%

Gallstone Ileus

Pathogenesis
• repeated inflammation causing a cholecystoenteric fistula (usually duodenal) → large gallstone enters the gut and impacts at or near the ileocecal valve, causing a true bowel obstruction (note: ileus is a misnomer in this context)

Clinical Features
• crampy abdominal pain, nausea, vomiting (see Bowel Obstruction, GS24)

Investigations
• AXR: dilated small intestine, air fluid levels, may reveal radiopaque gallstone, air in biliary tree (pneumobilia) (40%)
• CT: biliary tract air, obstruction, gallstone in intestine
• Rigler's triad: pneumobilia (air in biliary tree), small bowel obstruction (partial or complete), gallstone (usually in right iliac fossa)

American Society of Gastrointestinal Endoscopy 2010 Predictors for Risk of CBD Stones:
• Very strong:
  ▪ CBD stone on ultrasound
  ▪ Clinical ascending cholangitis
  ▪ Bilirubin >68 µmol/L
• Strong:
  ▪ CBD dilated >6 mm on ultrasound
  ▪ Bilirubin 31-68 µmol/L
• Moderate:
  ▪ Abnormal liver test (besides bilirubin)
  ▪ Age >55 yr
  ▪ Clinical gallstone pancreatitis

Charcot’s Triad
Fever, RUQ pain, jaundice.

Reynold’s Pentad
Fever, RUQ pain, jaundice, shock, confusion.

Common Bacteria in Biliary Tract
KEEPS
Klebsiella
Enterococcus
E. Coli, Enterobacter
Proteus, Pseudomonas
Serratia

Bouvetre’s Syndrome
Gastric outlet/duodenal obstruction caused by a large gallstone passing through a cholecystogastric or cholecystoduodenal fistula.

Rigler’s Triad of Gallstone Ileus:
• Pneumobilia
• Small bowel obstruction
• Gallstone
Treatment
- fluid resuscitation, NG decompression
- surgery: enterolithotomy and removal of stone, inspect small and large bowel for additional proximal stones
- may close fistula surgically or manage expectantly (can resolve spontaneously)
- cholecystectomy either during enterolithotomy or after recovery if patient experiences gallbladder symptoms

Carcinoma of the Gallbladder

Risk Factors
- chronic symptomatic gallstones (70% of cases), old age, female, gallbladder polyps, porcelain gallbladder, chronic infection (Salmonella, Helicobacter), abnormal pancreaticobiliary duct junction

Clinical Features
- majority are adenocarcinoma
- may be incidental finding on elective cholecystectomy (~1% of elective cholecystectomies)
- many patients are asymptomatic until late
- local: vague RUQ pain, palpable RUQ mass
- Courvoisier’s gallbladder: an enlarged, often palpable gallbladder in a patient with carcinoma of the head of the pancreas; associated with jaundice due to obstruction of the common bile duct
- systemic: jaundice (50%) due to invasion of CBD or compression of CBD by pericholedochal nodes, weight loss, malaise, anorexia
- early local extension to liver, may extend to stomach, duodenum
- early metastasis common to liver, lung, bone

Investigations
- U/S: mural thickening, calcification, loss of interface between gallbladder and liver, fixed mass
- endoscopic U/S (EUS): good for distinguishing carcinomas from other diagnoses such as polyps, good for staging, allows sampling of bile for cytology
- abdominal CT: polypoid mass, mural thickening, liver invasion, nodal involvement, distant metastases
- MRI/MRCP: good for distinguishing benign and malignant polyps

Treatment
- if carcinoma of the gallbladder is suspected preoperatively, an open cholecystectomy should be considered to avoid tumour seeding of the peritoneal cavity
- confined to mucosa (rare): cholecystectomy
- beyond mucosa: cholecystectomy, en bloc wedge resection of 3-5 cm underlying liver, dissection of hepatoduodenal lymph nodes

Prognosis
- poor 5 yr survival (10%) as gallbladder carcinoma is often detected late
- better outcomes when detected incidentally following cholecystectomy

Cholangiocarcinoma

Definition
- malignancy of extra- or intrahepatic bile ducts

Risk Factors
- age 50-70, gallstones, ulcerative colitis, primary sclerosing cholangitis, choledochal cyst, Clonorchis sinensis infection (liver fluke), chronic intrahepatic stones (hepatolithiasis)

Clinical Features
- majority are adenocarcinomas
- gradual signs of biliary obstruction: jaundice, pruritus, dark urine, pale stools
- anorexia, weight loss, RUQ pain, Courvoisier’s sign (if CBD obstructed), hepatomegaly
- early metastases are uncommon, but commonly tumour grows into portal vein or hepatic artery
- Klatskin tumour: cholangiocarcinoma located at bifurcation of common hepatic duct

Investigations
- LFTs show obstructive picture
- U/S, CT: bile ducts usually dilated, but not necessarily
- ERCP or PTC: to determine resectability, for biopsies
- CXR, bone scan: for metastatic workup

Obstructive jaundice is the most common presenting symptom for cholangiocarcinoma.

Courvoisier’s Sign
Palpable, nontender distended gallbladder due to CBD obstruction. Present in 33% of patients with pancreatic carcinoma. The distended gallbladder could not be due to acute cholecystitis or stone disease because the gallbladder would actually be scarred and smaller, not larger.
Pathogenesis
- GALLSTONE PANCREATITIS (35% of acute pancreatitis)
  - upper third lesions: duct resection + Roux-en-Y hepaticojejunostomy, ± liver resection
  - middle third lesions (uncommon): duct resection + Roux-en-Y hepaticojejunostomy
  - lower third lesions: Whipple procedure
- unresectable lesions: stent or choledochojejunostomy (surgical bypass)

Complications
- severe hypocalcemia
- encephalopathy
- coagulopathy/DIC
- ARDS/sepsis/multiorgan failure
- diabetes
- pancreatic ascites/pancreatic pleural effusion
- granulation tissue
- pseudocyst (collection of pancreatic secretions >4 wk old surrounded by a defined wall of granulation tissue)
- abscess/infection, necrosis
- splenic/mesenteric portal vessel thrombosis or rupture
- diabetes
- ARDS/sepsis/multiorgan failure
- coagulopathy/DIC
- severe hypocalcemia

Treatment
- generally palliative
- if resectable: biliary drainage and wide excision margin
- upper third lesions: duct resection + Roux-en-Y hepaticojejunostomy, ± liver resection
- middle third lesions (uncommon): duct resection + Roux-en-Y hepaticojejunostomy
- lower third lesions: Whipple procedure
- unresectable lesions: stent or choledochojejunostomy (surgical bypass)

Prognosis
- radiotherapy useful for additional palliation, chemotherapy may be helpful
- the more proximal to the liver, the worse the prognosis
- overall 5-yr survival: 15%

Pancreas

Acute Pancreatitis
- see Gastroenterology, G44

GALLSTONE PANCREATITIS (35% of acute pancreatitis)

Pathogenesis
- obstruction of pancreatic duct by large or small gallstones and biliary sludge
- backup of pancreatic enzymes can cause autodigestion of the pancreas

Clinical Features (pancreatitis of any etiology)
- pain (epigastric pain radiating to back), nausea, vomiting, ileus, peritoneal signs, jaundice, fever
- Inglefinger's sign: pain worse when supine, better when sitting forward
- rarely may have coexistent cholangitis or pancreatic necrosis
- Ranson's criteria for determining prognosis of acute pancreatitis (see sidebar)

Investigations
- high amylase (higher than alcoholic pancreatitis), lipase, leukocytosis
- elevated ALT (>150 IU/L), AST strongly suggest gallstone etiology of pancreatitis
- U/S may show multiple stones (may have passed spontaneously), edematous pancreas
- CXR, AXR, CT (if severe to evaluate for complications)

Treatment
- supportive
- enteral nutrition
- NPO, hydration, analgesia and antibiotics for severe cases of necrotizing pancreatitis or signs of sepsis
- stone often passes spontaneously (~90%); usually no surgical management in uncomplicated acute pancreatitis
- cholecystectomy during same admission (25-60% recurrence if no surgery)
- may need urgent ERCP + sphincterotomy if failure of conservative management (benefits of early ERCP controversial)
- early ERCP if concomitant cholangitis
- surgical indications in acute pancreatitis (rare):
  - debridement and drain placement for necrotizing pancreatitis if refractory to medical management, if septic or in ICU without other sources of sepsis

Complications
- pseudocyst (collection of pancreatic secretions >4 wk old surrounded by a defined wall of granulation tissue)
- abscess/infection, necrosis
- splenic/mesenteric portal vessel thrombosis or rupture
- pancreatic ascites/pancreatic pleural effusion
- diabetes
- ARDS/sepsis/multiorgan failure
- coagulopathy/DIC
- encephalopathy
- severe hypocalcemia

Ranson's Criteria

Interpretation
- ≥2 = difficult course
- ≥3 = high mortality (>15%)

Efficacy of Neoadjuvant Chemoradiation, Followed by Liver Transplantation, for Perihilar Cholangiocarcinoma at 12 US Centers

Purpose: To determine the effectiveness of neoadjuvant chemoradiation and liver transplantation for unresectable perihilar cholangiocarcinoma and to determine the appropriateness of the United Network of Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) criteria for model of end-stage liver disease (MELD) exception for patients with this disease.

Methods: Study conducted from 1993-2010 in 12 transplant centers. 287 patients included.

Results: Median follow-up was 2.5 yr. 43% of patients (n = 122) died after a median of 1.2 yr from presentation, and of these, 60 died pretransplant. Post-transplant, 43 patients had recurrences and 62 died. Recurrence-free survival at 2, 5, and 10 yr were 38%, 35%, and 59%, respectively. Intention-to-treat survival rates at 2 and 5 yr were 68% and 53%, respectively. 25% of patients left the waiting list after a median of 4.6 mo. The waiting list drop-out rate increased by an average of 11.5% every 3 mo. Patients who received transplantation outside of the criteria for MELD exception or who had a malignancy within 5 yr had significantly worse recurrence-free survival compared to those who met the criteria (HR = 2.98, 95% CI: 1.79, 4.95). Recurrence-free survival at 5 yr was shorter for patients with tumors >3 cm versus <3 cm (p < 0.001).

Conclusions: Neoadjuvant chemoradiation and liver transplantation are effective treatments for unresectable perihilar cholangiocarcinoma. Furthermore, the UNOS/OPTN criteria for MELD exception appear to be appropriate.
Chronic Pancreatitis

- see also Gastroenterology, G46

Surgical Treatment
- treatment is generally medical
- indications for surgery:
  - failure of medical treatment
  - debilitating abdominal pain
  - pseudocyst complications: persistence, hemorrhage, infection, rupture
  - CBD obstruction (e.g. strictures), duodenal obstruction
  - pancreatic fistula, variceal hemorrhage secondary to splenic vein obstruction
  - rule out pancreatic cancer (present in 15% of chronic pancreatitis treated surgically)
  - anatomical abnormality causing recurrent pancreatitis
- pre-op CT and/or ERCP are mandatory to delineate anatomy
- minimally invasive options:
  - endoscopic pancreatic duct decompression: less effective than surgery
  - extracorporeal shockwave lithotripsy: if pancreatic duct stones
  - celiac plexus block: lasting benefit in 30% patients, less effective in those <45 yr or with prior pancreatic surgery
- surgical options:
  - drainage procedures: only effective if ductal system is dilated
    - Puestow procedure (lateral pancreaticojejunostomy): improves pain in 80% of patients
  - pancreatectomy: best option in absence of dilated duct
    - proximal disease: Whipple procedure (pancreaticoduodenectomy) – pain relief in 80%
    - distal disease: distal pancreatectomy ± Roux-en-Y pancreaticojejunostomy
  - total pancreatectomy: refractory disease
  - denervation of celiac ganglion and splanchnic nerves
- pseudocyst (often resolve spontaneously with pancreatic rest):
  - cyst wall must be mature prior to drainage (4-6 wk)
  - pseudoaneurysm an absolute contraindication to endoscopic drainage, must embolize first
  - percutaneous catheter drainage
  - surgical drainage (gold standard):
    - cystgastrostomy
    - cystenterostomy
    - resection
  - endoscopic drainage:
    - cystgastrostomy
    - cystduodenostomy
- consider biopsy of cyst wall to rule out cystadenocarcinoma

Pancreatic Cancer

Epidemiology
- fourth most common cause of cancer-related mortality in both men and women in Canada
- M:F = 1.3:1, average age: 50-70

Risk Factors
- increased age
- smoking: 2-5x increased risk, most clearly established risk factor
- high fat/low fibre diets, heavy alcohol use
- obesity
- DM, chronic pancreatitis
- partial gastrectomy, cholecystectomy
- chemicals: betanaphthylamine, benzidine
- African descent

Clinical Features
- head of the pancreas (70%):
  - weight loss, obstructive jaundice, vague constant mid-epigastric pain (often worse at night, may radiate to back)
  - painless jaundice (occurs more often with peri-ampullary), Courvoisier’s sign (see sidebar GS49)
  - palpable tumour mass → generally incurable
- body or tail of pancreas (30%):
  - tends to present later and usually inoperable
  - weight loss, vague mid-epigastric pain
  - <10% jaundiced
  - sudden onset diabetes

Investigations
- serum chemistry is non-specific, can have elevated ALP and bilirubin >300 µmol/L
- CA 19-9 (most useful serum marker of pancreatic cancer)
- U/S, contrast CT (also evaluates metastasis and resectability), ERCP, MRI, MRCP
Pathology
- ductal adenocarcinoma: most common type (75-80%); exocrine pancreas
- intraductal papillary mucinous neoplasm (IPMN)
- other: mucinous cystic neoplasm (MCN), acinar cell carcinoma, islet-cell (insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma)
- see Surgical Endocrinology, GS60 for insulinoma

Treatment
- resectable (20% of pancreatic cancer)
  - no involvement of liver, peritoneum or vasculature (hepatic artery, SMA, SMV, portal vein, IVC, aorta), no distant metastasis
  - Whipple procedure (pancreaticoduodenectomy) for cure – 5% mortality
  - distal pancreatectomy ± splenectomy, lymphadenectomy if carcinoma of midbody and tail of pancreas
- borderline resectable
  - tumours that abut the SMA, SMV, portal vein, hepatic artery, or celiac artery
- non-resectable (palliative treatment)
  - relieve biliary/duodenal obstruction with endoscopic stenting or double bypass procedure (choledochointerostomy + gastroenterostomy)
  - chemotherapy (gemcitabine, folfirinox), radiotherapy – only slightly increase survival

Prognosis
- most important prognostic indicators are lymph node status, size >3 cm, perineural invasion (invasion of tumour into microscopic nerves of pancreas)
- overall 5-yr survival is 1%
- 20% 5-yr survival following resection
- median survival for unresectable disease: 8-12 mo if locally advanced, 3-6 mo if metastatic

Table 19. TNM Classification System for Exocrine and Endocrine Tumours of the Pancreas

<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX Primary tumour cannot be assessed</td>
<td>NX Regional lymph nodes cannot be assessed</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>T0 No evidence of primary tumour</td>
<td>N0 No regional lymph node metastasis</td>
<td>M1 Distant metastasis</td>
</tr>
<tr>
<td>Tis Carcinoma in situ</td>
<td>N1 Regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>T1 Tumour limited to pancreas, &lt;2 cm in greatest dimension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 Tumour limited to pancreas, &gt;2 cm in greatest dimension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 Tumour extends beyond pancreas, no involvement of celiac axis or superior mesenteric artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4 Tumour involves celiac axis or superior mesenteric artery (unresectable)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Steps of a Whipple Resection (Pancreaticoduodenectomy):
1. Assessment of metastatic disease (all peritoneal surfaces)
2. Mobilization of the duodenum and head of the pancreas with identification of the superior mesenteric vein
3. Mobilization of the stomach and proximal duodenum, transection of the stomach or proximal duodenum
4. Dissection of the hepatoduodenal ligament with skeletonization of the porta hepatis
5. Cholecystectomy and division of the bile duct
6. Mobilization and division of the proximal jejunum
7. Transection of the pancreatic neck and division of any remaining attachments
8. Reconstruction of gastrointestinal continuity: pancreaticojejunostomy, hepaticejejunostomy, gastroduodenojunostomy

Removed:
- Common bile duct
- Gallbladder
- Duodenum
- Pancreatic head
- Distal stomach (sometimes)
**Spleen**

**Splenic Trauma**
- typically from blunt trauma (especially in people with splenomegaly)
- most common intra-abdominal organ injury in blunt trauma
- may have Kehr’s sign

**Treatment**
- non-operative:
  - in stable patients: extended bed rest with serial hematocrit levels, close monitoring for 3-5 d; pediatric guidelines for days of bed rest is grade plus 1 (i.e. grade 3 splenic laceration requires 4 d of bed rest)
  - hemostatic control
  - splenic artery embolization if patient stable and one of: active contrast extravasation, splenic pseudoaneurysm, hemoperitoneum
- operative:
  - splenorrhaphy (suture of spleen) ± splenic wrapping with hemostatic mesh – if patient hemodynamically stable, patient has stopped bleeding and laceration does not involve hilum
  - partial splenectomy, rarely performed due to risk of recurrent hemorrhage
  - total splenectomy if patient unstable or high-grade injury

**Splenectomy**

**Indications**
- splenic trauma (most common reason for splenectomy), hereditary spherocytosis, primary hypersplenism, chronic immune thrombocytopenia purpura (ITP), splenic vein thrombosis causing esophageal varices, splenic abscess, thrombotic thrombocytopenia purpura (TTP), sickle cell disease
- does not benefit all thrombocytopenic states (e.g. infection, most malignancies involving the bone marrow, drugs/toxins)
- probability of cure of ITP by splenectomy is 60-70%, may be predicted by response to IVIg

**Complications**
- short-term:
  - injury to surrounding structures (e.g. gastric wall, tail of pancreas)
  - post-op thrombocytosis, leukocytosis
  - thrombosis of portal, splenic, or mesenteric veins
  - subphrenic abscess
- long-term:
  - post-splenectomy sepsis (encapsulated organisms): 4% of splenectomized patients (highest risk in those <16 yr old)
    - 50% mortality
    - prophylaxis with vaccinations, ideally 2 wk pre- or post-op *(pneumococcal, H. influenzae and meningococcus)*
    - liberal use of penicillin especially in children <6 yr old
  - splenosis: intra-abdominal “seeding” of splenic tissue during removal
Benign Breast Lesions

NON-PROLIFERATIVE LESIONS
- also known as fibrocystic change, chronic cystic mastitis, mammary dysplasia
- benign breast condition characterized by fibrous and cystic changes in the breast
- no increased risk of breast cancer
- age 30 to menopause (and after if HRT used)
- clinical features:
  - breast pain, focal areas of nodularity or cysts often in the upper outer quadrant, frequently bilateral, mobile, varies with menstrual cycle, nipple discharge (straw-like, brown or green)
- treatment:
  - evaluation of breast mass and reassurance
  - if >40 yr old: mammography every 3 yr
  - no strong evidence for avoidance of xanthine-containing products (coffee, tea, chocolate, cola)
  - analgesia (ibuprofen, ASA)
  - for severe symptoms: OCP, danazol, bromocriptine

PROLIFERATIVE LESIONS – No Atypia

Fibroadenoma
- most common benign breast tumour in women under age 30
- risk of subsequent breast cancer is increased only if fibroadenoma is complex, there is adjacent atypia or a strong family history of breast cancer
- clinical features:
  - nodules: smooth, rubbery, discrete, well-circumscribed, non-tender, mobile, hormone dependent
  - unlike cysts, needle aspiration yields no fluid
- investigations:
  - core or excisional biopsy required
  - ultrasound and FNA alone cannot differentiate fibroadenoma from Phyllodes tumour
- treatment:
  - generally conservative: serial observation
  - consider excision if size 2-3 cm and growing on serial ultrasound (q6mo x 2 yr is usual follow-up), if symptomatic or patient preference

Intraductal Papilloma
- solitary intraductal benign polyp
- present as nipple discharge (most common cause of spontaneous, unilateral, bloody nipple discharge), breast mass, nodule on U/S
- can harbour areas of atypia or DCIS
- treatment: excision of involved duct to ensure no atypia

DDx for Breast Mass
Benign:
- Fibrocystic changes
- Fibroepithelial lesions (fibroadenoma most common; benign phyllodes also)
- Fat necrosis
- Papilloma/papillomatosis
- Galactocele
- Duct ectasia
- Ductal/lobular hyperplasia
- Sclerosing adenosis
- Lipoma
- Neurofibroma
- Granulomatous mastitis (e.g. TB, granulomatosis with polyangiitis, sarcoidosis)
- Abscess
- Silicone implant

Malignant:
- Breast ca (likely invasive, DCIS rarely forms a breast mass)
- Malignant phyllodes
- Angiosarcoma (rare)
Ductal Hyperplasia Without Atypia
- increased number of cells within the ductal space
- cells retain benign cytology
- no treatment required
- slightly increased cancer risk if moderate or florid hyperplasia

PROLIFERATIVE LESIONS – With Atypia
Atypical Hyperplasias
- can involve ducts (ductal hyperplasia with atypia) or lobules (lobular hyperplasia with atypia)
- cells lose apical-basal orientation
- increased risk of breast cancer
- diagnosis: core or excisional biopsy
- treatment: complete resection, risk modification (avoid exogenous hormones), close follow-up

OTHER LESIONS
Fat Necrosis
- uncommon, result of trauma (may be minor, positive history in only 50%), after breast surgery (i.e. reduction)
- firm, ill-defined mass with skin or nipple retraction, ± tenderness
- regresses spontaneously, but complete imaging ± biopsy to rule out carcinoma

Mammary Duct Ectasia
- obstruction of a subareolar duct leading to duct dilation, inflammation, and fibrosis
- may present with nipple discharge, bluish mass under nipple, local pain
- risk of secondary infection (abscess, mastitis)
- resolves spontaneously

Montgomery Tubercle
- Montgomery tubercles (or Morgagni tubercles) are papular projections at the edge of the areola
- obstruction of these glands can lead to inflammation or cystic collections (cyst of Montgomery aka retroareolar cyst)
- if signs of secondary infection, start treatment for mastitis
- resolves spontaneously in weeks to years

Abscess
- lactational (see Obstetrics, OB51) vs. periductal/subareolar
- unilateral localized pain, tenderness, erythema, subareolar mass, nipple discharge, nipple inversion
- rule out inflammatory carcinoma, as indicated
- treatment: initially broad-spectrum antibiotics and I&D, if persistent total duct excision (definitive)
- if mass does not resolve: U/S to assess for presence of abscess, core biopsy to exclude cancer, consider MRI

Breast Cancer
Epidemiology
- 2nd leading cause of cancer mortality in women (1st is lung cancer)
- 1/9 of women in Canada will be diagnosed with breast cancer in their lifetime
- 1/27 of women in Canada will die from breast cancer

Risk Factors
- gender (99% female)
- age (80% >40 yr old)
- important risk factors are prior history of breast cancer and/or prior breast biopsy (regardless of pathology)
- 1st degree relative with breast cancer (greater risk if relative was premenopausal)
- increased risk with high breast density, nulliparity, first pregnancy >30 yr old, menarche <12 yr old, menopause >55 yr old
- decreased risk with lactation, early menopause, early childbirth
- radiation exposure (e.g. mantle radiation for Hodgkin’s disease)
- >5 yr HRT
**Investigations**
- mammography
  - indications:
    - screening refer to Family Medicine, FM3
    - findings indicative of malignancy:
      - mass that is poorly defined, spiculated border
      - microcalcifications
      - architectural distortion
      - interval mammographic changes
      - normal mammogram does not rule out suspicion of cancer based on clinical findings
- other radiographic studies:
  - U/S: differentiate between cystic and solid
  - MRI: high sensitivity, low specificity
  - galactogram/ductogram (for nipple discharge): identifies lesions in ducts
  - metastatic workup as indicated (usually after surgery or if clinical suspicion of metastatic disease): bone scan, abdominal U/S, CXR (or CT chest/abdomen/pelvis), head CT (only if specific neurological symptoms)

**Diagnostic Procedures**
- needle aspiration: for palpable cystic lesions; send fluid for cytology if blood or cyst does not completely resolve
- U/S or mammography guided core needle biopsy (most common)
- fine needle aspiration (FNA): for palpable solid masses; need experienced practitioner for adequate sampling
- excisional biopsy: only performed as second choice to core needle biopsy; should not be done for diagnosis if possible

**Genetic Screening**
- consider testing for BRCA1/2 if:
  - patient diagnosed with breast AND ovarian cancer
  - strong family history of breast/ovarian cancer
  - family history of male breast cancer
  - young patient (<35 yr old)
  - bilateral breast cancer in patients <50 yr old

**Staging** (see Table 20)
- clinical:
  - tumour size by palpation, mammogram
  - nodal involvement by palpation
  - metastasis by physical exam, CXR and abdominal U/S (or CT chest/abdomen/pelvis), bone scan (usually done post-op if node-positive disease)
- pathological:
  - tumour size
  - grade: modified Bloom and Richardson score (I to III) – histologic, nuclear and mitotic grade
  - number of axillary nodes positive for malignancy out of total nodes resected, extranodal extension, sentinel node positive/negative
  - estrogen receptor (ER) + progesterone receptor (PR) testing
  - Her2Neu receptor testing
  - margins: negative, <1 mm, positive
  - lymphovascular invasion (LVI)
  - extensive in situ component (EIC): DCIS in surrounding tissue
  - involvement of dermal lymphatics (inflammatory) – automatically Stage IIIb

**Table 20. Staging of Breast Cancer (American Joint Committee on Cancer)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumour</th>
<th>Nodes (regional) (clinical)</th>
<th>Metastasis</th>
<th>Survival (5-yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>in situ</td>
<td>None</td>
<td>None</td>
<td>99%</td>
</tr>
<tr>
<td>I</td>
<td>&lt;2 cm</td>
<td>None</td>
<td>None</td>
<td>94%</td>
</tr>
<tr>
<td>II A</td>
<td>&lt;2 cm</td>
<td>Mobile ipsilateral</td>
<td>None</td>
<td>85%</td>
</tr>
<tr>
<td>II B</td>
<td>2-5 cm or &gt;5 cm</td>
<td>None or mobile ipsilateral</td>
<td>None</td>
<td>70%</td>
</tr>
<tr>
<td>III A</td>
<td>Any size</td>
<td>Fixed ipsilateral or internal mammary</td>
<td>None</td>
<td>52%</td>
</tr>
<tr>
<td>III B</td>
<td>Skin/chest wall invasion</td>
<td>Any</td>
<td>None</td>
<td>48%</td>
</tr>
<tr>
<td>III C</td>
<td>Any size</td>
<td>Ipsilateral infraclavicular/internal mammary plus axillary nodes; ipsilateral supraclavicular node(s) ± axillary nodes</td>
<td>None</td>
<td>33%</td>
</tr>
<tr>
<td>IV</td>
<td>Any</td>
<td>Any</td>
<td>Distant</td>
<td>18%</td>
</tr>
</tbody>
</table>
Pathology

- non-invasive (cannot penetrate basement membrane):
  - ductal carcinoma *in situ* (DCIS):
    - proliferation of malignant ductal epithelial cells completely contained within breast ducts, often multifocal
    - 80% non-palpable, detected by screening mammogram
    - risk of invasive ductal carcinoma in same breast up to 35% in 10 yr
  - treatment:
    - lumpectomy with wide excision margins + radiation (5-10% risk invasive cancer)
    - mastectomy if large area of disease, high grade or multifocal (risk of invasive cancer reduced to 1%)
    - possibly tamoxifen as an adjuvant treatment
    - 99% 5-yr survival

- lobular carcinoma *in situ* (LCIS):
  - neoplastic cells completely contained within breast lobule
  - no palpable mass, no mammographic findings, usually incidental finding on breast biopsy for another indication
  - treatment
    - clinical follow-up
    - chemotherapy (tamoxifen)
    - surgery (uncommon)
  - not a precursor lesion, but considered a risk factor for breast cancer development

- invasive:
  - invasive ductal carcinoma (most common 80%):
    - originates from ductal epithelium and infiltrates supporting stroma
    - characteristics: hard, scirrhouous, infiltrating tentacles, gritty on cross-section
  - invasive lobular carcinoma (8-15%):
    - originates from lobular epithelium
    - 20% bilateral (i.e. more often than infiltrating ductal carcinoma)
  - Paget’s disease (1-3%):
    - ductal carcinoma that invades nipple with scaling, eczematoid lesion
  - inflammatory carcinoma (1-4%):
    - ductal carcinoma that invades dermal lymphatics
    - most aggressive form of breast cancer
    - clinical features: erythema, skin edema, warm, swollen and tender breast ± lump
    - peau d’orange indicates advanced disease (IIb-IV)
  - male breast cancer (<1%):
    - most commonly invasive ductal carcinoma
    - often diagnosed at later stages
    - stage-for-stage similar prognosis to breast cancer in females
    - consider genetic testing
  - sarcomas: rare
    - most commonly Phyllodes tumour, a variant of fibroadenoma with potential for malignancy
    - can also be angiosarcomas – after previous radiation
  - lymphoma: rare
  - other: papillary, medullary, mucinous, tubular cancers
    - generally better prognosis

Treatment

Table 21. Breast Cancer Treatment by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary Treatment Options</th>
<th>Adjuvant Systemic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (in situ)</td>
<td>BCS + radiotherapy</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>BCS alone if margins &gt; 1 cm and low nuclear grade</td>
<td>Mastectomy* ± SLNB</td>
</tr>
<tr>
<td>I</td>
<td>BCS + axillary node dissection + radiotherapy</td>
<td>May not be needed; discuss risks/benefits of chemotherapy and tamoxifen</td>
</tr>
<tr>
<td></td>
<td>Mastectomy* + axillary node dissection/SLNB</td>
<td>Chemotherapy for premenopausal women or postmenopausal and estrogen receptor (ER) negative, follow by tamoxifen if ER positive</td>
</tr>
<tr>
<td>II</td>
<td>BCS + axillary node dissection + radiotherapy</td>
<td>Neoadjuvant therapy may be considered i.e. preparative chemotherapy and/or hormone therapy. Adjuvant radiation and chemotherapy may also be appropriate (i.e. post-op)</td>
</tr>
<tr>
<td></td>
<td>Mastectomy* + axillary node dissection/SLNB</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Likely mastectomy + axillary node dissection + radiotherapy</td>
<td>Neoadjuvant therapy</td>
</tr>
<tr>
<td></td>
<td>Neoadjuvant therapy</td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Likely mastectomy + axillary node dissection + radiotherapy</td>
<td>Primary treatment is systemic therapy i.e. chemotherapy and/or hormone therapy</td>
</tr>
<tr>
<td>IV</td>
<td>Surgery as appropriate for local control</td>
<td></td>
</tr>
</tbody>
</table>

BCS = breast-conserving surgery; SLNB = sentinel lymph node biopsy

*If no reason to select mastectomy, the choice between BCS + radiotherapy and mastectomy can be made according to patient’s preference since choice of local treatment does not significantly affect survival if local control is achieved.*
Primary Surgical Treatment
- breast-conserving surgery (BCS): lumpectomy with wide local excision
  - for treatment of stage I and II disease
  - must be combined with radiation for survival equivalent to mastectomy
- contraindications:
  - high risk of local recurrence: extensive malignant-type calcifications on mammogram, multifocal primary tumours, or failure to obtain tumour-free margins after re-excision
  - contraindications to radiation therapy (pregnancy, previous radiation, collagen vascular disease)
  - large tumour size relative to breast
- mastectomy
  - radical mastectomy (rarely done anymore): removes all breast tissue, skin, pectoralis muscle, axillary nodes
  - modified radical mastectomy (MRM): removes all breast tissue, skin, and axillary nodes
  - simple mastectomy: removes all breast tissue and skin
  - see Plastic Surgery, PL32 for breast reconstruction
- axillary lymph node dissection (ALND)
  - performed if SLNB is positive or nodes are clinically concerning
  - risk of arm lymphedema (10-15%), decreased arm sensation, shoulder pain
- sentinel lymph node biopsy (SLNB)
  - technetium-99 ± blue dye injected at tumour site prior to surgery to identify sentinel node(s)
  - intraoperative frozen section
  - proceed with ALND if positive
  - 5% false negative rate

Adjuvant/Neoadjuvant
- radiation
  - indications:
    - decrease risk of local recurrence; almost always used after BCS, sometimes after mastectomy (if >4 nodes positive or tumour >5 cm)
    - inoperable locally advanced cancer
  - axillary nodal radiation may be added if nodal involvement
- hormonal
  - indications:
    - ER positive plus node-positive or high-risk node-negative
    - palliation for metastases
    - tamoxifen if premenopausal or aromatase inhibitors (e.g. anastrozole)
    - ovarian ablation (e.g. goserelin/GnRH agonist, oophorectomy), progestins (e.g. megestrol acetate), androgens (e.g. fluoxymesterone) are other options
- chemotherapy
  - indications:
    - ER negative plus node-positive or high-risk node-negative
    - ER positive and young age
    - stage I disease at high risk of recurrence (high grade, lymphovascular invasion)
    - palliation for metastatic disease

Post-Treatment Follow-up
- visits q3-6mo x 2 yr and annually thereafter (frequency is controversial)
- annual mammography; no other imaging unless clinically indicated
- psychosocial support and counseling

Local/Regional Recurrence
- recurrence in treated breast or ipsilateral axilla
- 1% per year up to maximum of 15% risk of developing contralateral malignancy
- 5x increased risk of developing metastases

Metastasis
- bone > lungs > pleura > liver > brain
- treatment is palliative: hormone therapy, chemotherapy, radiation

Twenty-year Follow-up of a Randomized Study comparing Breast-conserving Surgery with Radical Mastectomy for Early Breast Cancer
*N*EJM 2002;16:1227-1232

**Background:** Women enrolled in a randomized trial to compare the efficacy of radical mastectomy (RM) with that of breast-conserving surgery (BCS) were followed over a 20-yr period for long-term outcomes including disease recurrence and survival.

**Methods:** From 1973-1980, 701 women with breast cancers measuring <2 cm in diameter were randomly assigned to undergo RM (n = 349) or BCS followed by radiotherapy to the ipsilateral breast (n = 352).

**Results:** Rates of ipsilateral disease recurrence were lower in patients treated with RM compared to BCS (crude cumulative incidence 2.3% versus 8.8% after 20 yr; P < 0.001). However, there was no significant difference in rates of contralateral breast malignancies, metastatic spread, or second primary malignancies between the two groups. All-cause mortality rates were 41.7% in the BCS group and 41.2% in the RM group (P = 0.8), with mortality rates due to breast cancer of 26.1% and 24.3% respectively (P = 0.8).

**Conclusion:** The long-term survival rate among patients treated with breast-conserving surgery and adjuvant radiotherapy is the same as that among patients treated with radical mastectomy.

There is no survival benefit of mastectomy over lumpectomy plus radiation for stage I and II disease.
Surgical Endocrinology

Thyroid and Parathyroid

- see Endocrinology, E20 and Otolaryngology, OT34-OT37

Thyroidectomy
- indications: thyroid cancer, symptomatic thyroid mass or goiter, medically refractory Graves' or hyperthyroidism
- contraindications: uncontrolled severe hyperthyroidism (i.e. Graves') due to risk of intraoperative or postoperative thyroid storm
- preoperative workup: thyroid ultrasound for thyroid nodules, fine needle aspiration for large nodules, ultrasound of the neck for lesions suspicious for papillary or medullary thyroid cancer, CT neck useful to rule out extension, vocal cord function
- complications: hypocalcemia secondary to hypoparathyroidism, recurrent/superior laryngeal nerve injury, neck hematoma, infection, thyrotoxic storm

Parathyroidectomy
- indications: symptomatic primary hyperparathyroidism due to effects of PTH on bone or kidneys, asymptomatic primary hyperparathyroidism with specific laboratory criteria (elevated serum Ca, marked hypercalciuria, Cr clearance less than 30% normal, bone density reduction with T score less than 2.5, age less than 50)
- contraindications: familial hypocalciuric hypercalcaemia
- preoperative workup: 99mTc sestamibi scanning, ± SPECT or CT, ultrasound
- complications: recurrent/superior laryngeal nerve injury, postoperative hypocalcemia, infection, bleeding

Adrenal Gland

- see Endocrinology, E29
- functional anatomy:
  - cortex: glomerulosa (mineralocorticoids), fasciculata (glucocorticoids), reticularis (sex steroids)
  - medulla: catecholamines (epinephrine, norepinephrine)
- types: functional (e.g. Cushing's syndrome, Conn's syndrome) or non-functional

INCIDENTALOMA
- adrenal mass discovered by investigation of unrelated symptoms

Epidemiology
- benign adenoma (38%) > metastases to adrenal (22%) >> cyst, carcinoma, pheochromocytoma, neuroblastoma
- metastasis to adrenal gland from: lung > breast, colon, lymphoma, melanoma, kidney
- peak incidence of carcinoma: females age 50-60, risk decreases with increasing age and male gender

Investigations
- MRI, CT: size >6 cm is best predictor of primary adrenal carcinoma (92% are >6 cm)
- functional studies:
  - pheochromocytoma: 24 h urine epinephrine, norepinephrine, metanephrine, normetanephrine, VMA (vanillylmandelic acid)
  - Cushing's: 24 h urine cortisol or 1 mg overnight dexamethasone suppression test
  - aldosteronoma: electrolytes, aldosterone:renin level, saline suppression test if appropriate
  - adrenal androgens: 17-OH progesterone, DHEAS
- FNA biopsy: if suspect metastasis to adrenal (must exclude pheochromocytoma first)
  - indicated if history of cancer or patient is smoker
  - iodocholesterol scintigraphy: may distinguish benign vs. malignant disease

Treatment
- functional tumour: resect
- non-functioning tumour:
  - >4 cm: resect
  - <4 cm: follow-up imaging in 6-12 mo, resect if >1 cm enlargement
Pancreas

INSULINOMA
- Tumour that secretes insulin
- Most common pancreatic endocrine neoplasm; 10% associated with MEN1 syndrome

Clinical Features
- Whipple’s triad
- Palpitations, trembling, diaphoresis, confusion, seizure, personality changes

Investigations
- Bloodwork: decreased serum glucose and increased serum insulin and C-peptide
- U/S, CT: Insulinomas evenly distributed throughout head, body, tail of pancreas

Treatment
- Only 10% are malignant
- Enucleation of solitary insulinomas may be done endoscopically
- Tumours >2 cm located close to the pancreatic duct may require pancreatectomy or pancreaticoduodenectomy

GASTRINOMA
- Tumour secreting gastrin; cause of Zollinger-Ellison syndrome

Clinical Features
- Abdominal pain, peptic ulcer disease, severe esophagitis
- Multiple ulcers in atypical locations refractory to antacid therapy

Investigations
- Bloodwork: serum gastrin levels (usually >1000 pg/mL), secretin stimulation test
- U/S, CT: 70-90% found in Passaro’s triangle (head of pancreas, duodenum, lymphatic bed posterior and superior to the duodenum)
- Octreotide scintigraphy scan

Treatment
- 50% are malignant
- Surgical resection of tumour dependent on location
- Non-surgical treatment: chemotherapy, somatostatin analogues, interferon, chemoembolization
- If inoperable vagotomy can be performed for symptomatic control

VASOACTIVE INTESTINAL PEPTIDE-SECRETING TUMOUR
- Tumour secreting vasoactive intestinal peptide (VIP); commonly located in the distal pancreas and most are malignant when diagnosed

Clinical Features
- Severe watery diarrhea causing dehydration, weakness, electrolyte imbalance

Investigations
- Bloodwork: serum VIP levels
- U/S, CT

Treatment
- Somatostatin analogues
- Surgical resection/palliative debulking
# Pediatric Surgery

<table>
<thead>
<tr>
<th>Condition</th>
<th>Epidemiology and Risk Factors</th>
<th>Pathophysiology</th>
<th>Clinical Features and History</th>
<th>Physical Manifestations</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrocele</strong> (see Urology U29)</td>
<td>1-2% of live births Present at birth, majority close spontaneous by 1 yr M:F = 6:1 Prematurity</td>
<td>Communicating hydroceles: processus vaginalis fails to close with small opening for fluid to move freely between peritoneal cavity through patent processus (if opening progresses to allow passage of intestine, it is a hernia)</td>
<td>Painless scrotal mass Communicating hydroceles increase in size with standing or Valsalva, may be absent in the morning and large in the evening</td>
<td>Transillumination suggests hydrocele Silk glove sign: gently palpating hydrocele sac over pubic tubercle feels like rubbing silk on silk</td>
<td>U/S if suspect pathology</td>
<td>Most resolve spontaneously by 1 yr Surgical repair: – Persistence &gt; 2 yr – Pain – Fluctuating in size which suggests communication – Cosmetic reasons – Infection</td>
<td>&lt;2% recurrence</td>
</tr>
<tr>
<td><strong>Hypertrophic Pyloric Stenosis</strong></td>
<td>0.03-1.0% of live births Can present at 1-20 wk, most commonly at 6-8 wk M:F = 4:1 Early erythromycin exposure (&lt;13 d old)</td>
<td>Acquired pyloric circular muscle hypertrophy results in gastric outlet obstruction Hypovolemia caused by emesis of gastric content causes hypochloric aciduria Electrolyte exchange based volume retention in kidneys results in paradoxical aciduria</td>
<td>Projectile non-bilious vomiting Vomiting 30-60 min after feeds Hungry after vomiting Dehydration (variable severity)</td>
<td>Smooth oblong 1-2 cm mass palpable above umbilicus, “olive” Visible left-to-right gastric contraction “waves” after feeding</td>
<td>Electrolytes (assess hypochlorhemia, hypochloremia) U/S shows pyloric length &gt;14 mm, muscle thickness &gt;4 mm Upper GI series necessary only when U/S unavailable or non-diagnostic will show “string sign”</td>
<td>Fluid resuscitate with normal saline, correct electrolyte and acid/base abnormalities with D5, 1/2NS + 20 mEq/L KCl at maintenance rate. NG tube decompression unnecessary, if severe, Pyloromyotomy, open (Ramstedt vs. transumbilical or laparoscopic approach) Alternative therapies such as TPN/Wit or atropine impractical due to long time course of effect</td>
<td>Pyloromyotomy curative</td>
</tr>
<tr>
<td><strong>Congenital Diaphragmatic Hernias</strong></td>
<td>1 in 2000 to 5000 live births Presents within hours of life although some cases of delayed presentation M = F &gt;10% are associated with other congenital anomalies Prenatal diagnosis common</td>
<td><strong>Left-sided</strong>: small bowel, large bowel, stomach and solid visceras (spleen, left lobe of liver) herniate into thorax Early respiratory distress Cyanosis Scaphoid abdomen Prenatal diagnosis</td>
<td>Decreased air entry ± bowel sounds in the chest Displaced heart sounds</td>
<td>Prenatal US/MRI ABG CXR (bowel loops in hemithorax, shifted heart) Echocardiography Genetic consultation if warranted</td>
<td>Prenatal US/MRI</td>
<td>Intubate Orogastric suction Period of respiratory stabilization due to associated pulmonary hypoplasia (may require extracorporeal membrane oxygenation). Surgical repair after stable by hemia reduction and closure of diaphragmatic defect – open vs. thorascopic vs. laparoscopic with or without prosthetic or muscular patch depending on size of defect</td>
<td>Later presentations have better outcomes Hearing deficit (40%) Associated GERD MSK defects – chest wall and scoliotic defects a potential complication of thoracotomy. Need for long term surveillance for potential recurrence Failure to thrive Chronic lung disease if severe hypoplasia</td>
</tr>
</tbody>
</table>

---

**Table 22. Pediatric Surgery**

**Hypertrophic Pyloric Stenosis**

Non-bilious emesis in infant is the classic presentation.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Epidemiology and Risk Factors</th>
<th>Pathophysiology</th>
<th>Clinical Features and History</th>
<th>Physical</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meckel’s Diverticulum</td>
<td>Most common remnant of vitelline duct that connects yolk sac with primitive midgut</td>
<td>Failure of vitelline duct to regress 5-7 wk in uterus, 50% contain heterotopic tissue (e.g. gastric mucosa, ectopic pancreas); other associated anomalies include omphalomesenteric fistula, umbilical sinus, umbilical cyst, fibrous band</td>
<td>Bright red blood per rectum (heterotopic gastric mucosa in Meckel’s causing mucosal ulceration and bleeding in adjacent small bowel mucosa) Abdominal sepsis (Meckel’s diverticulitis ± perforation) Small bowel volvulus around fibrous band</td>
<td>Tenderness (lower abdomen) near umbilicus</td>
<td>AXR</td>
<td>Stabilize, resection by laparotomy or laparoscopy ± incidental appendectomy</td>
<td>Resection curative</td>
</tr>
</tbody>
</table>

**Malrotation**

1/500 live births 1/3 present by 1 wk of age, 3/4 by 1 mo of age, 80% by 1 yr of age M:F = 1:1; higher incidence among patients with cardiac anomalies, heterotaxy syndromes Failure of gut to normally rotate around superior mesenteric artery with associated abnormal intestinal attachments and anatomic positions Represent a spectrum of rotational abnormalities including complete non-rotation (which is not at high risk for volvulus) Bilious emesis is THE cardinal sign, especially if abdomen nondistended. If bilious emesis in ill child with distended abdomen, consider surgical exploration to rule out volvulus. Racial bleed (late/ominous signs) Intermittent symptoms Bilious drainage from NG tube Tachycardic, pale Diaphoretic Flat abdomen Tenderness AXR: obstruction of proximal small bowel, double-bubble sign, intestinal wall thickened Immediate UGI. Dilated duodenum, duodenojejunal segment (Ligament of Treitz) right of midline and not fixed posteriorly over spinal column, “corkscrew” sign indicating volvulus U/S: “whirlpool” sign, abnormal SMA/SMV relationship indicates UGI to rule out rotational anomalies IV antibiotics Fluid resuscitation EMERGENT LAPAROTOMY Ladd procedure: counter-clockwise reduction of midgut volvulus, division of Ladd’s bands, division of peritoneal attachments between cecum and abdominal wall that obstruct duodenum, broadening of the mesentery (open folded mesentery i.e. a book and divide congenital adhesions), ± appendectomy Positioning the bowel into non-rotation (small bowel in right abdomen, large bowel in left abdomen) Mortality related to length of bowel volvulus: 10% necrosis – 100% survival rate, 75% necrosis – 25% survival rate Recurrence 2-6%

**Gastrochisis**

1:2000 live births Antenatal diagnosis common Increases with younger maternal age and associated with IUGR M:F = 1:1 Defect of abdominal wall, with free extrusion of intestine into amniotic cavity No specific environmental factor identified Defect in embryogenesis unclear Not associated with genetic syndromes 10% with intestinal atresia Some cases associated with short bowel syndrome due to antenatal volvulus and necrosis of herniated bowel Hollow viscera (stomach, small and large bowels) Defect lateral to cord (usually right) Bowel may be inflamed, thickened, matted, foreshortened Defect size variable Hollow viscera (stomach, small and large bowels, often liver) Cord on the sac Prenatal ultrasound, elevated MS-AFP NG decompression IV fluids IV antibiotics Keep viscera moist and protected until surgical reduction with primary abdominal closure or staged closure with site May have bowel dysmotility requiring motility medications >90% survival rate

**Omphalocele**

1:5000 live birth Antenatal diagnosis common Lower gestational age Increased maternal age M:F = 1.5:1 Defect of abdominal wall, with extrusion of sac covered viscera (amnion, Wharton’s jelly, peritoneum) Duhameel’s theory – failure of body wall morphogenesis Associated with genetic syndromes 30-70% (e.g. Pentalogy of Cantrell, congenital heart disease, Beckwith-Wiedemann syndrome) Associated pulmonary hypoplasia Hollow viscera (stomach, small and large bowels, often liver) Cord on the sac Prenatal ultrasound Elevated MS-AFP NG decompression IV fluids IV antibiotics Small defect (<2 cm): Primary closure Medium (2-4 cm) and large (>4 cm) defects best treated with silver sulfadiazine to promote epithelialization coupled with compression dressing to allow gradual reduction, followed by future repair with or without mesh 40-70% survival rate Higher survival rates most likely related to antenatal mortality of fetuses with giant omphaloceles

---

Bilious vomiting in infant is a life-threatening emergency secondary to midgut volvulus until proven otherwise.

**Rule of 2s for Meckel’s Diverticulum**
- 2% of the population
- 2:1 male-to-female ratio
- Symptomatic in 2% of cases
- Found within 2 feet (10-90 cm) of the ileocecal (IC) valve
- 2 inches in length
- 2 inches in diameter
- 2 types of tissue (gastric, pancreatic)
- Often present by 2 yr of age
<table>
<thead>
<tr>
<th>Condition</th>
<th>Epidemiology and Risk Factors</th>
<th>Pathophysiology</th>
<th>Clinical Features and History</th>
<th>Physical</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Umbilical Hernias</strong></td>
<td>Incidence 2-14% Increases with prematurity Decreases with increasing age</td>
<td>Incapable closure of peritoneal and fascial layers within umbilicus by 5 yr</td>
<td>Majority asymptomatic Majority spontaneously resolve by age 5 Incarceration prior to age 5 very rare Most symptoms occur in late adolescence or adulthood</td>
<td>Protrusion from umbilicus Important to differentiate from less common abdominal wall hernias that don’t spontaneously resolve (e.g. epigastric hernias) Most umbilical fascial defects &gt; 1.5 cm in infancy will not close spontaneously</td>
<td>None if uncomplicated Repair if not spontaneously closed by age 5 Earlier repair of large “proboscoid” hernias with extensive skin stretching may be warranted for cosmetic reasons Simple primary closure of fascial defect</td>
<td>Low risk of recurrence</td>
<td></td>
</tr>
</tbody>
</table>
| **Intestinal Atresia** | Incidence 2-14% May be antenatally diagnosed by dilated bowel loops or “double-bubble” sign on x-ray for duodenal atresia Decreasing with increasing age                                                                                      | Duodenal – failure of bowel to recanalize after endodermal epithelium proliferation (wk 8-10) Jejunal/ileal – acquired as result of vascular disruption  
isoamnic necrosis  
resorption of necrotic tissue  
blind distal and proximal ends Colon – mechanism unknown, thought to be similar to small bowel atresia | Gastric distension and vomiting (usually bilious) Duodenal – may be associated with other anomalies  
(tracheoesophageal fistula, cardiac, renal and vertebral anomalies), 24-28% have Down syndrome Jejunal/ileal – within 2 d of birth, may be associated with cystic fibrosis Colonic – within 3 d of birth | Complete physical Special notice to abdominal exam Perineum and anus Include evaluation of respiratory distress and signs of volume depletion Congenital anomalies Jaundice | Contrast enema ± USI with small bowel follow through (SBFT) Group and screen INR and PTT if for surgery | NPO NG tube decompression Fluid resuscitate TPN Broad spectrum antibiotics Duodenal – duodenoduodenostomy or duodenojejunostomy Jejunal/ileal – primary anastomosis; or if atresia associated with short bowel then may create end stoma or defer surgery for bowel lengthening procedures Colonic – primary anastomosis | Long term survival Duodenal – 86% Jejunal/ileal – 84% Colonic – 100% |
| **Hirschsprung’s Disease** | 1:5000 births M:F = 3:1-4:1, approaches 1:1 when whole colon involved Can have aganglionosis of small bowel as well Familial Hirschsprung’s in < 5% of cases                                                                 | Defect in migration of neurocrest cells to intestine resulting in aganglionic bowel that fails to peristate and internal sphincter that fails to relax (internal anal sphincter achalasia) causing functional and partial mechanical obstruction, respectively always starts in the rectum and variable involvement proximally; RET mutation | Failure to pass meconium spontaneously within 48 h of life is the classic history (95% of normal children should pass meconium within 24 h, and the remaining 5% within 46 h) Symptoms of bowel obstruction: 
abdominal distension, constipation, bilious emesis Enterocolitis/sepsis Failure to thrive | ± abdominal distension Squat/burst sign Rectal biopsy (gold standard) – look for aganglionosis and neural hypertrophy AXR Contrast enema to find narrow rectum and transition zone Anal manometry unreliable in infants – classic finding is absence of rectoanal inhibitory reflex | Surgical resection of aganglionic intestinal segment and anastomosis of remaining intestine to anus Either in newborn period or staged if extensive aganglionosis | Most have normal/ near-normal anorectal function Complications: Fecal incontinence and constipation, post-operative enterocolitis (medical emergency if progresses to sepsis) |
| **Cryptorchidism**   | 2-5% of term males – most of these descend spontaneously by 6 mo of age 1% of males do not spontaneously descend                                                                                                                                 | Idiopathic Descent is mediated by descendin which is created in response to testosterone Descent usually begins at 28 wk | Palpable testicle within inguinal canal or testicle which can be milked down into scrotum (called retractile testis) Occasionally no palpable testis as it is intra-abdominal Consider other congenital abnormalities | Bi-annual testicular exam with palpation Distinguish truly undescended testis from retractile testis (which is “high” testes due to hypertrophic cremasteric muscles) | Depends on age of presentation U/S or MRI exam if no palpable testis Older child: LH, FSH, MIS, hCG stimulation test for gonadotropin production Infant: U/S, FSH, LH, karyotyping, MIS, 17-Hydroxyprogesterone | InCG to stimulate testosterone production and desent Orchidopexy – especially if descended by age 6 mo-2 yr | Orchidopexy Decreased risk of torsion and blunt trauma to testicle No effect on malignant potential of testicle Descent can preserve spermatogenesis if performed by 1 yr of age 1/1000 risk for testicular cancer (population risk is 1/4000) |
### Table 22. Pediatric Surgery (continued)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Epidemiology and Risk Factors</th>
<th>Pathophysiology</th>
<th>Clinical Features and History</th>
<th>Physical Features</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intussusception</strong></td>
<td>Most common cause of bowel obstruction between the ages of 6-36 mo. 26/100,000 newborns. More common in males (3:2). Pathologic lead points: enlarged Peyer’s patches due to viral infections.</td>
<td>Idiopathic is most common. Usually starts at ileocecal junction. Telescoping of bowel into itself causing an obstruction and vascular compromise.</td>
<td>Acute onset of abdominal pain which is classic episodic. &quot;colicky&quot; pain. Vomiting of bile or bilious stool. Abdominal mass. Current-jelly stool suggests mucosal necrosis and sloughing.</td>
<td>Abdominal exam</td>
<td>X-ray</td>
<td>If peritonitis, then consider operative management. Non-operative management involves reduction via air contrast enema. Operative reduction can be done open or laparoscopically. Resection of involved colon if failure to reduce or bowel appears compromised.</td>
<td>10% recurrence rate. If recurrent = more likely non-idiopathic. In successfully reduced by enema in older children allow 2 wk resolution of edema then perform SBFT to rule out pathologic lead points.</td>
</tr>
<tr>
<td><strong>Tracheoesophageal Fistula (TEF)</strong></td>
<td>Associated anomalies in 50%: VACTERL association (see Pediatrics. P41).</td>
<td>Varies with type of fistula. May have history of maternal polyhydramnios. May present after several months (if no associated esophageal atresia) of non-bilious vomiting, coughing, cyanosis of mass may be noted.</td>
<td>X-ray: anatomic abnormalities, NG tube curled in pouch.</td>
<td>Investigate for other congenital anomalies, early repair by surgical ligation to prevent lung damage and maintain nutrition and growth.</td>
<td>Complications: pneumonia, sepsis, reactive airways disease. Following repair: esophageal stenosis and strictures at repair site, gastroesophageal reflux and poor swallowing (i.e. dysphagia, regurgitation).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inguinal Hernias</strong></td>
<td>5% of all term newborns. 2x risk and more likely bilateral if pre-term. More common in males (4:1). Low birth weight increases risk. 1/5 inguinal hernias will become incarcerated if patient is &lt; 1 yr old. Incarceration is more common in females. Associated with other conditions: androgen insensitivity, connective tissue diseases.</td>
<td>All infant hernias are indirect. Descent of the internal inguinal ring through the patent inguinal canal.</td>
<td>Physical exam is gold standard. U/S only if physical exam uncertain (e.g. polyhydramnios).</td>
<td>Manual reduction – to relieve acute symptoms. Herniorraphy – definitive treatment by reduction of herniated contents and high ligation of sac for indirect hernias.</td>
<td>10% recurrence rate. If recurrent = more likely non-idiopathic. In successfully reduced by enema in older children allow 2 wk resolution of edema then perform SBFT to rule out pathologic lead points.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Skin Lesions

- see Dermatology, D5; Emergency, ER17; Plastic Surgery, PL5

All inguinal hernias of infancy and childhood require repair at the earliest convenience. Emergent repair if incarcerated/strangulated!
Common Medications

Antimicrobials
- dimenhydrinate (Gravol®) 25-50 mg PO/IV/IM q4-6h pm
- prochlorperazine (Stemetil®) 5-10 mg PO/IV/IM bid-tid pm
- metoclopramide (Maxeran®) 10 mg IV/IM q2-3h pm, 10-15 mg PO qid (30 min before meals and qhs)
- ondansetron (Zofran®) 4-8 mg PO qd pm
- granisetron (Kytril®) 1 mg PO bid (for nausea from chemotherapy/radiation)

Analgesics
- acetaminophen ± codeine (Tylenol® #3,plain) 1-2 tabs q4-6h PO/PR pm
- morphine 2.5-10 mg IM/SC q 4-6h pm + 1-2 mg IV q1h pm for breakthrough
- ketorolac (Toradol®) 30-60 mg IM/IV q6h pm
- Percocet® (acetaminophen/oxycodeine, 325/5 mg) 1-2 tabs PO q4-6h pm

DVT Prophylaxis
- heparin 5000 units SC bid, if cancer patient then heparin 5000 units SC tid
- dalteparin (Fragmin®) 5000 units SC daily
- enoxaparin (Lovenox®) 40 mg SC daily

Antidiarrheals
- loperamide (Imodium®) 4 mg PO initially, then 2 mg PO after each loose stool up to 16 mg/d
- diphenoxylate + atropine (Lomotil®) 2 tabs/10 mL PO qid

Laxatives
- sennosides (Senokot®) 1-2 tabs qhs
- docusate sodium (Colace®) 100 mg PO bid
- glycerine suppository 1 tab PR pm
- lactulose 15-30 mL PO qid pm
- milk of magnesia (MOM) 30-60 mL PO qid pm
- bisacodyl (Dulcolax®) 10-15 mg PO pm

Sedatives
- zopiclone (Imovane®) 5-7.5 mg PO qhs pm
- lorazepam (Ativan®) 0.5-2 mg PO/SL qhs pm

Antibiotics
- cefazolin (Ancef®) 1 g IV/IM on call to OR or q8h – GP except Enterococcus, GN only
- cefalexin (Keflex®) 250-500 mg PO qid – Listeria, GP except Enterococcus, GN only
- ceftriaxone 1-2 g IM/IV q24h – broad covering including Pseudomonas
- ampicillin 1-2 g IV q4-6h – Listeria, GP (Enterococcus) except Streptococcus and E. coli, oral anaerobes except Bacteroides
- gentamicin 3-5 mg/kg IM/IV divided q8h; monitor creatinine, gentamicin levels – GN including Pseudomonas
- ciprofloxacin 400 mg IV q12h, 500 mg PO bid – GN including Pseudomonas
- metronidazole (Flagyl®) 500 mg PO/IV bid, (500 mg PO tid for C. difficile) – anaerobes
- clindamycin 600-900 mg IV q8h, 150-400 mg PO qid – GP except Enterococcus, anaerobes

Over-the-Counter Medications
- Pepcid-Bismol® (bismuth subsalicylate) 2 tabs or 30 mL PO q30min-1h up to 8 doses/d
- Pepto-Bismol® (aluminum hydroxide and magnesium hydroxide) 2 tabs or 30 mL PO q30min-1h up to 8 doses/d
- Alka-Seltzer® (ASA + citrate + bicarbonate) 2 tabs in 4 oz water PO q4h pm, max 8 tabs
- Maalox® (aluminum hydroxide + magnesium hydroxide) 10-20 mL or 1-4 tabs PO pm
- Tums® (calcium carbonate) 1-3 g PO q2h pm
- Rolaid® (calcium carbonate and magnesium hydroxide) 2-4 tabs PO q1h pm, max 12 tabs/d

References

Geriatric Medicine

Evelyn Cheung and Christopher Yarnell, chapter editors
Grace Lam and Hamed Nazzari, associate editors
Gautam Goel, EBM editor
Dr. Barry J. Goldlist, staff editor

Seniors in Canada and the U.S. ............ 2
Health Status

Physiology and Pathology of Aging ........ 2

Differential Diagnoses of Common Presentations ........ 3
Constipation
Delirium, Dementia and Depression
Elder Abuse
Falls
Frailty (Failure to Thrive)
Incontinence
Gait Disorders
Hazards of Hospitalization
Hypertension
Immobility
Immunizations
Malnutrition
Osteoporosis
Presbycusis
Pressure Ulcers

Driving Competency .......................... 10
Reporting Requirements
Conditions that may Impair Driving

Health Care Institutions .................... 11

Palliative and End-of-Life Care ............ 12
Principles and Quality of Life
End-of-Life Care Discussions
Power of Attorney
Instructional Advance Directives
Symptom Management

Geriatric Pharmacology ..................... 13
Pharmacokinetics
Pharmacodynamics
Polypharmacy
Inappropriate Prescribing in the Elderly

Common Medications ...................... 15

Landmark Geriatric Trials .................. 16

References .............................. 17

Acronyms
ACEI angiotensin converting enzyme inhibitor
ARB angiotensin receptor blocker
BPH benign prostatic hypertrophy
CABG coronary artery bypass graft
CHF congestive heart failure
C0 cardiac output
CVA cerebrovascular accident
DHPRCB dihydropyridine calcium channel blocker
ESAS Edmonton symptom assessment scale
FAP familial adenomatous polyposis
GCA giant cell arteritis
HR heart rate
IBD inflammatory bowel disease
IBS irritable bowel syndrome
ICP intracranial pressure
LOC level of consciousness
MMSE mini mental status examination
NE norepinephrine
NSTEMI non ST elevation myocardial infarction
PPI proton pump inhibitor
PPS palliative performance scale
PTH parathyroid hormone
RA rheumatoid arthritis
SLE systemic lupus erythematosus
UTI urinary tract infection
Seniors in Canada and the U.S.

Health Status

Table 1. Causes of Mortality and Morbidity in Canadian and American Seniors

<table>
<thead>
<tr>
<th>Mortality (Can\textsuperscript{1}/U.S.\textsuperscript{2})</th>
<th>Morbidity\textsuperscript{1,2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diseases of the heart and circulatory system (30.0/27.0%)</td>
<td>1. Hypertension</td>
</tr>
<tr>
<td>2. Malignant neoplasms (20.0/22.0%)</td>
<td>2. Arthritis</td>
</tr>
<tr>
<td>3. Cerebrovascular disease (8.0/6.0%)</td>
<td>3. Heart disease</td>
</tr>
<tr>
<td>4. Chronic lower respiratory disease (5.1/7.0%)</td>
<td>4. Diabetes</td>
</tr>
<tr>
<td>5. Accidents (2.9%)</td>
<td>5. Ulcers</td>
</tr>
<tr>
<td>6. Alzheimer’s (4.2/5.0%)</td>
<td>6. Stroke</td>
</tr>
<tr>
<td>7. Asthma</td>
<td>7. Asthma</td>
</tr>
<tr>
<td>8. Allergies</td>
<td>8. Allergies</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Statistics Canada, 2005
\textsuperscript{2}Minino AM, 2009

Physiology and Pathology of Aging

Definition

- major categories of impairment that appear with old age and affect the physical, mental and social domains of the elderly, usually due to many predisposing and precipitating factors, rather than a single cause

Table 2. Changes Occurring Frequently with Aging

<table>
<thead>
<tr>
<th>System</th>
<th>Physiological Changes</th>
<th>Pathological Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td>Decreased wakefulness, brain mass, cerebral blood flow</td>
<td>Increased insomnia, neurodegenerative disease, stroke, decreased reflex response</td>
</tr>
<tr>
<td>Special Senses</td>
<td>Decreased lacrimal gland secretion, lens transparency, dark adaptation, decreased sense of smell and taste</td>
<td>Increased glaucoma, cataracts, macular degeneration, presbycusis, presbyopia, tinnitus, vertigo, oral dryness</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Increased sBP, dBP, decreased HR, CO</td>
<td>Increased atherosclerosis, CAD, MI, CHF, hypertension, arrhythmias</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Increased tracheal cartilage calcification, mucus gland hypertrophy Decreased elastic recoil, mucociliary clearance, pulmonary function reserve</td>
<td>Increased COPD, pneumonia, pulmonary embolism</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Increased intestinal villous atrophy Decreased esophageal peristalsis, gastric acid secretion, liver mass, hepatic blood flow, calcium and iron absorption</td>
<td>Increased cancer, diverticulitis, constipation, fecal incontinence, hemorrhoids, intestinal obstruction</td>
</tr>
<tr>
<td>Renal and Urologic</td>
<td>Increased proteinuria, urinary frequency Decreased renal mass, creatinine clearance, urine acidification, hydroxylation of vitamin D, bladder capacity</td>
<td>Increased urinary incontinence, nocturia, BPH, prostate cancer, pyelonephritis, nephrolithiasis, UTI</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Decreased androgen, estrogen, sperm count, vaginal secretion Decreased ovary, uterus, vagina, breast size</td>
<td>Increased breast and endometrial cancer, cystocele, rectocele, atrophic vaginitis</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Increased NE, PTH, insulin, vasopressin Decreased thyroid and adrenal corticosteroid secretion</td>
<td>Increased DM, hypothyroidism, stress response</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Increased calcium loss from bone Decreased muscle mass, cartilage</td>
<td>Increased arthritis, bursitis, osteoporosis, muscle weakness with gait abnormalities, polymyalgia rheumatica</td>
</tr>
<tr>
<td>Integumentary</td>
<td>Atrophy of sebaceous and sweat glands Decreased epidermal and dermal thickness, dermal vascularity, melanocytes, collagen synthesis</td>
<td>Increased lentigo, cherry hemangiomas, pruritus, seborrheic keratosis, herpes zoster, decubitus ulcers, skin cancer</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>None</td>
<td>Increased depression, dementia, delirium, suicidality, substance abuse, anxiety, insomnia</td>
</tr>
</tbody>
</table>
**Differential Diagnoses of Common Presentations**

**Constipation**
- see *Gastroenterology*, G24

**Definition**
- less than 3 bowel movements in one week and/or hard stools, straining, sense of blockage, needing manual maneuvers or incomplete evacuation on more than 25% of occasions for at least 12 wk (does not need to be consecutive)

**Epidemiology**
- chronic constipation increases with age (up to 1/3 of patients >65 yr experience constipation)

**Pathophysiology**
- impaired rectal sensation (increased rectal distention required to stimulate the urge to defecate)
- colorectal dysmotility

**Treatment**
- non-pharmacological
  - increase fibre intake
  - ensure adequate fluid intake
  - discourage chronic laxative use
  - engage in regular exercise
  - review medication regime, reduce dosages or substitute
- pharmacologic
  - see *Common Medications*, GM15

**Risk Factors for Constipation in the Elderly**
- Immobility
- Diet: low fibre/calorie diet, dehydration
- Medications:
  - Polypharmacy
  - Drugs: narcotics, calcium channel blockers, anticholinergics
- GI: obstructive lesions (bowel obstruction, cancer, diverticular disease, IBD, strictures, uterine prolapse), altered colonic motility (IBS, colonic inertia)
- Neurological: spinal cord injury, Parkinson’s disease, stroke, autonomic dysfunction
- Metabolic: diabetes, hypokalemia, hypercalcemia
- Psychiatric: depression, dementia

**Figure 1. Treatment algorithm for the management of chronic constipation in the elderly**
Adapted from: Clin Interv Aging 2010;5:163-171

**Delirium, Dementia and Depression**
- see *Psychiatry*, PS19, PS20, PS9 and *Neurology*, N17

**Definition**
- pathologic decrease in memory, language, or executive function

**Differential Diagnosis**
- delirium, dementia, or pseudodementia of depression
Table 3. Differentiating the Three Ds of Cognitive Impairment

<table>
<thead>
<tr>
<th></th>
<th>Dementia</th>
<th>Delirium</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Gradual</td>
<td>Acute (hours-days)</td>
<td>Subacute</td>
</tr>
<tr>
<td>Duration</td>
<td>Months-years</td>
<td>Days-weeks</td>
<td>Variable</td>
</tr>
<tr>
<td>Natural History</td>
<td>Progressive, usually irreversible</td>
<td>Fluctuating, reversible</td>
<td>Recurrent, Usually reversible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High morbidity/mortality in very old</td>
<td></td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td>Normal</td>
<td>Fluctuating</td>
<td>Normal</td>
</tr>
<tr>
<td>Attention</td>
<td>Intact initially</td>
<td>Decreased, wandering</td>
<td>Difficulty concentrating</td>
</tr>
<tr>
<td>Orientation</td>
<td>Intact initially</td>
<td>Impaired, fluctuates</td>
<td>Intact</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Disinhibition, loss of ADL/IADLs, personality change</td>
<td>Severe agitation/retardation</td>
<td>Importuning, self-harm/ suicide</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>Normal</td>
<td>Fluctuates between extremes</td>
<td>Slowing</td>
</tr>
<tr>
<td>Sleep-Wake Cycle</td>
<td>Fragmented sleep at night</td>
<td>Reversed sleep-wake cycle</td>
<td>Early morning awakening</td>
</tr>
<tr>
<td>Mood and Affect</td>
<td>Decreased executive function, paucity of thought</td>
<td>Fluctuation preceded by mood changes</td>
<td>Concentration impaired</td>
</tr>
<tr>
<td>Cognition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory Loss</td>
<td>Recent, eventually remote</td>
<td>Marked recent</td>
<td>Recent</td>
</tr>
<tr>
<td>Language</td>
<td>Agnosia, aphasia, decreased comprehension, repetition</td>
<td>Dyssomia, dysgraphia, speech rambling, subject changes, incoherence</td>
<td>Not affected</td>
</tr>
<tr>
<td>Delusions</td>
<td>Compensatory</td>
<td>Nightmarish, poorly formed</td>
<td>Nihilistic, somatic</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Variable, Vacuous, bland</td>
<td>Visual common, frightening/bizarre</td>
<td>Self-deprecatory</td>
</tr>
</tbody>
</table>

Delirium Prevention in Elderly
- ensure optimal vision and hearing to support orientation (e.g. clean, appropriate eyewear and hearing aids)
- provide adequate nutrition and hydration (up in chair to eat and drink whenever feasible)
- encourage regular mobilization to build and maintain strength, balance and endurance
- avoid unnecessary medications and monitor for drug interactions
- avoid bladder catheterization if possible
- ensure adequate sleep

Elder Abuse

Definition
- includes physical abuse, sexual abuse, emotional/psychological abuse, financial abuse, abandonment and neglect
- elder abuse is a criminal offence under the Criminal Code of Canada
- in the U.S., most states have criminal penalties for elder abuse

Epidemiology
- in Canada, approximately 4% of elderly persons living in private homes have suffered abuse
- in the U.S., estimates of the frequency of elder abuse range from 3-8%
- physician reporting is mandatory only in Newfoundland, Nova Scotia and Prince Edward Island; in Ontario, only abuse occurring in nursing homes is mandatory to report
- insufficient evidence to include/exclude screening in the Periodic Health Exam

Risk Factors

Table 4. Risk Factors for Elder Abuse

<table>
<thead>
<tr>
<th>Situational Factors</th>
<th>Victim Characteristics</th>
<th>Perpetrator Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolation</td>
<td>Physical or emotional dependence on caregiver</td>
<td>Related to victim</td>
</tr>
<tr>
<td>Unstable or unsafe living arrangements</td>
<td>Lack of close family ties</td>
<td>Living with victim</td>
</tr>
<tr>
<td>Lack of family, community or living facility resources for additional care</td>
<td>History of family violence</td>
<td>Long duration of care for victim (mean 0.5 yr)</td>
</tr>
<tr>
<td></td>
<td>Dementia or recent deterioration in health</td>
<td>Financial, marital, occupational or other stressors</td>
</tr>
</tbody>
</table>
Caregiver Abuse Screen (CASE)

- **Instructions:**
  1. Answer “yes” to any of the following questions.
  2. Ask the person if the abuse is occurring.
  3. Do not answer “yes” to any of the following questions.
  4. Ask the person if the abuse is occurring.

- **Screening Tool:**
  1. Do you often feel you are being forced to act out of character or do things you feel badly about?
  2. Do you often feel you are being forced to act out of character or do things you feel badly about?
  3. Do you often feel you are being forced to act out of character or do things you feel badly about?
  4. Do you often feel you are being forced to act out of character or do things you feel badly about?
  5. Do you often feel you are being forced to act out of character or do things you feel badly about?
  6. Do you often feel you are being forced to act out of character or do things you feel badly about?
  7. Do you often feel you are being forced to act out of character or do things you feel badly about?

From: NICE. Case: Caregiver Abuse Screen. 2010. Reproduced with permission from NICE.

Management

- Assess safety and determine capacity to make decisions about living arrangements.
- Establish need for hospitalization or alternative accommodation (e.g., immediate risk of physical harm by self or caregiver).
- Involve multidisciplinary team (e.g., nurse, social worker, family members and physicians, including geriatrician, psychiatrist or family physician).
- Educate and assist caregiver, contact local resources (e.g., legal aid, crisis support, PSW, caregiver support groups).
- Interpret critical and lab findings that are key in exclusion, differentiation and diagnosis.

Falls

**Epidemiology**

- 30-40% of people >65 yr old and ~50% of people >80 yr old fall each year.
- Equally common between men and women, but more likely to result in injury in women.
- 5% of falls lead to hospitalization.
- 5-10% associated with serious injuries (e.g., hip fracture, head injury, laceration).
- 1-2% of falls associated with hip fracture.
- 15% die in hospital, 33% 1-yr mortality.
- Between 25-75% do not recover to previous level of ADL function.
- Mortality increases with age (171/100,000 in men >85 yr old) and type of injury (25% with hip fracture die within 6 mo).

**Etiology**

- Multifactorial.
- Extrinsic:
  - Environmental (e.g., home layout, lighting, stairs, footwear), accidental, abuse.
  - Medications/substances (e.g., alcohol).
- Intrinsic:
  - Orthostatic/syncopal.
  - Age-related changes and diseases associated with aging: musculoskeletal (arthritis, muscle weakness), sensory (visual, proprioceptive, vestibular), cognitive (depression, dementia, delirium, anxiety), cardiovascular (CAD, arrhythmia, MI, low BP), neurologic (stroke, decreased LOC, gait disturbances/ataxia), metabolic (glucose, electrolytes).
- Past history of a fall.

**Investigations**

- Directed by history and physical.
- Comprehensive geriatric assessment to identify all potential causes.
- CBC, electrolytes, BUN, creatinine, glucose, Ca++, TSH, B12, urinalysis, cardiac enzymes, ECG, CT head.

**Prevention**

- Multidisciplinary, multifactorial, health and environment risk factor screening and intervention programs in the community.
- Muscle strengthening, balance retraining and group exercise programs (e.g., tai chi).
- Home hazard assessment and modification (e.g., remove rugs, add shower bars, etc.).
- Prescription of vitamin D 1000 IU daily.
- Tapering or gradually discontinuation of psychotropic medication.
- Postural hypotension, heart rate, and rhythm abnormalities management.
- Eyesight and footwear optimization.
Table 5. Common Medical Conditions Associated with Failure to Thrive

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Cause of Failure to Thrive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Metastases, malnutrition, cachexia</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Chronic steroid use</td>
<td>Steroid myopathy, diabetes, osteoporosis, vision loss</td>
</tr>
<tr>
<td>Cirrhosis, hepatitis</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Depression, other psychiatric disorder</td>
<td>Major depression, psychosis, poor functional status, cognitive loss</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Malabsorption, poor glucose homeostasis, end-organ damage</td>
</tr>
<tr>
<td>Gastrointestinal surgery</td>
<td>Malabsorption, malnutrition</td>
</tr>
<tr>
<td>Hip, long bone fracture</td>
<td>Functional impairment</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Malabsorption, malnutrition</td>
</tr>
<tr>
<td>Myocardial infarction, congestive heart failure</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Recurrent UUT, pneumonia</td>
<td>Chronic infection, functional impairment</td>
</tr>
<tr>
<td>Rheumatologic disease (GCA, RA, SLE)</td>
<td>Chronic inflammation</td>
</tr>
<tr>
<td>Stroke</td>
<td>Dysphagia, depression, cognitive loss, functional impairment</td>
</tr>
<tr>
<td>Tuberculosis, other systemic infection</td>
<td>Chronic infection</td>
</tr>
</tbody>
</table>

Source: Clin Geriat Med 1997;13:769-778
FECAL INCONTINENCE

Epidemiology
- second leading cause of nursing home placement

Etiology
- commonly multifactorial
  - structural abnormalities
  - trauma (e.g. prior vaginal delivery, surgery)
  - prolapse
  - tumour/trauma (e.g. brain, spinal cord, cauda equina)
  - overflow (e.g. encopresis, impaction)
- functional abnormalities
  - neurologic conditions – neuropathy, multiple sclerosis, stroke, dementia
- others
  - constipation with overflow may be a factor
  - psychosis (willful soiling)
  - age >80 yr: decreased external sphincter strength and weak anal squeeze, increased rectal compliance, decreased resting tone and internal sphincter, impaired anal sensation
  - medications (e.g. laxatives, anticholinergics, antidepressants, caffeine, muscle relaxants)

Investigations (if cause not apparent from history and physical)
- differentiate true incontinence from frequency and urgency (i.e. IBS, IBD)
- stool studies
- endorectal ultrasound
- colonoscopy, sigmoidoscopy, anoscopy
- anorectal manometry/functional testing

Management
- diet/bulking agent if stool is liquid or loose
- disimpaction, prevent impaction
- anti-diarrheal agents (e.g. loperamide)
- regular defecation program in patients with dementia
- counsel about biofeedback therapy (retraining of pelvic floor muscles)
URINARY INCONTINENCE

- see Urology, U6

Epidemiology

- 15-30% prevalence dwelling in community and at least 50% of institutionalized seniors
- morbidity: cellulitis, pressure ulcers, urinary tract infections, falls with fractures, sleep deprivation, social withdrawal, depression, sexual dysfunction
- not associated with increased mortality

Pathophysiology

- not a normal part of aging, urinary incontinence is a loss of control due to a combination of:
  - genitourinary pathology: increased post-void residual volume, increased involuntary bladder contractions (urge incontinence)
  - age-related changes: decreased bladder capacity
  - comorbid conditions and medications
  - functional impairment
- in elderly women: decline in bladder outlet and urethral resistance pressure promoting stress incontinence
- in elderly men: prostatic enlargement can cause overflow and urge incontinence

## Gait Disorders

- see Neurology, N29

## Hazards of Hospitalization

<table>
<thead>
<tr>
<th>Sequela</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnutrition</td>
<td>No dietary restrictions (except diabetes), assistance, dentures if necessary, sitting in a chair to eat</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Medication review, remove environmental barriers, discontinue use of catheter</td>
</tr>
<tr>
<td>Depression</td>
<td>Routine screening</td>
</tr>
<tr>
<td>Adverse drug event</td>
<td>Medication review</td>
</tr>
<tr>
<td>Confusion/delirium</td>
<td>Orientation, visual and hearing aids, volume repletion, noise reduction, early mobilization, medication review, remove restraints</td>
</tr>
<tr>
<td>Pressure ulcers</td>
<td>Low-resistance mattress, daily inspection, repositioning every 2 h</td>
</tr>
<tr>
<td>Infection</td>
<td>Early mobilization, remove unnecessary IV lines, catheters, NG tubes</td>
</tr>
<tr>
<td>Falls</td>
<td>Appropriate footwear, assistive devices, early mobilization, remove restraints, medication review</td>
</tr>
<tr>
<td>Hypertension/dehydration</td>
<td>Early recognition and repletion</td>
</tr>
<tr>
<td>Diminished aerobic capacity/loss of muscle strength/contractures</td>
<td>Early mobilization</td>
</tr>
<tr>
<td>Decreased respiratory function</td>
<td>Incentive spirometry, physiotherapy</td>
</tr>
</tbody>
</table>

## Hypertension

- see Family Medicine, FM37

- 60-80% of elderly (>65 yr old) have hypertension
- 60% of these have isolated systolic HTN
- the benefit of treating hypertension in the elderly is 2-4 times greater than that achieved in the treatment of younger patients with primary hypertension
- systolic and pulse pressure are major predictors of outcome in the elderly patient
- in older adults, base treatment on sBP
- target BP: sBP <140, 65<dBP<90; for patients with DM: sBP <130, dBP <80
- not recommended to lower BP below 120/80
- treatment:
  - non-pharmacologic treatments are first-line, then thiazide monotherapy is recommended
  - add ACEI/ARB if also atherosclerosis, DM, CHF or chronic kidney disease
  - add β-blockers if also angina or CHF

## Treatment of Hypertension in Patients 80 Years of Age or Older

**NEJM 2008;358:1887-1898**

- Study: Randomized, double-blind, placebo-controlled, multicentre trial.
- Subjects: 3845 patients who were 80 yr of age or older and had a sustained systolic blood pressure of 160 mmHg were followed for a median 1.8 yr.
- Intervention: Indapamide (sustained release, 1.5 mg) or matching placebo. The angiotensin-converting enzyme inhibitor perindopril (2 or 4 mg), or matching placebo, was added if necessary to achieve the target blood pressure of 150/90 mmHg.
- Primary Outcome: Fatal or nonfatal stroke.
- Results: Mean BP was 173.0/90.8 mmHg. At 2 yr, the mean BP while sitting was 151.0/71.1 mmHg lower in the treatment group than in the placebo group. Treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (95% CI, –1 to 81; p=0.00), 39% reduction in the rate of death from stroke (95% CI, 1 to 82; p=0.05), 21% reduction in the rate of death from any cause (95% CI, 4 to 35; p=0.02), 23% reduction in the rate of death from cardiovascular causes (95% CI, –1 to 40; p=0.08), and 64% reduction in the rate of heart failure (95% CI, 42 to 78; p<0.001). Fewer serious adverse events were reported in the treatment group (356 vs. 448 in the placebo group; p=0.001).
- Conclusions: Antihypertensive treatment with indapamide (sustained release, with or without perindopril), in persons 80 yr of age or older reduces death from stroke, death from any cause and the incidence of heart failure.
**Immobility**

**Complications**
- cardiovascular: orthostatic hypotension, venous thrombosis, embolism
- respiratory: decreased ventilation, atelectasis, pneumonia
- gastrointestinal: anorexia, constipation, incontinence, dehydration, malnutrition
- genitourinary: infection, urinary retention, bladder calculi, incontinence
- musculoskeletal: atrophy, contractures, bone loss
- skin: pressure ulcers
- psychological: sensory deprivation, delirium, depression

**Immunizations**
- the following immunizations are recommended for people 65 yr of age and older
  - tetanus: every 10 yr
  - pneumococcus: every 5 yr
  - influenza: every autumn
  - herpes zoster: Zostivax®

**Malnutrition**

**Definition**
- involuntary weight loss of ≥5% baseline body weight or ≥5 kg
- hypoalbuminemia, hypocholesterolemia

**Etiology**
- nutritional
  - decreased assimilation: impaired transit, maldigestion, malabsorption
  - decreased intake: financial, psychiatric (depression), cognitive deficits, anorexia associated with chronic disease, functional deficits (e.g. difficulty shopping, preparing meals or feeding oneself due to functional impairment)
- stress: acute or chronic illness/infection, chronic inflammation, abdominal pain
- mechanical: dental problems, dysphagia
- age-related changes: appetite dysregulation, decreased thirst
- mixed: increased energy demands (e.g. hyperthyroidism), abnormal metabolism, protein-losing enteropathy

**Clinical Features**
- history
  - recent or chronic illness
    - depression, GI symptoms
  - functional disability: impaired ADLs and IADLs
  - social factors: economic barriers, dental problems and living situation (e.g. living alone)
  - constitutional symptoms e.g. recent weight loss
- physical examination
  - BMI <23.5 in males, <22 in females should raise concern
  - temporal wasting, muscle wasting, presence of triceps skin fold
  - assess cognition

**Investigations**
- CBC, electrolytes, Ca²⁺, Mg²⁺, PO₄⁻³, creatinine, LFTs (albumin, INR, bilirubin), B₁₂, folate, TSH, transferrin, lipid profile, urinalysis, ESR, CXR

**Osteoporosis**
- see Endocrinology, E42

**Presbycusis**
- see Otolaryngology, OT19
Pressure Ulcers

• see Plastic Surgery, PL16

Risk Factors
• extrinsic factors: friction, pressure, shear force
• intrinsic factors: immobility, malnutrition, moisture, sensory loss

Table 7. Classification of Pressure Ulcers

| Stage I | Changes include skin temperature, tissue consistency or sensation |
| Stage II | Partial thickness skin loss involving the epidermis, dermis or both |
| Stage III | Full thickness skin loss involving damage or necrosis of subcutaneous tissue which may extend down to, but not through, underlying fascia |
| Stage IV | Full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures |

Prevention
• pressure reduction
  • frequent repositioning
  • pressure-reducing devices (static, dynamic)
• maintaining nutrition, encouraging mobility and managing incontinence

Treatment
• optimize nutritional status
• minimize pressure on wound
• analgesia
• wound debridement (mechanical, enzymatic, autolytic) and dressing application
• maintain moist wound environment to enable re-epithelialization
• treatment of wound infections (topical gentamicin, silver sulfadiazine, mupirocin)
• swab wounds not demonstrating clinical improvement for C&S; biopsy chronic wounds to rule out malignancy
• stage IV ulcers typically warrant surgical debridement
• consider other treatment options
  • negative pressure wound therapy/vacuum-assisted closure (VAC)
  • biological agents: application of fibroblast growth factor, platelet-derived growth factor to wound
  • non-contact normothermic wound therapy
  • electrotherapy

Driving Competency

Reporting Requirements
• physician-reporting to the Ministry of Transportation is mandatory in all provinces and territories except in Quebec, Nova Scotia and Alberta, where it is discretionary
• not an issue unique to geriatrics – any patient may suffer from a medical condition that impairs their ability to drive should be reported
• in the U.S., varies by state

Conditions that may Impair Driving

Table 8. Conditions that Impair Driving

| Alcohol | Patients with history of impaired driving and those with high probability of future impaired driving should not drive until further assessed |
| Alcohol | Alcohol dependence or abuse: if suspected, should be advised not to drive |
| Alcohol | Alcohol withdrawal seizure: must complete a rehabilitation program and remain abstinent and seizure-free for 6 mo before driving |
| Blood Pressure Abnormalities | Hypertension: sustained BP >170/110 should be evaluated carefully |
| Blood Pressure Abnormalities | Hypotension: if syncopal, discontinue until attacks are treated and preventable |
### Table 8. Conditions that Impair Driving (continued)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Impairment/Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Disease</td>
<td>Suspected asymptomatic CAD or stable angina: no restrictions</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>TIA: should not be allowed to drive until a medical assessment is completed</td>
</tr>
<tr>
<td>Cognitive Impairment/Dementia</td>
<td>Moderate to severe dementia is a contraindication to driving; defined as the &quot;inability to independently perform 2 or more IADLs or any basic ADL&quot;</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Diet controlled or oral hypoglycemic agent: no restrictions in absence of diabetes complications that may impair ability to drive (e.g. retinopathy, nephropathy, neuropathy, cardiovascular or cerebrovascular disease)</td>
</tr>
<tr>
<td>Drugs</td>
<td>Be aware of: analgesics, anticholinergics, anticonvulsants, antidepressants, antipsychotics, opiates, sedatives, stimulants</td>
</tr>
<tr>
<td>Hearing Loss</td>
<td>Effect of impaired hearing on ability to drive safely is controversial</td>
</tr>
<tr>
<td>Musculoskeletal Disorders</td>
<td>If treated appropriately: contraindicated to drive if &lt;120° along horizontal meridian and 15° continuous above and below fixation with both eyes examined simultaneously</td>
</tr>
<tr>
<td>Seizures</td>
<td>First, single, unprovoked: no driving for 3 mo until complete neurologic assessment, EEG, CT head</td>
</tr>
<tr>
<td>Sleep Disorders</td>
<td>If patient is believed to be at risk due to a symptomatic sleep disorder but refuses investigation with a sleep study or refuses appropriate treatment, the patient should not drive</td>
</tr>
<tr>
<td>Visual Impairment</td>
<td>Visual acuity: contraindicated to drive if &lt;20/50 with both eyes examined simultaneously</td>
</tr>
</tbody>
</table>

N.B: guidelines included refer specifically to private driving; please see CMA guidelines for commercial driving

### Table 9. Classification of Health Care Services and Institutions

<table>
<thead>
<tr>
<th>Institution/Service</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community Support Services</td>
<td>Health care services offered at home for those who can live independently at home or under the care of family members including professional health care services, personal care and support (IADL assistance), homemaking (IADL assistance), community support services (e.g. transportation, meal delivery, day programs, caregiver relief, security checks, etc.)</td>
</tr>
<tr>
<td>Residential</td>
<td>Divided into short (&lt;60-90 d/yr) and long (indefinite) stay</td>
</tr>
<tr>
<td>a) Seniors Affordable Housing</td>
<td>Seniors who live independently and manage their own care but prefer to live near other seniors; usually has accessibility features and rent is adjusted based on income</td>
</tr>
<tr>
<td>b) Retirement/Nursing Home</td>
<td>Residents are fairly independent and require minimal support with ADLs and IADLs; often privately owned</td>
</tr>
<tr>
<td>c) Supportive Housing</td>
<td>Residents require minimal to moderate assistance with daily activities while living independently; often rental units in an apartment and may offer some physiotherapy and rehabilitation services</td>
</tr>
<tr>
<td>d) Long-term Care/Skilled Nursing Facility</td>
<td>Around the clock nursing care and on-call physician coverage; often offers occupational therapy, physiotherapy, respiratory therapy and rehabilitation services; may be used short-term for caregiver respite or for supportive patient care to regain strength and confidence after leaving the hospital</td>
</tr>
<tr>
<td>e) Hospice</td>
<td>Free-standing facility or designated floor in a hospital or nursing home for care of terminally ill patients and their families; focus is on quality of life and often requires prognosis ≤3 mo</td>
</tr>
</tbody>
</table>
Palliative and End-of-Life Care

Principles and Quality of Life

- support, educate and treat both patient and family
- address physical, psychological, social and spiritual needs
- focus on symptom management and comfort measures
- offer therapeutic environment and bereavement support
- ensure maintenance of human dignity

End-of-Life Care Discussions

When to Initiate End-of-Life Care Discussions

- recent hospitalization for serious illness
- severe progressive medical condition(s)
- death expected within 6-12 mo
- patient inquires about end-of-life care

Suggested Topics for Discussion

- goals of care (disease vs. symptom management)
- advance directives, power of attorney, public guardian and trustee
- treatment options and likelihood of success
- common medical interventions
  - mechanical ventilation
  - antibiotic therapy
  - feeding tubes
- resuscitation options and likelihood of success (Full Code vs. DNR status including preferences for CPR, intubation, ICU admission, artificial hydration)

Power of Attorney

- see Ethical, Legal and Organizational Aspects of Medicine, ELOAM8

Instructional Advance Directives

- see Ethical, Legal and Organizational Aspects of Medicine, ELOAM8

Symptom Management

Assessment Tools

- Edmonton Symptom Assessment System (ESAS): a tool that asks patients to rate the intensity of symptoms from 0 to 10 and and allows for tracking of the efficacy of interventions. Assesses: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well being, shortness of breath, and "other problem"
- Palliative Performance Scale (PPS): a tool that uses functional status to predict survival in terminally ill patients. Assesses 5 components: ambulation, activity and evidence of disease, self-care, intake and conscious level

Source: Journal of Palliative Care, 1991;7:6-9 and Palliative Performance Scale, Victoria Hospice Society, 2006;120-121
Table 10. Management of Common End-of-Life Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Non-Pharmacologic Management</th>
<th>Pharmacologic Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Rule out obstruction, impaction, anorectal disease; hydration and high fibre intake; increase mobility</td>
<td>Stop unnecessary opioids and medications with anticholinergic side effects; provide stool softern (e.g. docusate sodium), increase peristalsis (e.g. senna), after water and electrolyte secretion (e.g. magnesium hydroxide)</td>
</tr>
<tr>
<td>Death Rattle/Increased Pulmonary Secretions</td>
<td>Oral suctioning</td>
<td>Scopolamine SC or transdermal</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Oral hygiene q2h, ice cubes, sugarless gum</td>
<td>Artificial saliva substitutes, bethanechol, plicarpine 1% solution as mouth rinse</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Frequent small feeds, ideally seated, keep head of bed elevated for 30 min after eating, suction as necessary</td>
<td>Treat painful mucositis (diphenhydramine: lidocaine: Maalox® in a 1:2:8 mixture), candiissias (flunonazole)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Elevate head of bed, eliminate allergens, open window/use fan</td>
<td>Oxygen, bronchodilators, opioids (e.g. morphine, hydromorphone)</td>
</tr>
<tr>
<td>Hiccups</td>
<td>Dry sugar, breathing in paper bag</td>
<td>Chlorpromazine, haloperidol, metoclopramide, bacoslen, marijuana</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>Frequent and small meals, avoid offensive strong odours, treat constipation if present</td>
<td>Raised ICP: dexamethasone Anticipatory nausea, anxiety: lorazepam Vestibular disease, vertigo: dexamethasone Drug induced, hepatic or renal failure: prochlorperazine, haloperidol GERD: PI or HZ antagonist Gastric stasis: metoclopramide Bowel obstruction: metoclopramide, dexamethasone, octreotide</td>
</tr>
<tr>
<td>Pain</td>
<td>Hot and cold compresses, music therapy, relaxation techniques, individualized program of physical activity designed to improve flexibility, strength and endurance</td>
<td>Nociceptive pain: non-opioids (NSAIDs, acetaminophen), weak opioids (codeine, hydrocodone, oxycodone), strong opioids (morphine, hydromorphone, oxycodone, fentanyl) Neuropathic pain: anticonvulsants (gabapentin, pregabalin), antidepressants (TCAs, SSRIs), steroids (dexamethasone) Bony pain: non-opioids, weak opioids, bisphosphonates, radiation therapy</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Bathing with tepid water, avoid soap, bath oils; sodium bicarbonate for jaundice</td>
<td>Antihistamines, phenothiazines, topical corticosteroids, calamine lotion</td>
</tr>
<tr>
<td>Weakness</td>
<td>Modify environment and activities to decrease energy expenditure</td>
<td>Treat insomnia, anemia, depression; consider psychostimulants</td>
</tr>
</tbody>
</table>


Geriatric Pharmacology

Pharmacokinetics

Table 11. Age-Associated Pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age Effect</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption (less significant)</td>
<td>Increased gastric pH; delayed gastric emptying</td>
<td>Drug-drug and drug-food interactions are more likely to affect absorption</td>
</tr>
<tr>
<td>Distribution</td>
<td>Increased total body fat and c1-glycoprotein; decreased lean body mass, total body water and albumin</td>
<td>Lipophilic drugs have a larger volume of distribution and a higher binding of basic drugs</td>
</tr>
<tr>
<td>Metabolism (less significant)</td>
<td>Decreased hepatic mass and hepatic blood flow; impaired phase I reactions (oxidative system)</td>
<td>Lower doses may be therapeutic</td>
</tr>
<tr>
<td>Elimination</td>
<td>Decreased renal blood flow, GFR, tubular secretion and renal mass</td>
<td>For every x% reduction in clearance, decrease the dose by x% and increase the interval by x%</td>
</tr>
</tbody>
</table>

WHO’s Pain Relief Ladder

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Non-opioid ± Adjuvant</td>
</tr>
<tr>
<td>2</td>
<td>Opioid for mild to moderate pain ± Non-opioid ± Adjuvant</td>
</tr>
<tr>
<td>3</td>
<td>Opioid for moderate to severe pain ± Non-opioid ± Adjuvant</td>
</tr>
</tbody>
</table>

Opioid Equivalent Doses (to 10 mg of IV morphine)

<table>
<thead>
<tr>
<th>Opioid</th>
<th>SC/IV dose</th>
<th>PO dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>20-30 mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>Not rec</td>
<td>180-240 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15-15 mg</td>
<td>Not rec</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2 mg</td>
<td>4-6 mg</td>
</tr>
</tbody>
</table>
| Fentanyl transdermal 20 µg/h = morphine 90 mg PO/24 h, however fentanyl takes 12-16 h to reach steady state

Geriatric Pharmacology

Pharmacokinetics

Table 11. Age-Associated Pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age Effect</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption (less significant)</td>
<td>Increased gastric pH; delayed gastric emptying</td>
<td>Drug-drug and drug-food interactions are more likely to affect absorption</td>
</tr>
<tr>
<td>Distribution</td>
<td>Increased total body fat and c1-glycoprotein; decreased lean body mass, total body water and albumin</td>
<td>Lipophilic drugs have a larger volume of distribution and a higher binding of basic drugs</td>
</tr>
<tr>
<td>Metabolism (less significant)</td>
<td>Decreased hepatic mass and hepatic blood flow; impaired phase I reactions (oxidative system)</td>
<td>Lower doses may be therapeutic</td>
</tr>
<tr>
<td>Elimination</td>
<td>Decreased renal blood flow, GFR, tubular secretion and renal mass</td>
<td>For every x% reduction in clearance, decrease the dose by x% and increase the interval by x%</td>
</tr>
</tbody>
</table>

Note: Serum creatinine does not reflect creatinine clearance in the elderly. Instead, use:

\[\text{CrCl} = \frac{(\text{weight in kg}) \times (140 – \text{age})}{(\text{serum creatinine in } \mu\text{mol/L})}\]

Multiply by 0.85 for females.
Pharmacodynamics

Drug Sensitivity
- changes in pharmacokineti cs as well as intrinsic sensitivity lead to altered drug responses
- increased sensitivity to warfarin, sedatives, antipsychotics, digoxin and narcotics
- decreased sensitivity to β-blockers in majority of elderly patients, though some may have increased sensitivity

Decreased Homeostasis
- poorer compensatory mechanisms leading to more adverse reactions (e.g. bleeding with NSAIDs/anticoagulants, altered mental status with anticholinergic/sympathomimetic/anti-Parkinsonian drugs)

Polypharmacy

Definition
- prescription, administration or use of many medications at the same time

Epidemiology
- in Canada, over 25% of elderly women and about 20% of elderly men reported using ≥3 medications
- hospitalized elderly are given an average of 10 medications during admission

Risk Factors for Non-Compliance
- risk of non-compliance correlates with medication factors, not age
  - number of medications – compliance with 1 medication is 80%, but drops to 25% with ≥6 medications
  - increased dosing frequency, complicated container design, financial constraints, and cognitive impairment

Adverse Drug Reactions (ADRs)
- any noxious or unintended response to a drug that occurs at doses used for prophylaxis or therapy
- risk factors in the elderly
  - intrinsic: co-morbidities, age-related changes in pharmacokinetics and pharmacodynamics
  - extrinsic: number of medications, multiple prescribers, unreliable drug history
- 90% of ADRs are from: ASA, analgesics, anticoagulants, antimicrobials, antineoplastics, digoxin, diuretics, hypoglycemics, steroids

Preventing Polypharmacy
- consider drug: safer side effect profiles, convenient dosing schedules, convenient route, efficacy
- consider patient: other medications, clinical indications, medical co-morbidities
- consider patient-drug interaction risk factors for ADRs
- review drug list regularly to eliminate medications with no clinical indication or with evidence of toxicity
- avoid treating an ADR with another medication

Inappropriate Prescribing in the Elderly

Epidemiology
- the estimated prevalence of potentially inappropriate prescribing ranges from 12-40%

Beers Criteria
- a list of medications to avoid in adults 65 and older due to safety concerns
- examples include long-acting benzodiazepines, strong anticholinergics, high-dose sedatives
- the elderly are also often under-treated (ACEI, ASA, β-blockers, thrombolytics, warfarin)
## Common Medications

### Table 12. Common Medications

| Drug Name      | Brand Name       | Dosing Schedule          | Indications                                                                 | Contraindications                                           | Side Effects                                                                                          | Mechanism of Action                                      |
|---------------|------------------|--------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| **ANALGESICS (non-opioid)** |                  |                          |                                                                              |                                                             |                                                                                                        |                                                          |
| acetaminophen | Tylenol®         | 325-650 mg PO q4-6h pm   | Fever, mild pain                                                             | Lower doses for hepatic and renal disease, chronic alcoholism, known hypersensitivity | Hepatotoxicity (in overdose)                                                                         | Prostaglandin-synthesis inhibition, no anti-inflammatory effects |
| ibuprofen     | Advil®/Motrin®    | 200-800 mg PO q4-6h pm   | Mild to moderate pain, inflammatory disorders, fever                         | Active GI bleed/ ulcer disease, known hypersensitivity, severe renal or hepatic disease Geriatrics: more susceptible to adverse effects | Dyspepsia, nausea, diarrhea, dizziness, rash, GI toxicity (ulcer, perforation, bleed)                  | Prostaglandin-synthesis inhibition, anti-inflammatory effects |
| celecoxib     | Celebrex®        | 200 mg PO daily or 100 mg PO bid | Osteoarthritis, rheumatoid arthritis, FAP                                      |                                                             | GI symptoms (pain, diarrhea, dyspepsia, flatus), GI bleed, serious cardiovascular events               |                                                          |
| **ANALGESICS (opioid)** – see Anesthesia and Peri-Operative Medicine, A26 |                  |                          |                                                                              |                                                             |                                                                                                        |                                                          |
| **ANTI-HYPERTENSIVES** |                  |                          |                                                                              |                                                             |                                                                                                        |                                                          |
| thiazide diuretic | Hydractin®      | 12.5-25 mg PO daily      | Hypertension, edema                                                           | Anuria, hepatic coma, pre-coma, known sensitivity to thiazides | Hypotension, transient hyperlipidemia, hypokalemia and other electrolyte disturbances, hyperuricemia, GI symptoms | Inhibition of Na⁺/Cl⁻-co-transporter                                                                          |
| ACEI e.g. ramipril | Altace®         | 2.5-20 mg PO daily       | Essential hypertension, post-MI, cardiovascular disease, renal protection       | Known hypersensitivity, angioedema                           | Hypotension, cough, headache, dizziness, asthma, chest pain, nausea, peripheral edema, arthritis, dyspepsia, angioedema, hyperkalemia | Inhibition of angiotensin-converting enzyme                                                               |
| ARB e.g. losartan | Cozaar®      | 50-100 mg PO daily       | Essential hypertension (= diabetes mellitus)                                   | Known hypersensitivity                                       | Dizziness, hypotension, fatigue, headache, hyperkalemia                                                                 | Antagonizes angiotensin II via blockade of the angiotensin type 1 receptor                               |
| DHP CCB e.g. amlodipine | Norvasc®     | 2.5-10 mg PO daily (initially) | Essential hypertension, chronic stable angina                                | Known hypersensitivity, severe hypertension, caution in aortic stenosis | Edema, muscle cramps, dizziness, headache, constipation, heartbeat                                      | Calcium ion influx inhibition                                                                             |
| **COGNITIVE ENHANCERS** |                  |                          |                                                                              |                                                             |                                                                                                        |                                                          |
| donepezil     | Aricept®         | 5-10 mg PO daily         | Moderate to severe dementia of Alzheimer’s type                               | Known hypersensitivity, caution in pulmonary disease, sick sinus syndrome, seizure disorder | N/V, diarrhea, anorexia, falls, hip fracture, increase need for pacemaker insertion                  | Reversible inhibition of acetylcholinesterase                                                           |
| galantamine   | Reminyl®         | 8-12 mg PO bid           | Mild to moderate dementia of Alzheimer’s type                                 | Known hypersensitivity, caution in sick sinus syndrome, seizure disorder, pulmonary disease, low body weight | N/V, diarrhea, anorexia, falls, hip fracture, increase need for pacemaker insertion                  | Reversible inhibition of acetylcholinesterase                                                           |
| rivastigmine  | Exelon®          | 1.5 mg PO daily and up to 6 mg PO bid | Mild to moderate dementia of Alzheimer’s type                                 | Known hypersensitivity, severe hepatic disease, caution in sick sinus syndrome, pulmonary disease, seizure disorder | N/V, diarrhea, anorexia, falls, hip fracture, increase need for pacemaker insertion                  | Acetylcholinesterase inhibition (reversible but very slow)                                             |
| memantine     | Ebixa®/Namenda®  | 5 mg PO daily (starting) up to 10 mg PO bid | Mild to moderate dementia of Alzheimer’s type                                | Known hypersensitivity, conditions that alkalize urine, caution in cardiovascular conditions | Agitation, fatigue, dizziness, headache, hypertension, constipation                                      | NMDA-receptor antagonist                                  |
Table 12. Common Medications (continued)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAXATIVES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bran</td>
<td>All-Bran®</td>
<td>1 cup/d</td>
<td>Constipation</td>
<td>Bloating, flatus</td>
<td>Bulk-forming laxative</td>
<td></td>
</tr>
<tr>
<td>psyllium</td>
<td>Metamucil®</td>
<td>1 tsp PO tid</td>
<td>Constipation, hypercholesterolemia</td>
<td>N/V, abdominal pain, obstruction</td>
<td>Bloating, flatus</td>
<td>Bulk-forming laxative</td>
</tr>
<tr>
<td>lactulose</td>
<td>Chronulac®</td>
<td>15-30 cc PO daily/bid</td>
<td>Constipation, hepatic encephalopathy, bowel evacuation following barium exam</td>
<td>Patients on low galactose diets</td>
<td>Abdominal pain, N/V</td>
<td>Hyperosmolar agent, lowers pH of colon to decrease blood ammonia levels</td>
</tr>
<tr>
<td></td>
<td>Prodiem Plain®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kristalose®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sorbent</td>
<td>SmoKot®/Ex-lax®/ Glyssenid®</td>
<td>1-2 tabs PO daily or 10-15 cc syrup PO daily</td>
<td>Constipation</td>
<td>Abdominal pain, N/V</td>
<td>Cramps, griping, dependence</td>
<td>Stimulant laxative</td>
</tr>
<tr>
<td>sorbent</td>
<td>Dulcolax®</td>
<td>5-15 mg PO (10 mg PR)</td>
<td>Constipation</td>
<td>Ileus, obstruction, abdominal pain, N/V, severe dehydration</td>
<td>Cramps, pain, diarrhea</td>
<td>Stimulant laxative</td>
</tr>
<tr>
<td>PARKINSONIAN AGENTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLEEPING MEDICATIONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>zopiclone</td>
<td>Imovane®</td>
<td>3.75 mg PO qhs (initially)</td>
<td>Insomnia</td>
<td>Known hypersensitivity, caution in myasthenia gravis, severe hepatic disease</td>
<td>Bitter taste, palpitations, vomiting, anorexia, sialorrhea, confusion, agitation, anxiety, tremor, sweating</td>
<td>Short-acting hypnotic (no tolerance effects)</td>
</tr>
<tr>
<td>temazepam</td>
<td>Restori®</td>
<td>15 mg PO qhs</td>
<td>Short-term management of insomnia</td>
<td>Known hypersensitivity, myasthenia gravis, sleep apnea</td>
<td>Drowsiness, dizziness, impaired coordination, hangover, lethargy, dependence</td>
<td>Benzodiazepine: generalized CNS depression mediated by GABA</td>
</tr>
<tr>
<td>lorazepam</td>
<td>Ativan®</td>
<td>0.5 mg PO qhs (initially)</td>
<td>Anxiety, insomnia</td>
<td>Known hypersensitivity, myasthenia gravis, narrow-angle glaucoma</td>
<td>Dizziness, drowsiness, lethargy, dependence</td>
<td>Benzodiazepine: generalized CNS depression mediated by GABA</td>
</tr>
</tbody>
</table>

Note: Docusate has been shown to be ineffective for the prevention/treatment of constipation in the elderly

Landmark Geriatric Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil and Memantine for Moderate-to-Severe Alzheimer’s Disease</td>
<td>NEJM 2012; 366:893-903</td>
<td>Continued treatment with donepezil was associated with cognitive benefits over the course of 12 mo in patients with moderate or severe Alzheimer’s disease</td>
</tr>
<tr>
<td>Early palliative care for metastatic lung cancer</td>
<td>NEJM 2010; 363:733-742</td>
<td>Among patients with metastatic non-small-cell lung cancer, early palliative care led to significant improvements in both quality of life and mood. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end-of-life but longer survival</td>
</tr>
<tr>
<td>Hip protectors for fracture prevention</td>
<td>NEJM 2000; 343:1506-1513</td>
<td>The risk of hip fracture can be reduced in frail elderly adults by the use of an anatomically designed external hip protector</td>
</tr>
<tr>
<td>HYVET</td>
<td>NEJM 2008; 358:1887-1898</td>
<td>Antihypertensive treatment with indapamide (sustained release), with or without perindopril, in adults 80 yr or older is beneficial</td>
</tr>
<tr>
<td>PROFET</td>
<td>Lancet 1999; 353:93-97</td>
<td>Demonstrates that an interdisciplinary approach to elderly adults with a previous history of falls can significantly decrease the risk of further falls and limit functional impairment</td>
</tr>
<tr>
<td>Yale Delirium Prevention Trial</td>
<td>NEJM 1999; 340:669-676</td>
<td>A risk-factor intervention strategy can result in significant reductions in the number and duration of episodes of delirium in hospitalized older patients</td>
</tr>
</tbody>
</table>
References

Health Status

Physiology and Pathology of Aging

Constipation

Delirium, Dementia and Depression

Elder Abuse

Falls

Frailty

Hazard of Hospitalization

Hypertension

Immunizations

Malnutrition

Pressure Ulcers

Driving Competency
Grabowski DC, Campbell CM, Morrissey MA. Elderly licensure laws and motor vehicle fatalities. JAMA 2004;291:2840-2846.
Wiseman EH. The older driver: a handy tool to assess competence behind the wheel. Geriatrics 1996;51:36-45

Health Care Institutions

Palliative and End-of-Life Care

Pharmacology
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acronyms</td>
<td>2</td>
</tr>
<tr>
<td>Basic Anatomy Review</td>
<td>2</td>
</tr>
<tr>
<td>Menstruation</td>
<td>3</td>
</tr>
<tr>
<td>Stages of Puberty</td>
<td></td>
</tr>
<tr>
<td>Menstrual Cycle</td>
<td></td>
</tr>
<tr>
<td>Premenstrual Syndrome (PMS)</td>
<td></td>
</tr>
<tr>
<td>Premenstrual Dysphoric Disorder (PMDD)</td>
<td></td>
</tr>
<tr>
<td>Differential Diagnoses of Common Presentations</td>
<td>6</td>
</tr>
<tr>
<td>Abnormal Uterine Bleeding (AUB)</td>
<td></td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td></td>
</tr>
<tr>
<td>Vaginal Discharge/Pruritus</td>
<td></td>
</tr>
<tr>
<td>Pelvic Pain</td>
<td></td>
</tr>
<tr>
<td>Pelvic Mass</td>
<td></td>
</tr>
<tr>
<td>Dyspareunia</td>
<td></td>
</tr>
<tr>
<td>Common Investigations</td>
<td>8</td>
</tr>
<tr>
<td>Bloodwork</td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
</tr>
<tr>
<td>Common Procedures</td>
<td>9</td>
</tr>
<tr>
<td>Genital Tract Biopsy</td>
<td></td>
</tr>
<tr>
<td>Colposcopy</td>
<td></td>
</tr>
<tr>
<td>Vacuum Aspiration</td>
<td></td>
</tr>
<tr>
<td>Dilatation and Curettage (D&amp;C)</td>
<td></td>
</tr>
<tr>
<td>Laparoscopy</td>
<td></td>
</tr>
<tr>
<td>Hysteroscopy</td>
<td></td>
</tr>
<tr>
<td>Endometrial Ablation</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy</td>
<td></td>
</tr>
<tr>
<td>Disorders of Menstruation</td>
<td>12</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td></td>
</tr>
<tr>
<td>Abnormal Uterine Bleeding (AUB)</td>
<td></td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td>16</td>
</tr>
<tr>
<td>Adenomyosis</td>
<td>17</td>
</tr>
<tr>
<td>Leiomyomata (Fibroids)</td>
<td>17</td>
</tr>
<tr>
<td>Contraception</td>
<td>19</td>
</tr>
<tr>
<td>Hormonal Methods</td>
<td></td>
</tr>
<tr>
<td>Intrauterine Device (IUD)</td>
<td></td>
</tr>
<tr>
<td>Emergency Postcoital Contraception (EPC)</td>
<td></td>
</tr>
<tr>
<td>Infertility</td>
<td>22</td>
</tr>
<tr>
<td>Female Factors</td>
<td></td>
</tr>
<tr>
<td>Male Factors</td>
<td></td>
</tr>
<tr>
<td>Gynecological Infections</td>
<td>24</td>
</tr>
<tr>
<td>Physiologic Discharge</td>
<td></td>
</tr>
<tr>
<td>Vulvovaginitis</td>
<td></td>
</tr>
<tr>
<td>Sexually Transmitted Infections (STIs)</td>
<td></td>
</tr>
<tr>
<td>Bartholinitis/Bartholin Gland Abscess</td>
<td></td>
</tr>
<tr>
<td>Pelvic Inflammatory Disease (PID)</td>
<td></td>
</tr>
<tr>
<td>Toxic Shock Syndrome</td>
<td></td>
</tr>
<tr>
<td>Surgical Infections</td>
<td></td>
</tr>
<tr>
<td>Sexual Abuse</td>
<td>31</td>
</tr>
<tr>
<td>Sexuality and Sexual Dysfunction</td>
<td>31</td>
</tr>
<tr>
<td>Menopause</td>
<td>32</td>
</tr>
<tr>
<td>Hormone Replacement Therapy (HRT)</td>
<td></td>
</tr>
<tr>
<td>Urogynecology</td>
<td>34</td>
</tr>
<tr>
<td>Pelvic Relaxation/Prolapse</td>
<td></td>
</tr>
<tr>
<td>Urinary Incontinence</td>
<td></td>
</tr>
<tr>
<td>Gynecological Oncology</td>
<td>36</td>
</tr>
<tr>
<td>Uterus</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td></td>
</tr>
<tr>
<td>Vulva</td>
<td></td>
</tr>
<tr>
<td>Vagina</td>
<td></td>
</tr>
<tr>
<td>Fallopian Tube</td>
<td></td>
</tr>
<tr>
<td>Gestational Trophoblastic Disease/Neoplasia</td>
<td></td>
</tr>
<tr>
<td>(GTD/GTN)</td>
<td></td>
</tr>
<tr>
<td>Common Medications</td>
<td>51</td>
</tr>
<tr>
<td>References</td>
<td>52</td>
</tr>
</tbody>
</table>
Basic Anatomy Review

Figure 1. Vulva and perineum

A. EXTERNAL GENITALIA (Figure 1)
- referred to collectivley as the vulva
- blood supply: internal pudendal artery
- sensory innervation: pudendal nerve
- lymphatic drainage: inguinal nodes

B. VAGINA
- muscular canal extending from cervix to vulva, anterior to rectum and posterior to bladder
  - lined by rugated, stratified-squamous epithelium
  - upper vagina separated by cervix into anterior, posterior and lateral fornices
  - blood supply: vaginal branch of internal pudendal artery with anastomoses from uterine, inferior vesical and middle rectal arteries

C. UTERUS
- thick walled, muscular organ between bladder and rectum, consisting of two major parts:
  - uterine corpus
    - blood supply: uterine artery (branch of the internal iliac artery)
  - cervix
    - blood supply: cervical branch of uterine artery
  - supported by the pelvic diaphragm, the pelvic organs and 4 paired sets of ligaments
  - round ligaments: travel from anterior surface of uterus, through broad ligaments and inguinal canals then terminate in the labia majora
    - function: anteversion
  - blood supply: Sampson’s artery (branch of uterine artery running through round ligament)
  - uterosacral ligaments: arise from sacral fascia and insert into posterior inferior uterus
    - function: mechanical support for uterus and contain autonomic nerve fibres
  - cardinal ligaments: extend from lateral pelvic walls and insert into lateral cervix and vagina
    - function: mechanical support, prevent prolapse
  - broad ligaments: pass from lateral pelvic wall to sides of uterus; contain fallopian tube, round ligament, ovarian ligament, nerves, vessels and lymphatics
    - infundibulopelvic ligament: continuous tissue that connects ovary to pelvic wall
    - contains the ovarian artery, ovarian vein, ovarian plexus, lymphatic vessels
  - position of the uterus (Figure 3)
    - antverted (majority)
    - retroverted

Figure 2. External genital organs

Acronyms

- hCG beta-human chorionic gonadotropin
- AFP alpha-fetoprotein
- AIS androgen insensitivity syndrome
- AUB abnormal uterine bleeding
- BMI body mass index
- BSD bilateral salpingo-oophorectomy
- CAH congenital adrenal hyperplasia
- CMV cytomegalovirus
- DcC dilation and curettage
- DES diethylstilbestrol
- DHEA dihydroepiandosterone
- DM diabetes mellitus
- DUB dysfunctional uterine bleeding
- EPC emergency postcoital contraception
- FSH follicle stimulating hormone
- GA gestational age
- GIFT gamete intrafallopian transfer
- GnRH gonadotropin-releasing hormone
- GTD gestational trophoblastic disease
- GTN gestational trophoblastic neoplasia
- HMG human menopausal gonadotropin
- HPO hypothalamic-pituitary-ovarian
- HRT hormone replacement therapy
- HSQ hysterosalpingography
- HSIL high grade squamous intraepithelial lesion
- HSV herpes simplex virus
- IBD inflammatory bowel disease
- ICSI intracytoplasmic sperm injection
- IPP immune thrombocytopenic purpura
- IUD intrauterine device
- IUI intrauterine insemination
- IVF intravenous drug use
- IVF in vitro fertilization
- IVF in vitro maturation
- JRA juvenile rheumatoid arthritis
- LEEP loop electrosurgical excision procedure
- LH luteinizing hormone
- LRH LRH releasing hormone
- LMP last menstrual period
- LN lymph node
- LNMP last normal menstrual period
- MRS Mayer-Rokitansky-Kuster-Hauser
- NK natural killer
- OCP oral contraceptive pill
- PCOS polycystic ovarian syndrome
- PCR polymerase chain reaction
- PG progestin
- PID pelvic inflammatory disease
- PMDD premenstrual dysphoric disorder
- PMN polymorphonuclear neutrophils
- PMAS premenstrual syndrome
- PRP rapid plasma reagin
- SERMs selective estrogen receptor modifiers
- SHBG sex hormone binding globulin
- SHG sonohysterography
- STI sexually transmitted infection
- TAH total abdominal hysterectomy
- TB tuberculosis
- TET tubal embryo transfer
- TH total hysterectomy
- TSH thyroid stimulating hormone
- TZ transformation zone
- VDRL venereal disease research laboratory
- VWD von Willebrand’s disease
- w/d withdrawal
- ZIFTzygote intrafallopian transfer
D. FALLOPIAN TUBES
- 8-14 cm muscular tubes extending laterally from the uterus to ovary
- interstitial, isthmic, ampullary and infundibular segments; terminates at fimbriae
- mesosalpinx: peritoneal fold that attaches fallopian tube to broad ligament
- blood supply: uterine and ovarian arteries

E. OVARIES
- consist of cortex with ova and medulla with blood supply
- supported by infundibulopelvic ligament (suspensory ligament of ovary)
- mesovarium: peritoneal fold that attaches ovary to broad ligament
- blood supply: ovarian arteries (branches off aorta), left ovarian vein (drains into left renal vein), right ovarian vein (drains into inferior vena cava)

Figure 3. Positioning of uterus

Anteversion: forward-tilted uterus.
Anteflexion: bending of uterus so the fundus is thrust forward.
Retroversion: backward-tilted uterus.
Retroflexion: bending of uterus so the fundus is thrust backward.

Figure 4. Vascular supply

"Water under the bridge"
The ureters run posterior to the uterine arteries.

Menstruation

Stages of Puberty

- see Pediatrics, P31
- adrenarche: increase in secretion of adrenal androgens; usually precedes gonadarche by 2 yr
- gonadarche: increased secretion of gonadal sex steroids; ~age 8
- thelarche: breast development
- pubarche: pubic and axillary hair development
- menarche: onset of menses, usually following peak height velocity and/or 2 yr following breast budding
Figure 5. Events of the normal menstrual cycle

**Menstrual Cycle**

**FOLLICULAR/PROLIFERATIVE PHASE (Variable Duration)**

<table>
<thead>
<tr>
<th>Initiating events</th>
<th>Early</th>
<th>Mid</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPO axis</td>
<td>↑ GnRH pulse frequency</td>
<td>↑ FSH</td>
<td>↑ LH pulse frequency</td>
</tr>
<tr>
<td>Hormones</td>
<td>↑ E from follicles (ovary)</td>
<td>↑ E from follicles, esp. from dominant follicle</td>
<td></td>
</tr>
<tr>
<td>Feedback on HPO axis</td>
<td>Negative feedback E → ↓ FSH, ↓ LH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovaries</td>
<td>↑ FSH → follicular growth in 3-30 follicles</td>
<td>↑ follicular growth (by reducing atresia) → ↑ E</td>
<td></td>
</tr>
<tr>
<td>Endometrium</td>
<td>Menses from P withdrawal (from end of previous cycle)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical Mucus</td>
<td>Cervical mucus: Clear, ↑ amount, Spinnbarkeit 8-10 cm, more stringy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**LUTEAL/SECRETORY PHASE (Fixed Duration - 14 days)**

<table>
<thead>
<tr>
<th>OVULATION</th>
<th>Early-Mid</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden switch from negative to positive feedback (E and P now ↑ FSH &amp; LH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ ↑ LH pulse amplitude (LH surge)</td>
<td>↓ LH</td>
<td></td>
</tr>
<tr>
<td>E peaks → LH surge → ovulation</td>
<td>↑ P from corpus luteum</td>
<td>↓ P secondary to degeneration of corpus luteum</td>
</tr>
<tr>
<td>Positive feedback: E and P → ↑ FSH, ↑ LH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative feedback P → ↓ FSH, ↓ LH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>~36 h after LH surge, dominant follicle releases oocyte; corpus luteum (remnant of dominant follicle) produces P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P stabilizes endometrium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal of P → menses</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Menarche 10-15 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average 12.2 yr</td>
<td></td>
</tr>
<tr>
<td>Entire cycle 28: 7 d with bleeding for 1-6 d</td>
<td></td>
</tr>
<tr>
<td>25-80 mL blood loss per cycle</td>
<td></td>
</tr>
</tbody>
</table>

**Estrogen**

ESTROGEN is the main hormone in the follicular/proliferative phase and is stimulated by FSH. Increased estrogen mainly decreases FSH. The majority of estrogen is secreted by the dominant follicle.

**Estrogen effects:**
- On the follicles in the ovaries:
  - Reduces atresia
- On the endometrium:
  - Proliferation of glandular and stromal tissue
- On all target tissues:
  - Decreases E receptors

**Progesterone**

PROGESTERONE is the main hormone in the luteal/secretory phase and is stimulated by LH. Increased progesterone mainly decreases LH and is secreted by the corpus luteum (remnant of dominant follicle).

**Progesterone effects:**
- On the endometrium:
  - Cessation of mitoses (stops building endometrium up)
  - “Organization” of glands (initiates secretions from glands)
  - Inhibits macrophages, interleukin-8 and enzymes from degrading endometrium
- On all target tissues:
  - Decrease E receptors (the “anti-estrogen” effect)
  - Decrease P receptors
Premenstrual Syndrome (PMS)

- **synonyms:** "ovarian cycle syndrome," "menstrual molimina" (moodiness)

**Etiology**
- not completely understood, multifactorial, genetics likely play a role
- CNS-mediated neurotransmitter interactions with sex steroids (progesterone, estrogen and testosterone)
- serotonergic dysregulation – currently most plausible theory

**Diagnostic Criteria for Premenstrual Syndrome**
- at least one affective and one somatic symptom during the 5 d before menses in each of the three prior menstrual cycles
  - affective: depression, angry outbursts, irritability, anxiety, confusion, social withdrawal
  - somatic: breast tenderness, abdominal bloating, headache, swelling of extremities
- symptoms relieved within 4 d of onset of menses
- symptoms present in the absence of any pharmacologic therapy, drug or alcohol use
- symptoms occur reproducibly during 2 cycles of prospective recording
- patient suffers from identifiable dysfunction in social or economic performance

**Treatment**
- goal: symptom relief
- psychological support
- diet/supplements
  - avoid sodium, simple sugars, caffeine and alcohol
  - calcium (1200-1600 mg/d), magnesium (400-800 mg/d), vitamin E (400 IU/d), vitamin B6
- medications
  - NSAIDs for discomfort, pain
  - spironolactone for fluid retention: used during luteal phase
  - SSRI antidepressants: used during luteal phase x 14 d or continuously
  - OCP: primarily beneficial for physical/somatic symptoms
  - danazol: an androgen that inhibits the pituitary-ovarian axis
  - GnRH agonists if PMS is severe and unresponsive to treatment
- mind/body approaches
  - regular aerobic exercise
  - cognitive behavioural therapy
  - relaxation, light therapy biofeedback and guided imagery
- herbal remedies (variable evidence)
  - evening primrose oil, black cohosh, St. John's wort, kava, ginkgo, agnus castus fruit extract
- BSO if symptoms severe

Premenstrual Dysphoric Disorder (PMDD)

**Definition**
- official diagnosis in the DSM-IV-TR
- described as a more severe form of PMS with specific diagnostic criteria
- treatment with SSRIs (first line), and Yaz® OCP (highly effective)
Differential Diagnoses of Common Presentations

Abnormal Uterine Bleeding (AUB)

- see Disorders of Menstruation, GY14
- definition: change in frequency, duration or amount of menstrual flow
- classified as amenorrhea, oligomenorrhea, menorrhagia/hypermenorrhea, hypomenorrhea, metrorrhagia, menometrorrhagia, polymenorrhea, postmenopausal bleeding
  - hypomenorrhea: bleeding that is decreased in amount
  - oligomenorrhea: bleeding occurring at intervals >35 d
  - polymenorrhea: bleeding occurring at intervals <21 d
  - menorrhagia/hypermenorrhea: bleeding at regular intervals that is prolonged in duration (>7 d) or excessive in amount (>80 cc per menstrual cycle)
  - metrorrhagia: bleeding at irregular intervals, particularly between expected menstrual periods
  - menometrorrhagia: excessive bleeding at usual time of menstrual periods and at other irregular intervals
  - postmenopausal bleeding: any bleeding that presents >1 yr after menopause; must rule out endometrial cancer

Dysmenorrhea

- see Disorders of Menstruation, GY15
- primary/idiopathic
- secondary (acquired)
  - endometriosis
  - adenomyosis
  - uterine polyps
  - uterine anomalies (e.g. non-communicating uterine horn)
  - leiomyoma
  - intrauterine synechiae
  - ovarian cysts
  - cervical stenosis
  - imperforate hymen, transverse vaginal septum
  - pelvic inflammatory disease (PID)
  - IUD (copper)
  - foreign body

Vaginal Discharge/Pruritus

- see Gynecological Infections, GY24
- physiologic discharge and cervical mucus production
- non-physiologic
  - genital tract infection
    - vulvovaginitis: candidiasis, trichomoniasis, bacterial vaginosis (BV), polymicrobial superficial infection
    - chlamydia, gonorrhea
    - pyosalpinx, salpingitis
  - genital tract inflammation (non-infectious)
  - local: chemical irritants, douches, sprays, foreign body, trauma, atrophic vaginitis, desquamative inflammatory vaginitis, focal vulvitis
  - neoplasia: vulvar, vaginal, cervical, endometrial
  - systemic: toxic shock syndrome, Crohn's disease, collagen disease, dermatologic (e.g. lichen sclerosis)
  - IUD, OCP (secondary to progesterone)
Pelvic Pain

- Acute
  - Gynecological
    - Appendicitis
    - Mesenteric adenitis
    - Diverticulitis
  - Non-gynecological
    - UTI (e.g., cystitis, pyelonephritis)
    - Renal colic
- Chronic
  - Pregnancy-related
    - Labour
    - Ectopic pregnancy
  - Gynecological
    - Chronic PID
    - Endometritis
    - Dysmenorrhea
  - Non-gynecological
    - Referred pain
    - Urinary retention

Adnexal
- Mittelschmerz
- Ruptured ovarian cyst
- Ruptured ectopic pregnancy
- Hemorrhage into cyst/neoplasm
- Ovarian/tubal torsion

Uterine
- Fibroid degeneration
- Torsion of pedunculated fibroid
- Pyometra/hematometra

Infectious
- Acute PID
- Endometritis

20% of chronic pelvic pain patients have a history of previous sexual abuse/assault. Remember to ask about it!

Pelvic Mass

- Ovarian
  - Functional Cysts
    - (always benign)
    - Corpus luteum cyst
    - Follicular cyst
    - Theca lutein cyst
    - Hemorrhagic cyst
  - Neoplasm
    - Benign
      - Dermoid cyst
        - (most common)
      - Malignant
        - Epithelial cell
          - (most common in >40 yr)
        - Germ cell
          - (most common in <20 yr)
      - PCOS
      - Endometrioma
      - Tube-ovarian abscess
      - Luteoma of pregnancy
  - Other
    - PCOS
    - Endometrioma
    - Hematometra/pyometra
    - Endometrial cancer
    - Imperforate hymen

- Uterine
  - Symmetrical
    - Pregnancy
    - Adenomyosis
    - Hematometra/pyometra
    - Endometrial cancer
    - Imperforate hymen
  - Asymmetrical
    - Leiomyoma
    - Leiomyosarcoma

- Other
  - Gynecological
    - Ectopic pregnancy
    - Pelvic adhesions
    - (resulting in fluid entrapment)
  - Paratubal cysts
  - Pyosalpinx/Hydrosalpinx
  - Primary fallopian tube neoplasms

Gastrointestinal
- Appendiceal abscess
- Diverticular abscess
- Diverticulitis, diverticulosis
- Carcinoma of rectum/colon

Genitourinary
- Distended bladder
- Pelvic kidney
- Carcinoma of bladder
- Lymphoma

Pelvic Pain

- Acute
  - Gynecological
  - Non-gynecological
- Chronic
  - Pregnancy-related
  - Gynecological
  - Non-gynecological

Pelvic Mass

- Ovarian
  - Functional Cysts
    - (always benign)
    - Corpus luteum cyst
    - Follicular cyst
    - Theca lutein cyst
    - Hemorrhagic cyst
  - Neoplasm
    - Benign
      - Dermoid cyst
        - (most common)
      - Malignant
        - Epithelial cell
          - (most common in >40 yr)
        - Germ cell
          - (most common in <20 yr)
      - PCOS
      - Endometrioma
      - Tube-ovarian abscess
      - Luteoma of pregnancy
  - Other
    - PCOS
    - Endometrioma
    - Hematometra/pyometra
    - Endometrial cancer
    - Imperforate hymen

- Uterine
  - Symmetrical
    - Pregnancy
    - Adenomyosis
    - Hematometra/pyometra
    - Endometrial cancer
    - Imperforate hymen
  - Asymmetrical
    - Leiomyoma
    - Leiomyosarcoma

- Other
  - Gynecological
    - Ectopic pregnancy
    - Pelvic adhesions
    - (resulting in fluid entrapment)
  - Paratubal cysts
  - Pyosalpinx/Hydrosalpinx
  - Primary fallopian tube neoplasms

Gastrointestinal
- Appendiceal abscess
- Diverticular abscess
- Diverticulitis, diverticulosis
- Carcinoma of rectum/colon

Genitourinary
- Distended bladder
- Pelvic kidney
- Carcinoma of bladder
- Lymphoma
**Dyspareunia**

Dyspareunia can be classified into three main categories: introital, midvaginal, and deep. Each category may involve different underlying conditions:

- **Introital:**
  - Inadequate lubrication
  - Vaginismus
  - Rigid/intact hymen
  - Bartholin’s or Skene’s gland infection
  - Lichen sclerosis
  - Vulvovaginitis: atrophic (hypoestrogen), chemical, infectious (chlamydia, trichomoniasis)

- **Midvaginal:**
  - Urethritis
  - Short vagina
  - Trigonitis
  - Congenital abnormality of the vagina (e.g., vaginal septum)

- **Deep:**
  - Endometriosis
  - Adenomyosis
  - Leiomyomata/fibroids
  - PID (acute vs. chronic)
  - Hydrosalpinx
  - Tubo-ovarian abscess
  - Uterine retroversion
  - Ovarian cyst

**Bloodwork**

- **CBC:** evaluation of severity of abnormal uterine bleeding, pre-op investigation ± ferritin if anemic
- **β-hCG:** investigation of possible pregnancy, ectopic pregnancy, ovarian germ cell tumour
  - work-up for GTD/GTN
  - monitored after medical management of ectopic pregnancy and GTN to assess for cure or recurrence
- **LH, FSH, TSH, free T4, prolactin, DHEA, testosterone, estradiol, androstenedione:** investigation of amenorrhea, menstrual irregularities, menopause, infertility

**Imaging**

**Ultrasound (U/S):**

- transabdominal or transvaginal U/S is the imaging modality of choice for pelvic structures
- transvaginal U/S provides better resolution of uterus and adnexal structures
  - detects early pregnancy if β-hCG ≥1500 (β-hCG must be ≥6500 for transabdominal U/S)
- may be used to identify pelvic pathology
  - identify ectopic pregnancy, intrauterine pregnancy
  - assess uterine, adnexal, cul-de-sac, ovarian masses (e.g., solid or cystic)
  - determine endometrial thickness, locate/characterize fibroids
  - monitor follicles during assisted reproduction
  - assess endometrial lining in postmenopausal women

**Sonohysterography (SHG):**

- saline infusion into endometrial cavity expands endometrial cavity, improving visualization of uterus and fallopian tubes
- useful for investigation of:
  - abnormal uterine bleeding (AUB)
  - uncertain endometrial findings on transvaginal U/S
  - infertility (tubal patency)
  - congenital/acquired uterine abnormalities (e.g., fibroids, endometrial polyps)
- easily done, minimal cost, well-tolerated, sensitive and specific
- frequently avoids need for diagnostic hysteroscopy

**Hysterosalpingography (HSG):**

- x-ray contrast introduced through the cervix into the uterus
- used for evaluation of size, shape, configuration of uterus, congenital uterine abnormalities, tubal patency, or obstruction
- useful for investigation of infertility
- often replaced by sonohysterogram with Echovist® to look at tubes

Every woman of childbearing age presenting to ER with abdominal or pelvic pain should have β-hCG measured. Check for STIs before performing SHG and HSG to prevent PID in high-risk individuals. Consider pre-treatment with doxycycline.
Common Procedures

Genital Tract Biopsy

Vulvar Biopsy
- performed under local anesthetic
- Keyes/punch biopsy
- hemostasis achieved with local pressure and Monsel's solution (ferric sulfate), silver nitrate or suture (rarely)

Vaginal Biopsy and Cervical Biopsy
- anesthetic not necessary
- punch biopsy or biopsy forceps
- hemostasis with Monsel's solution and pressure

Endometrial Biopsy
- performed in the office using an endometrial suction curette (pipelle) guided through the cervix to aspirate fragments of endometrium
  - pre-treatment with misoprostol (Cytotec®) if nulliparous or postmenopausal
- more invasive procedure (D&C) may be done in the office or operating room ± hysteroscopy

Colposcopy
- diagnostic use
  - magnifies surface structures of the vulva, vagina, cervix and perianal region
  - 1% acetic acid wash applied to cervix dehydrates cells and reveals “acetowhite” areas that correspond to increased nucleus-to-cytoplasm ratio (abnormal)
  - allows biopsy of acetowhite lesions for early identification of dysplasia and cancer
- therapeutic use
  - cryotherapy: nitrous oxide or carbon dioxide freezes dysplastic lesions, genital warts
  - laser vaporization: used to treat dysplastic lesions of the exocervix and benign ectropion
  - loop electrosurgical excision procedure (LEEP): excision of transformation zone with the cervical lesion; provides a specimen for pathological examination

Vacuum Aspiration
- procedure to empty the contents of the uterus through a plastic or metal cannula (thin tube) attached to a vacuum source

Indications
- termination of pregnancy in 1st trimester

Manual Vacuum Aspiration (≤10 wk gestation)
- source of vacuum: hand-held, portable aspirator
- anesthesia: local (paracervical block) in most cases
- can be performed in an office setting
- suction curette connected to aspirator empties the uterus

Electric Vacuum Aspiration (≤13 wk gestation)
- source of vacuum: electric pump
- anesthesia: local (paracervical block) and conscious sedation or general anesthetic
- dilatation of cervix with dilators of increasing diameter
- suction curette connected to electric pump empties the uterus
- after aspiration, uterine cavity can be gently explored with sharp curette

Complications
- bleeding
- infection
- perforation of uterus, laceration of cervix
  - reduce risk with preprocedural cervical dilatation (misoprostol or osmotic dilators)
- retained products of conception
  - requires reaspiration, rare (2/1000)
**Dilatation and Curettage (D&C)**

- determine depth with uterine sound prior to procedure
- dilatation of cervix with dilators of increasing diameter
- scrape entire uterine cavity with sharp curette
- anesthesia: general or local

**Indications**

- diagnostic (rarely done without hysteroscopy)
  - abnormal uterine bleeding (AUB)
  - dysfunctional uterine bleeding (DUB)
- therapeutic
  - removal of retained products of conception following abortion
  - termination of pregnancy in 1st trimester
  - removal of small uterine polyps or pedunculated submucosal fibroids

**Complications**

- bleeding
- infection
- perforation of uterus, laceration of cervix
  - reduce risk with preoperative misoprostol (Cytotec®) inserted per vagina to soften cervix and stimulate uterine contraction
- incompetent cervix – extremely rare
- Asherman's syndrome

---

**Laparoscopy**

- laparoscope (fibre optic camera) used to view pelvic/abdominal contents through small incisions

**Indications**

- diagnostic
  - evaluation of infertility, pelvic pain, pelvic masses, congenital anomalies, hemoperitoneum and endometriosis
- therapeutic
  - tubal ligation
  - lysis of adhesions
  - excision of ectopic pregnancy
  - excision/ablation of endometriosis
  - retrieval of lost IUDs
  - cystectomy, salpingo-oophorectomy and hysterectomy
  - myomectomy
  - treatment of stress urinary incontinence

**Contraindications**

- bowel obstruction
- large hemoperitoneum
- clinically unstable patient
- inability to maintain pneumoperitoneum
- multiple previous abdominal surgeries (i.e. adhesions)

**Complications**

- general anesthesia related
- insufflation of the preperitoneal abdominal wall
- injury to surrounding structures (e.g. aorta, inferior epigastric vessels, bowel, bladder, ureters)
- may need to convert to laparotomy
- infection

---

**Hysteroscopy**

- flexible or rigid scope inserted through cervix into uterus to visualize uterine cavity
- distension medium is used to allow inspection of this potential space

**Indications**

- diagnostic
  - detection of uterine anomalies or pathology (e.g. infertility work-up)
  - AUB
  - DUB
- therapeutic
  - removal of uterine polyps, fibroids, adhesions, septa
  - endometrial ablation
Complications
- perforation of uterus, laceration of cervix
- bleeding
- infection
- absorption of excess distension medium (when sugar solutions utilized, e.g. glucose, mannitol)
  - fluid overload, hyponatremia
    - procedure should be abandoned if the fluid deficit rises to 1 L; consider stopping at 500 cc
- air emboli
- anaphylactic shock

Endometrial Ablation
- alternative invasive procedure to hysterectomy for treatment of AUB; performed as outpatient
- rationale is to coagulate or resect the endometrium basalis layer to prevent monthly build-up and reduce menstrual losses

Methods
- rollerball electrode coagulation or resection
- microwave endometrial ablation
- thermoablation (hot water), balloon ablation
- laser photocoagulation

Complications
- infection
- injury to pelvic viscera if uterus perforated
- hematometra
- absorption of excess distention medium \(\rightarrow\) fluid overload, hyponatremia
- failure (i.e. bleeding/menorrhagia persists)
- recurrence of symptoms (~20% at 5 yr), may eventually require hysterectomy

Hysterectomy

Indications
- uterine fibroids
- endometriosis, adenomyosis
- uterine prolapse
- pelvic pain
- AUB
- cancer (endometrium, ovaries, fallopian tubes, cervix)

Complications
- general anesthetic
- bleeding
- infection
- injury to other organs (ureter, bladder, rectum)
- loss of ovarian function (if ovaries removed, iatrogenic menopause)

Approaches
1. vaginal vs. abdominal
  - indications for vaginal approach: mobile uterus, uterine size <12 wk
  - advantages of vaginal approach: less pain, faster recovery time, allows for simultaneous repair of rectocele/cystocele/enterocele, improved aesthetics
2. open vs. laparoscopic-assisted
  - advantages of laparoscopy: less pain, faster recovery, improved aesthetics, shorter hospital stay
3. robotic
  - similar advantages to laparoscopy
  - more dexterous

Approaches to Hysterectomy
- Abdominal hysterectomy: uterus removed via transverse or vertical laparotomy
- Vaginal hysterectomy: uterus removed via vagina. No visualization or entry into abdomen unless laparoscopic-assisted
- Laparoscopic/Robotic: uterus removed via vagina or morcellation
Table 1. Classification of Hysterectomy

<table>
<thead>
<tr>
<th>Classification</th>
<th>Tissues Removed</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal hysterectomy</td>
<td>Uterus</td>
<td>Inaccessible cervix (e.g. adhesions) Patient choice/preference</td>
</tr>
<tr>
<td>Total hysterectomy (extrafascial simple hysterectomy/type 1)</td>
<td>Uterus, cervix, uterine artery ligated at uterus</td>
<td>Uterine fibroids Endometriosis Adenomyosis Menorrhagia DUB</td>
</tr>
<tr>
<td>Total hysterectomy (extrafascial simple hysterectomy/type 1) + bilateral salpingo-oophorectomy (TAH/BSO)</td>
<td>Uterus, cervix, uterine artery ligated at uterus, fallopian tubes, ovaries</td>
<td>Endometrial cancer Malignant adnexal masses &gt;45 yr old Consider for endometriosis</td>
</tr>
<tr>
<td>Modified radical hysterectomy (type 2)</td>
<td>Uterus, cervix, proximal 1/3 parametria, uterine artery ligated medial to the ureter, mid point of uterosacral ligaments and upper 1-2 cm vagina</td>
<td>Cervical cancer (up to stage IBI, see Table 24)</td>
</tr>
<tr>
<td>Radical hysterectomy (type 3)</td>
<td>Uterus, cervix, upper 1/3-1/2 vagina, entire parametria, uterine artery ligated at its origin from internal iliac artery, uterosacral ligament at most distal attachment (rectum)</td>
<td>Cervical cancer</td>
</tr>
</tbody>
</table>

Disorders of Menstruation

Amenorrhea

Differential Diagnosis of Amenorrhea

Table 2. Differential Diagnosis of Primary Amenorrhea

<table>
<thead>
<tr>
<th>With Secondary Sexual Development</th>
<th>Without Secondary Sexual Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal breast and pelvic development</td>
<td>Normal breast, abnormal uterine development</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>High FSH (hypergonadotropin hypergonadism)</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Low FSH (hypergonadotropin hypergonadism)</td>
</tr>
<tr>
<td>PCOS</td>
<td>Gonadal dysgenesis</td>
</tr>
<tr>
<td>Hypothalamic dysfunction</td>
<td>• Abnormal sex chromosome</td>
</tr>
<tr>
<td></td>
<td>• Turner’s X0</td>
</tr>
<tr>
<td></td>
<td>• Normal sex chromosome (46XX, 46XY)</td>
</tr>
<tr>
<td>Androgen insensitivity</td>
<td>Constitutional delay (most common)</td>
</tr>
<tr>
<td>Anatomic abnormalities</td>
<td>Congenital abnormalities</td>
</tr>
<tr>
<td>• Müllerian agenesis, uterovaginal septum, imperforate hymen</td>
<td>• Isolated GnRH deficiency</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>• Pituitary failure (Kallman syndrome, head injury, pituitary adenoma, etc.)</td>
</tr>
<tr>
<td>PCOS</td>
<td>Acquired</td>
</tr>
<tr>
<td>Hypothalamic dysfunction</td>
<td>• Endocrine disorders (T1DM)</td>
</tr>
<tr>
<td></td>
<td>• Pituitary tumors</td>
</tr>
<tr>
<td></td>
<td>• Systemic disorders (IBD, JRA, chronic infections, etc.)</td>
</tr>
</tbody>
</table>

Oligomenorrhea

Episodic vaginal bleeding occurring at intervals >35 d.

Table 3. Differential Diagnosis of Secondary Amenorrhea

<table>
<thead>
<tr>
<th>With Hyperandrogenism</th>
<th>Without Hyperandrogenism</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCOS</td>
<td>Hypergonadotropic hypergonadism (aka premature ovarian failure: high FSH, low estradiol)</td>
</tr>
<tr>
<td>Autonomous hyperandrogenism (androgen secretion independent of the HPO axis)</td>
<td>• Idiopathic</td>
</tr>
<tr>
<td>• Ovarian: tumour, hyperthecosis</td>
<td>• Autoimmune: T1DM, autoimmune thyroid disease, Addison’s disease</td>
</tr>
<tr>
<td>• Adrenal androgen-secreting tumour</td>
<td>• Iatrogenic: cyclophosphamide drugs, radiation</td>
</tr>
<tr>
<td>Late onset or mild congenital adrenal hyperplasia (rare)</td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>Endocrinopathies: most commonly hyper or hypothyroidism</td>
<td>Endocrinopathies: most commonly hyper or hypothyroidism</td>
</tr>
<tr>
<td>Hypogonadotropic hypergonadism (low FSH):</td>
<td>Hypogonadotropic hypergonadism (low FSH):</td>
</tr>
<tr>
<td>Pituitary compression or destruction: pituitary adenoma, craniosphenyngioma, lymphocytic hypophysitis, infiltration (sarcoidosis), head injury, Sheehan’s syndrome</td>
<td>Pituitary compression or destruction: pituitary adenoma, craniosphenyngioma, lymphocytic hypophysitis, infiltration (sarcoidosis), head injury, Sheehan’s syndrome</td>
</tr>
<tr>
<td>Functional hypothalamic amenorrhea (often related to stress excessive exercise and/or anorexia)</td>
<td>Functional hypothalamic amenorrhea (often related to stress excessive exercise and/or anorexia)</td>
</tr>
</tbody>
</table>

Primary Amenorrhea

No menses by age 14 in absence of 2º sexual characteristics or no menses by age 16 with 2º sexual characteristics.

Secondary Amenorrhea

No menses for >6 mo or 3 cycles after documented menarche.

Oligomenorrhea

Episodic vaginal bleeding occurring at intervals >35 d.

Prolactinoma Symptoms

Galactorrhea, visual changes, headache.

2º amenorrhea is pregnancy until proven otherwise.

Functional hypothalamic amenorrhea is the most common cause of amenorrhea.
Investigations

**Amenorrhea**

### 1° Amenorrhea
- **History and Physical Exam**
  - **β-hCG, hormonal workup (TSH, prolactin, FSH, LH, androgens, estradiol)**
  - **Progesterone challenge to assess estrogen status**
    - Medroxyprogesterone acetate (Provera®) 10 mg PO OD for 10-14 d
    - Any uterine bleed within 2-7 d after completion of Provera® is considered to be a positive test/withdrawal bleed
    - Withdrawal bleed suggests presence of adequate estrogen to thicken the endometrium; thus withdrawal of progesterone results in bleeding
    - If no bleeding occurs, there may be inadequate estrogen (hypoestrogenism) or excessive androgens
  - **Karyotype:** indicated if premature ovarian failure or absent puberty
  - **U/S to confirm normal anatomy, identify PCOS**

### 2° Amenorrhea
- **β-hCG**
  - **Negative**
    - Prolactin (PL) Abnormal
    - Progesterone challenge
  - **High**
    - HP axis dysfunction
      - MRI hypothalamus, pituitary
      - Measure other pituitary hormones
      - Common etiology:
        - Weight loss
        - Excessive exercise
        - Systemic diseases
    - Premature ovarian failure
      - MRI MRKH syndrome
      - AIP
      - Müllerian dysgenesis
      - Mullerian agenesis
      - Transverse vaginal septum
      - Imperforate hymen
      - Cervical agenesis

### Treatment

**Table 4. Management of Amenorrhea**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1° AMENORRHEA</strong></td>
<td></td>
</tr>
</tbody>
</table>
| AIS | • Gonadal resection after puberty  
• Psychological counselling  
• Creation of neo-vagina |
| Anatomical | • Surgical management |
  - Imperforate hymen  
  - Transverse vaginal septum  
  - Cervical agenesis |
| Müllerian dysgenesis (MRKH syndrome) | • Psychological counselling  
• Creation of neo-vagina with dilation  
• Diagnostic study to confirm normal urinary system and spine |
| **2° AMENORRHEA** | |
| Uterine defect | • Evaluation with hysterosalpingography or sonohysterography  
• Hysteroscopy: excision of synechiae |
| Asherman’s syndrome | |
| HP-axis dysfunction | • Identify modifiable underlying cause  
• Combined OCP to decrease risk of osteoporosis, maintain normal vaginal and breast development |
| Premature ovarian failure | • Screen for diabetes mellitus, hypothyroidism, hypoparathyroidism, hypocorticalism  
• Hormonal therapy with estrogen + progesterin to decrease risk of osteoporosis. Can use OCP |
| Hyperprolactinemia | • MRI/CT head to r/o lesion  
• If no demonstrable lesions by MRI:  
  - Bromocriptine, cabergoline if fertility desired  
  - Combined OCPs if no fertility desired  
• Demonstrable lesions by MRI: surgical management |
| Polycystic ovarian syndrome | |
Abnormal Uterine Bleeding (AUB)

![Diagram of Abnormal Uterine Bleeding](https://example.com/diagram)

**Figure 10. Approach to abnormal uterine bleeding**

**Table 5. Comparison of Anovulatory and Ovulatory Abnormal Uterine Bleeding**

<table>
<thead>
<tr>
<th>Anovulatory</th>
<th>Ovulatory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>90%</td>
</tr>
<tr>
<td><strong>Definition</strong></td>
<td>Unpredictable endometrial bleeding of variable flow and duration; sex steroids are produced but not cyclically, resulting in irregular bleeding</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>PCOS, Thyroid dysfunction, Elevated prolactin levels, Rare estrogen-producing tumors, Stress, weight loss, exercise, Liver and kidney disease</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Estrogen-dependent breakthrough bleeding: chronic estrogen production unopposed by adequate progesterone production → continued proliferation of the endometrium → thickened endometrium outgrows its blood supply → focal necrosis with partial shedding not uniformly → bleeding is usually irregular, prolonged, and heavy</td>
</tr>
</tbody>
</table>

**Investigations**
- CBC, serum ferritin
- β-hCG
- TSH, free T₃
- coagulation profile (especially in adolescents): rule out von Willebrand’s disease
- prolactin if amenorrheic
- FSH, LH
- serum androgens (especially free testosterone)
- day 21 (luteal phase) progesterone to confirm ovulation
- Pap test
- pelvic U/S: detect polyps, fibroids; measure endometrial thickness (postmenopausal)
- SHG: very sensitive for intrauterine pathology (polyps, submucous fibroids)
- HSG
- endometrial biopsy: consider biopsy in women >40 yr
  - must do endometrial biopsy in all women presenting with postmenopausal bleeding to exclude endometrial cancer
- D&C: not for treatment; diagnosis only (usually with hysteroscopy)
Treatment
- treat underlying disorders
  - if anatomic lesions and systemic disease have been ruled out, consider dysfunctional uterine bleeding (DUB)
- medical
  - mild DUB (see sidebar)
    - NSAIDs
    - anti-fibrinolytic (e.g. Cyklokapron®) at time of menses
    - combined OCP
    - progestins (Provera®) on first 10-14 d of each month if oligomenorrheic
    - Mirena® IUD
    - danazol
  - acute, severe DUB
    - replace fluid losses, consider admission
    - a) estrogen (Premarin®) 25 mg IV q4h x 24h with Gravol® 50 mg IV/PO q4h
    - b) Ovral®, or any OCP with minimum 50 µg estradiol 1 tab PO q4h x 24 h with Gravol® 50 mg IV/PO q4h
      - taper Ovral® to 1 tab tid x 2 d → bid x 2 d → OD
    - after (a) or (b), maintain patient on monophasic OCP for next several months or consider alternative medical treatment
    - clomiphene citrate
      - consider in patients who are anovulatory and who wish to get pregnant
- surgical
  - endometrial ablation; consider pretreatment with danazol or GnRH agonists
  - if finished childbearing
  - repeat procedure may be required if symptom reoccur
  - hysterectomy: definitive treatment

Dysmenorrhea

Etiology
- see Differential Diagnoses of Common Presentations, GY6

<table>
<thead>
<tr>
<th></th>
<th>Primary Dysmenorrhea</th>
<th>Secondary Dysmenorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Features</td>
<td>Menstrual pain in absence of organic disease. Begins 6 mo-2 yr after menarche (once ovulatory cycles established)</td>
<td>Menstrual pain due to organic disease. Usually begins in women who are in their 20s, worsens with age May improve temporarily after childbirth</td>
</tr>
<tr>
<td>Signs and Symptoms</td>
<td>Colicky pain in abdomen, radiating to the lower back, labia, and inner thighs beginning hours before onset of bleeding and persisting for hours or days (48-72 h) Associated symptoms: nausea, vomiting, altered bowel habits, headaches, fatigue (prostaglandin-associated)</td>
<td>Associated dyspareunia, abnormal bleeding, infertility</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Associated dyspareunia, abnormal bleeding, infertility</td>
<td>Bimanual exam: uterine or adnexal tenderness, fixed uterine retroflexion, uterosacral nodularity, pelvic mass, or enlarged irregular uterus (findings are rare in women &lt; 20 yr) U/S, laparoscopy and hysteroscopy may be necessary to establish the diagnosis</td>
</tr>
<tr>
<td>Treatment</td>
<td>PG synthetase inhibitors (e.g. Anaprox®): should be started before onset of pain OCP: suppress ovulation/reduce menstrual flow</td>
<td>Treat underlying cause</td>
</tr>
</tbody>
</table>
Endometriosis

Etiology
- not fully understood
- proposed mechanisms (combination likely involved)
  - retrograde menstruation (Sampson’s theory)
    - seeding of endometrial cells by transtubal regurgitation during menstruation
    - endometrial cells most often found in dependent sites of the pelvis
  - immunologic theory: altered immunity may limit clearance of transplanted endometrial cells from pelvic cavity (may be due to decreased NK cell activity)
  - metaplasia of coelomic epithelium
    - undefined endogenous biochemical factor may induce undifferentiated peritoneal cells to develop into endometrial tissue
  - extrapelvic disease may be due to aberrant vascular or lymphatic dissemination of cells
    - e.g. ovarian endometriosis may be due to direct lymphatic flow from uterus to ovaries

Epidemiology
- incidence: 15-30% of pre-menopausal women
- mean age at presentation: 25-30 yr
- regresses after menopause

Risk Factors
- family history (7-10 fold increased risk if affected 1st degree relative)
- obstructive anomalies of the genital tract (earlier onset) – resolve with treatment of anomaly
- nulliparity
- age >25 yr

Sites of Occurrence
- ovaries: 60% patients have ovarian involvement
- broad ligament, vesicouterine fold
- peritoneal surface of the cul-de-sac, uterosacral ligaments
- rectosigmoid colon, appendix
- rarely may occur in sites outside abdomen/pelvis, including lungs

Clinical Features
- may be asymptomatic
- history
  - menstrual symptoms
    - cyclic symptoms due to growth and bleeding of ectopic endometrium, usually precede menses (24-48 h) and continue throughout and after flow
    - secondary dysmenorrhea
    - sacral backache with menses
    - pain may eventually become chronic, worsening perimenstrually
    - premenstrual and postmenstrual spotting
    - deep dyspareunia
  - infertility
    - 30-40% of patients with endometriosis will be infertile
    - 15-30% of those who are infertile will have endometriosis
  - bowel and bladder symptoms
    - frequency, dysuria, hematuria
    - diarrhea, constipation, hematochezia, dyschezia
- physical
  - tender nodularity of uterine ligaments and cul-de-sac felt on rectovaginal exam
  - fixed retroversion of uterus
  - firm, fixed adnexal mass (endometrioma)
  - physical findings not present in adolescent population

Investigations
- definitive diagnosis requires:
  - direct visualization of lesions typical of endometriosis at laparoscopy
  - biopsy and histologic exam of specimens (2 or more of: endometrial epithelium, glands, stroma, hemosiderin-laden macrophages)
- laparoscopy
  - mulberry spots: dark blue or brownish-black implants on the uterosacral ligaments, cul-de-sac or anywhere in the pelvis
  - endometrioma: “chocolate” cysts on the ovaries
  - “powder-burn” lesions on the peritoneal surface
  - early white lesions and clear blebs
  - peritoneal “pockets”
- CA-125
  - may be elevated in patients with endometriosis
Treatment
- depends on certainty of the diagnosis, severity of symptoms, extent of disease, desire for future fertility and impact to GI/GU systems (e.g. intestinal obstruction)
- medical
  - NSAIDs (e.g. naproxen sodium – Anaprox®)
  - pseudopregnancy
    - cyclic/continuous estrogen-progestin (OCP)
    - medroxyprogesterone (Depo-Provera®)
    - dienogest (Visanne®)
  - pseudomenopause
    - 2nd line: only short-term (<6 mo) due to osteoporotic potential with prolonged use, unless combined with add-back therapy (e.g. estrogen/progesterone or SERM). If long-term use required, add-back estrogen+progesterone
    - danazol (Danocrine®): weak androgen
      - side effects: weight gain, fluid retention, acne, hirsutism, voice change
    - leuprolide (Lupron®): GnRH agonist (suppresses pituitary)
      - side effects: hot flashes, vaginal dryness, reduced libido
      - can use ≥12 mo with add-back progestin or estrogen
- surgical
  - conservative laparoscopy using laser, electrocautery ± laparotomy
  - ablation/resection of implants, lysis of adhesions, ovarian cystectomy of endometriomas
  - definitive: bilateral salpingo-oophorectomy ± hysterectomy
  - ± follow-up with medical treatment for pain control not shown to impact on preservation of fertility
  - best time to become pregnant is immediately after conservative surgery

Adenomyosis
- synonym: “endometriosis interna” (uterine wall may be diffusely involved)

Epidemiology
- 15% of females >35 yr old; found in 20-40% of hysterectomy specimens
- mean age at presentation: 40-50 yr old (older age group than seen in endometriosis)
- adenomyosis is a common histologic finding in asymptomatic patients

Clinical Features
- often asymptomatic
- menorrhagia, secondary dysmenorrhea, pelvic discomfort
- dyspareunia, dyschezia
- uterus symmetrically bulky, usually <14 cm, mobility not restricted, no associated adnexal pathology
- Halban sign: tender, softened uterus on premenstrual bimanual exam

Investigations
- clinical diagnosis
- U/S or MRI can be helpful
- endometrial sampling to rule out other pathology

Treatment
- iron supplements as necessary
- analgesics, NSAIDs
- OCP, medroxyprogesterone (Depo-Provera®)
- low dose danazol 100-200 mg PO OD (trial x 4 mo)
- GnRH agonists (e.g. leuprolide)
- definitive: hysterectomy (no conservative surgical treatment)

Leiomyomata (Fibroids)

Epidemiology
- diagnosed in approximately 40-50% of pre-menopausal women >35 yr
- more common in African Americans, where they are also larger and occur at earlier age
- common indication for major surgery in females
- minimal malignant potential (1:1000)
- typically regress after menopause; enlarging fibroids in a postmenopausal woman should prompt consideration of malignancy
  - 50% of leiomyosarcomas originate from within fibroids
**Pathogenesis**

- estrogen stimulates monoclonal smooth muscle proliferation
- progesterone stimulates production of proteins that inhibit apoptosis
- degenerative changes (occur when tumour outgrows blood supply)
  - hyaline degeneration (most common degenerative change)
  - cystic degeneration (from breakdown of hyaline)
  - red/carnearious degeneration (hemorrhage into tumour, may occur in pregnancy)
  - fatty degeneration
  - calcification
  - sarcomatous degeneration (rare)
- parasitic myoma: tumour becomes attached to another organ (typically omentum or small bowel mesentery), develops new blood supply and loses connection to uterus

**Clinical Features**

- majority asymptomatic (60%), often discovered as incidental finding on pelvic exam or U/S
- abnormal uterine bleeding (30%): dysmenorrhea, menorrhagia
- pressure/bulk symptoms (20-50%)
  - pelvic pressure/heaviness
  - increased abdominal girth
  - urinary frequency and urgency
  - acute urinary retention (extremely rare but surgical emergency!)
  - constipation, bloating (rare)
- acute pelvic pain
- fibroid degeneration
- fibroid torsion (pedunculated subserosal)
- infertility, recurrent pregnancy loss
- pregnancy complications (potential enlargement and increased pain, obstructed labour, difficult C-section)

**Investigations**

- bimanual exam: uterus asymmetrically enlarged, usually mobile
- CBC: anemia
- U/S: to confirm diagnosis and assess location of fibroids
- sonohysterogram: useful for differentiating endometrial polyps from submucosal fibroids, or if intracavitary growth
- endometrial biopsy to rule out uterine cancer for abnormal uterine bleeding (especially if intracavitary growth)
- MRI is used for pre-op planning (e.g. before myomectomy)

**Treatment**

- only if symptomatic, rapidly enlarging, if menorrhagia or menometrorrhagia, if intracavitary growth
- treat anemia if present
- conservative approach (watch and wait) if:
  - symptoms absent or minimal
  - fibroids <6-8 cm or stable in size
  - not submucosal (submucosal fibroids are more likely to be symptomatic)
  - currently pregnant due to increased risk of bleeding (follow-up U/S if symptoms progress)
- medical approach
  - antiprostaglandins (ibuprofen, other NSAIDs)
  - tranexamic acid (Cyklokapron®)
  - OCP/Depo-Provera®
  - GnRH agonist: leuprolide (Lupron®), danazol (Danocrine®)
    - short-term use only (6 mo)
    - often used pre-myomectomy or pre-hysterectomy to reduce fibroid size
    - reduced bleeding
  - ulipristal acetate: a partial progesterone receptor agonist
- interventional radiology approach
  - uterine artery embolization (occludes both uterine arteries) → shrinks fibroids by 50% at 6 mo; improves menorrhagia in 90% of patients within 1-2 mo; not an option in women considering childbearing
- surgical approach
  - myomectomy (hysteroscopic, transabdominal or laparoscopic); preserves fertility
  - hysteroscopic resection of fibroid and endometrial ablation for menorrhagia
  - hysterectomy (see Hysterectomy, GY11)
- note: avoid operating on fibroids during pregnancy (due to vascularity and potential pregnancy loss); expectant management usually best

**Figure 11. Possible anatomic locations of uterine leiomyomata**

The effect of pregnancy on fibroid size is variable.

**Ulipristal Acetate versus Leuprolide Acetate for Uterine Fibroids**

**Study**: Phase III, double-blind RCT of the efficacy and side-effect profile of ulipristal acetate versus leuprolide acetate for the treatment of symptomatic uterine fibroids before surgery.

**Outcomes**: Control of uterine bleeding at week 13 was the primary outcome. Secondary outcomes included bleeding pattern, amenorrhea, changes in fibroid/uterine volume, and global pain score.

**Patients**: 307 premenopausal women with symptomatic fibroids and excessive uterine bleeding were randomly assigned to oral ulipristal acetate (5 mg or 10 mg) or intramuscular injections of leuprolide acetate.

**Results**: Control of bleeding at week 13 was not significantly different between the treatment groups. All three treatments reduced uterine volume, although this decrease was significantly greater in the leuprolide group (47% reduction) than in the ulipristal groups (20-22%). 40% of the leuprolide group reported moderate-to-severe hot flashes, but only 17% (5 mg) and 10% (10 mg) of the ulipristal groups did.

**Conclusions**: Oral ulipristal acetate (5 mg or 10 mg) is noninferior to intramuscular leuprolide acetate for control of uterine bleeding due to fibroids, and it had a better side-effect profile.

**Suppression of Ovarian Activity with a Drosperone-Containing Oral Contraceptive in a 24/4 Regimen**

**Suppression of ovarian activity**: A 24/4 regimen is associated with greater ovarian suppression than the 21/7 regimen.

**Study**: Double-blind randomized.

**Patients**: Women aged 18-35 yr, post-ovulation or had a follicular diameter ≥15 mm before day 23 during a pre-treatment cycle.

**Intervention**: Drospirenone 3 mg plus ethinyl estradiol 20 µg administered in 24/4 regimen vs. 21/7 regimen.

**Outcome**: Suppression of ovarian activity (Hoogland score).

**Results**: Women on a 24/4 regimen had greater and more consistent ovarian suppression than the 21/7 group. More women in the 24/4 group had no ovarian activity compared to women in the 21/7 group.

**Conclusion**: A 24/4 regimen is associated with greater ovarian suppression than a 21/7 regimen.
Contraception

- see Family Medicine, FM20

Table 7. Classification of Contraceptive Methods

<table>
<thead>
<tr>
<th>Type</th>
<th>Effectiveness (perfect use, typical use)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological</td>
<td></td>
</tr>
<tr>
<td>Withdrawal/cotus interruptus</td>
<td>77%</td>
</tr>
<tr>
<td>Rhythm method/calendar/mucus/symptothermal</td>
<td>98%, 76%</td>
</tr>
<tr>
<td>Lactational amenorrhea</td>
<td>98% (first 6 mo postpartum)</td>
</tr>
<tr>
<td>Chance – no method used</td>
<td>10%</td>
</tr>
<tr>
<td>Abstinence of all sexual activity</td>
<td>100%</td>
</tr>
<tr>
<td>Barrier Methods</td>
<td></td>
</tr>
<tr>
<td>Condom alone</td>
<td>98%, 85%</td>
</tr>
<tr>
<td>Spermicide alone</td>
<td>82%, 71%</td>
</tr>
<tr>
<td>Sponge – Parous</td>
<td>80%, 68%</td>
</tr>
<tr>
<td>– Nulliparous</td>
<td>91%, 84%</td>
</tr>
<tr>
<td>Diaphragm with spermicide</td>
<td>94%, 84%</td>
</tr>
<tr>
<td>Female condom</td>
<td>95%, 79%</td>
</tr>
<tr>
<td>Cervical cap – Parous</td>
<td>74%, 68%</td>
</tr>
<tr>
<td>– Nulliparous</td>
<td>91%, 84%</td>
</tr>
<tr>
<td>Hormonal</td>
<td></td>
</tr>
<tr>
<td>OCP</td>
<td>99.7%, 92%</td>
</tr>
<tr>
<td>Nuva Ring®</td>
<td>99.7%, 92%</td>
</tr>
<tr>
<td>Transdermal (Ortho Evra®)</td>
<td>99.7%, 92%</td>
</tr>
<tr>
<td>Depo-Provera®</td>
<td>99.7%, 97%</td>
</tr>
<tr>
<td>Progestin-only pill (Micronor®)</td>
<td>90-99%</td>
</tr>
<tr>
<td>Minora® IUD</td>
<td>99.9%</td>
</tr>
<tr>
<td>Copper IUD</td>
<td>99.3%</td>
</tr>
<tr>
<td>Surgical</td>
<td></td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>99.65%</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>99.9%</td>
</tr>
<tr>
<td>Emergency Postcoital Contraception (EPC)</td>
<td></td>
</tr>
<tr>
<td>“Yuzpe” method</td>
<td>98% (within 24 h), decreases by 30% at 72 h</td>
</tr>
<tr>
<td>“Plan B” levonorgestrel only</td>
<td>98% (within 24 h), decreases by 70% at 72 h</td>
</tr>
<tr>
<td>Postcoital IUD</td>
<td>99.9%</td>
</tr>
</tbody>
</table>

Effectiveness: percentage of women reporting no pregnancy after 1 yr of use.

Hormonal Methods

Combined Oral Contraceptive Pills (OCPs)
- most contain low dose ethinyl estradiol (20-35 μg) plus progestin (norethindrone, norgestrel, levonorgestrel, desogestrel, norgestimate, drospirenone)
- failure rate (0.3% to 8%) depending on compliance
- monophasic or triphasic formulations (varying amount of progestin throughout cycle)

Transdermal (Ortho Evra®)
- continuous release of 6 mg norelgestromin and 0.60 mg ethinyl estradiol into bloodstream
- applied to lower abdomen, back, upper arm, buttocks, NOT breast
- worn for 3 consecutive weeks (changed every wk) with 1 wk off to allow for menstruation
- as effective as OCP in preventing pregnancy (>99% with perfect use)
- may be less effective in women >90 kg
- may not be covered by drug plans

Contraceptive Ring (Nuva Ring®)
- thin flexible plastic ring; releases etonogestrel 120 μg/d and estradiol 15 μg/d
- works for 3 wk then removed for 1 wk to allow for menstruation
- as effective as OCP in preventing pregnancy (98%)
- avoids first pass effect
- side effects: vaginal infections/irritation, vaginal discharge
- may have better cycle control; i.e. decreased breakthrough bleeding

Starting Hormonal Contraceptives
- thorough history and physical examination, including blood pressure and breast exam
- follow-up visit 6 wk after hormonal contraceptives prescribed
- pelvic exam can be delayed until a subsequent visit

Contraceptive Ring (Nuva Ring®)

Transdermal (Ortho Evra®)

Combined Oral Contraceptive Pills (OCPs)

Barrier Methods

Physiological

Withdrawal/cotus interruptus
Rhythm method/calendar/mucus/symptothermal
Lactational amenorrhea
Chance – no method used
Abstinence of all sexual activity

Barrier Methods

Condom alone
Spermicide alone
Sponge – Parous
– Nulliparous
Diaphragm with spermicide
Female condom
Cervical cap – Parous
– Nulliparous

Effectiveness: percentage of women reporting no pregnancy after 1 yr of use.

Cervical cap – Parous
Female condom
Diaphragm with spermicide
Sponge – Parous
Spermicide alone
Condom alone
Abstinence of all sexual activity

Hormonal

OCP
Nuva Ring®
Transdermal (Ortho Evra®)
Depo-Provera®
Progestin-only pill (Micronor®)
Minora® IUD

Emergency Postcoital Contraception (EPC)

“Yuzpe” method
“Plan B” levonorgestrel only
Postcoital IUD

Effect of ethinyl estradiol dose
ALL OCPs with ≤35 μg ethinyl estradiol carry a lower risk of VTE compared with oral contraceptives with 50 μg.

Effect of progestin type
Drospirenone: third generation progestin, e.g. Yasmin® and Yaz®
Levonorgestrel: second generation progestin, e.g. Alesse®

J Obstet Gyn Canada 2010;32:1192-1197

Rates of venous thromboembolism
(VTE: DVT and PE) expressed in women/yr
Non-users of reproductive age
4-5/10 000
Oral contraceptive (OCP) users
9-10/10 000
Pregnancy
29/10 000
Immediate post-partum
300-400/10 000
* Risk is highest in the first months of use and in medication switch.

Abstinence of all sexual activity
Condom alone
Spermicide alone
Diaphragm with spermicide
Female condom
Cervical cap – Parous
– Nulliparous

Counselling the Adolescent about Contraception

More than 90% of adolescent pregnancies are unintended, and ~50% of all pregnancies occur within the first 6 mos of initiating sexual activity. In addition, 85% of sexually active women become pregnant within 1 yr if no contraception is used and even some of the least effective contraceptive methods markedly decrease the risk of pregnancy.

Emergency Postcoital Contraception (EPC)

“Yuzpe” method
“Plan B” levonorgestrel only
Postcoital IUD

Effect of ethinyl estradiol dose
ALL OCPs with ≤35 μg ethinyl estradiol carry a lower risk of VTE compared with oral contraceptives with 50 μg.

Effect of progestin type
Drospirenone: third generation progestin, e.g. Yasmin® and Yaz®
Levonorgestrel: second generation progestin, e.g. Alesse®

Two high quality research studies found comparable VTE rates with drospirenone-containing OCPs and other approved products.
1. Dinger et al., Contraception 2007;75:344-354

Two reports with significant methodological flaws found increased VTE risk. Results and conclusions may have been distorted by residual confounding.
1. Liedgard et al., BMJ 2008;339:a2680
2. Van Hylckama Vlieg et al., BMJ 2009;339:b2890

Conclusion
Occurrence of serious risks, such as VTE, is rare with all contemporary OCPs.
Individualized risk assessment is mandatory.
For most healthy women of reproductive age, the benefits of OCPs will outweigh the risks.

Risk of Non-Fatal Venous Thromboembolism in Women Using Oral Contraceptives Containing Drospirenone Compared with Women Using Oral Contraceptives Containing Levonorgestrel: A Case-Control Study Using United States Claims Data
BMJ 2011;342:d2151

Study: Nested case-control and cohort study.
Patients: Women aged 15-44 yr receiving oral contraceptives
Intervention: Drospirenone-containing contraceptive vs. Levonorgestrel-containing contraceptive.
Outcome: Non-fatal venous thromboembolism.
Results: Women receiving drospirenone-containing oral contraceptives had twice as likely to develop non-fatal VTE compared to women receiving levonorgestrel-containing contraceptives (age-adjusted incidence rate ratio was 2.0).
Table 8. Combined Estrogen and Progestin Contraceptive Methods

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Advantages</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulatory suppression through inhibition of LH and FSH</td>
<td>Highly effective</td>
<td>Nausea</td>
<td>Absolute</td>
</tr>
<tr>
<td>Decidualization of endometrium</td>
<td>Reversible</td>
<td>Breast changes (tenderness, enlargement)</td>
<td>Known/suspected pregnancy</td>
</tr>
<tr>
<td>Thickening of cervical mucus resulting in decreased sperm penetration</td>
<td>Cycle regulation</td>
<td>Fluid retention/bloating/edema</td>
<td>Undiagnosed abnormal vaginal bleeding</td>
</tr>
<tr>
<td></td>
<td>Decreased dysmenorrhea and menorrhagia (less amenorrhea)</td>
<td>Weight gain (rare)</td>
<td>Prior thromboembolic events, thromboembolic disorders (Factor V Leiden mutation; protein C, S or antithrombin III deficiency), active thrombophilias</td>
</tr>
<tr>
<td></td>
<td>Decreased benign breast disease and ovarian cyst development</td>
<td>Migraine, headaches</td>
<td>Cerebrovascular or coronary artery disease</td>
</tr>
<tr>
<td></td>
<td>Decreased risk of ovarian and endometrial cancer</td>
<td>Thromboembolic events</td>
<td>Estrogen-dependent tumours (breast, uterus)</td>
</tr>
<tr>
<td></td>
<td>Increased cervical mucus which may lower risk of STIs</td>
<td>Liver adenoma (rare)</td>
<td>Impaired liver function associated with acute liver disease</td>
</tr>
<tr>
<td></td>
<td>Decreased PMS symptoms</td>
<td>Breakthrough bleeding (low estradiol levels)</td>
<td>Congenital hyperthryoidism/dermiasia</td>
</tr>
<tr>
<td></td>
<td>Improved acne</td>
<td></td>
<td>Smoker age &gt;35 yr</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis protection (possibly)</td>
<td></td>
<td>Migraines with focal neurological symptoms (excluding aura)</td>
</tr>
</tbody>
</table>

Table 9. Selected Examples of OCPs

<table>
<thead>
<tr>
<th>Type</th>
<th>Active Compounds (estriol and progestin derivative)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alesse®</td>
<td>17 µg ethinyl estradiol and 0.5 mg levonorgestrel</td>
<td>Low-dose therefore often a good starting OCP</td>
<td>Low-dose pills can often result in breakthrough bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can improve acne and help regulate menstrual cycles</td>
<td>If this persists for longer than 3 mo, patient should be switched to an OCP with higher estrogen content</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tri-cyclen®</td>
<td>35 µg ethinyl estradiol and 0.180/0.250 mg norgestimate</td>
<td>Low androgenic activity can help with acne</td>
<td>Triphasic OCPs should not be used continuously (unless monophasic formulations), although should be used continuously for 1 pack</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yasmin® and Yaz®</td>
<td>Yasmin®: 30 µg ethinyl estradiol + 3 mg drospirenone (a new progestin)</td>
<td>Decreased perception of cyclic weight gain/bloating</td>
<td>Hyperkalemia (rare, contraindicated in renal and adrenal insufficiency)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fewer PMS symptoms</td>
<td>Check potassium if patient also on ACE inhibitor, ARB, K+- sparing diuretic, heparin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved acne</td>
<td>Continue use of spironolactone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increased risk of DVT-PE</td>
</tr>
</tbody>
</table>

Table 10. Progestin Only Contraceptive Methods

<table>
<thead>
<tr>
<th>Indications</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suitable for postpartum women</td>
<td>Progestin prevents LH surge</td>
<td>Irregular menstrual bleeding</td>
<td>Absolute</td>
</tr>
<tr>
<td>(does not affect breast milk supply)</td>
<td>Thickening of cervical mucus</td>
<td>Weight gain</td>
<td>None</td>
</tr>
<tr>
<td>Women with contraindications to combined OCP (e.g. thromboembolic or myocardial disease)</td>
<td>Decrease tubal motility</td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Women intolerant of estrogenic side effects of combined OCPs</td>
<td>Endometrial decidualization</td>
<td>Breast tenderness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ovulation suppression – oral progestins (not IM) do not consistently suppress compared to combined OCPs</td>
<td>Mood changes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Functional ovarian cysts</td>
<td>Acne/oily skin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acne/oily skin</td>
<td>Hirsutism</td>
<td></td>
</tr>
</tbody>
</table>

Reference: World Health Organization Guidelines for Oral Contraceptive Use

Missed Combined OCPs

- Miss 1 pill in <24 h
  - Take 1 pill ASAP and the next pill at the usual time
- Miss ≥1 pill in a row in first wk
  - Take 1 pill ASAP and continue taking one pill daily until the end of the pack
  - Use back-up contraception for 7 d. EPC may be necessary
- Miss <3 pills in 2nd or 3rd wk of cycle
  - Take 1 pill ASAP and continue taking one pill daily until the end of the pack
  - Do not take placebo (28-d packs) or do not take a hormone free interval (21-d packs)
  - Start the next pack immediately after finishing the previous one
  - No need for back-up contraception

PROGESTIN-ONLY METHOD
Selected Examples of Progestin-Only Methods

Progestin-Only Pill ("minipill")
- Micronor® 0.35 mg norethindrone
- taken daily at same time of day to ensure reliable effect; no pill free interval
- higher failure rate (1.1-13% with typical use, 0.51% with perfect use) than other hormonal methods
- ovulation inhibited in 60% of women; most have regular cycles (but may cause oligo/amenorrhoea)
- highly effective if also post-partum breastfeeding, or if >3.5 yr

Depo-Provera®
- injectable depot medroxyprogesterone acetate
- dose 150 mg IM q12-14wk (convenient dosing)
- initiate within 5 d of beginning of normal menses, immediately postpartum in breastfeeding women
- irregular spotting progresses to complete amenorrhea in 70% of women (after 1-2 yr of use)
- highly effective 99%; failure rate 0.3%
- side effect: decreased bone density (may be reversible)
- disadvantage: restoration of fertility may take up to 1-2 yr

Intrauterine Device (IUD)

Table 11. IUD Contraceptive Methods

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Copper-containing IUD (Nova-T®): mild foreign body reaction in endometrium toxic to sperm and alters sperm motility</td>
<td>• Both Copper and Progesterone IUD</td>
<td>• Both Copper and Progesterone IUD</td>
</tr>
<tr>
<td>• Progestrone-releasing IUD (Mirena®): decidualization of endometrium and thickening of cervical mucus; minimal effect on ovulation</td>
<td>• Breakthrough bleeding</td>
<td>• Known or suspected pregnancy</td>
</tr>
<tr>
<td>• Highly effective (95-99%); failure rate 0-1.2%</td>
<td>• Expulsion (5% in the first year, greatest in first month and in nulliparous women)</td>
<td>• Undiagnosed genital tract bleeding</td>
</tr>
<tr>
<td>• Contraceptive effects last 5 yr</td>
<td>• Uterine wall perforation (1/1000) on insertion</td>
<td>• Acute or chronic PID</td>
</tr>
<tr>
<td>• Reversible, private, convenient</td>
<td>• If pregnancy occurs with an IUD, increased risk of ectopic</td>
<td>• Lifestyle risk for STIs*</td>
</tr>
<tr>
<td>• May be used in women with contraindications to OCPs or wanting long-term contraception</td>
<td>• Increased risk of PID (within first 10 d of insertion only)</td>
<td>• Copper IUD:</td>
</tr>
<tr>
<td></td>
<td>• Copper IUD: increased blood loss and duration of menses, dysmenorrhea</td>
<td>• Known allergy to copper</td>
</tr>
<tr>
<td></td>
<td>• Progestrone IUD: bleeding, headache</td>
<td>• Wilson’s disease</td>
</tr>
</tbody>
</table>

* Cervical swabs for gonorrhea and chlamydia should be done prior to IUD insertion.

Assessing the Risk of Venous Thromboembolic Events in Women Taking Progestin-Only Contraception: A Meta-Analysis
BMJ 2012;345:e4944
Published online 2012 August 7. doi: 10.1136/ bmj.e4944
Study: Systematic review and meta-analysis of RCTs and observational studies to see if there is an increased risk of VTE on progestin only OCP and if route of administration had any effect.
Results: They found 9 observational studies. Across all 8 studies, 167 women had VTEs. The adjusted relative risk of a VTE for users versus non-users of a progestin-only contraceptive was 1.03 (95% CI 0.76 to 1.39).
Conclusion: Oral and intracervical route made no difference. The relative risk of a VTE for users of an injectable progestin versus non-users was 2.67 (1.29 to 5.53).

New SOGC Recommendations for Depo-Provera® Users
- Inform patients of potential risks and benefits at intervals throughout course of treatment
- Recommend ways to improve bone health such as calcium, vitamin D, weight-bearing exercise, smoking cessation, decreased alcohol and caffeine intake
- There is no evidence to suggest routine BMD testing


Missed Progestin-Only Pills > 3 hours
Use back-up contraceptive method for at least 48 h. Continue to take remainder of pills as prescribed.

Missed Depo-Provera
- If last injection given 13-14 wk prior: give next injection immediately
- If > 14 wk prior, do β-hCG:
  - If β-hCG is positive, give EPC and no injection
  - If β-hCG is negative, give next injection right away and:
    - Intercourse occurred in last 5 d: give EPC, use back-up contraception for 7 d. Repeat β-hCG in 3 wk
    - Intercourse occurred > 5 d ago but within the last 14 d: use back-up contraception for 7 d. Repeat β-hCG in 3 wk
    - Intercourse occurred > 14 d ago: use back-up contraception for 7 d
- No evidence of fetal abnormalities if conceived on DMPA


Medroxyprogesterone (Depo-Provera®) and Bone Mineral Density Loss
CMAJ 2005;172:174
Extended use (up to 5 yr) of medroxyprogesterone acetate has been found to decrease spine and hip bone mineral density (BMD) by 4% to 6.9%. 2 yr after discontinuation, only partial recovery of BMD has been noted.

Canadian Consensus Guideline on Continuous and Extended Hormonal Contraception
J Obstet Gyn Canada 2007;29:S1-32
Definitions
- Extended Use: The use of combined hormonal contraceptives without hormone-free intervals.
- Continuous Use: Uninterrupted use of combined hormonal contraceptives without hormone-free intervals.

What can be used?
Oral, transdermal and vaginally administered combined hormonal contraceptives, including those originally designed for cyclic use, can be administered in a variety of Continuous and Extended (CE) regimens.

Efficacy and Adherence
Continuous combined hormonal contraceptive regimes are as effective as cyclic regimes in preventing pregnancy. Use of CE combined hormonal contraceptives may be more “forgiving” about missed doses because of the absence of a hormone-free interval.

Side Effects
The side effect profile of CE combined hormonal contraceptive regimes is not worse than with cyclic regimes, and may even be improved.

Medical/Non-contraceptive Use
For women in the perimenopausal transition who may be ovulating, CE combined hormonal contraceptive is preferred to hormonal replacement therapy for controlling problematic bleeding and vasomotor symptoms.
Emergency Postcoital Contraception (EPC)

Table 12. Emergency Contraceptive Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HORMONAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yuzpe Method</td>
<td>• Used within 72 h of unprotected intercourse; limited evidence of benefit up to 5 d</td>
<td>• Unknown; theories include:</td>
<td>• Pre-existing pregnancy (although not teratogenic)</td>
</tr>
<tr>
<td></td>
<td>• Ovral® 2 tablets then repeat in 12 h (ethinyl estradiol 100 µg/levonorgestrel 500 µg)</td>
<td>• Suppresses ovulation or causes</td>
<td>• Caution in women with contraindications to OCP (although NO absolute contraindications)</td>
</tr>
<tr>
<td></td>
<td>• Can substitute with any OCP as long as same dose of estrogen used</td>
<td>deficient luteal phase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 2% overall risk of pregnancy</td>
<td>• Alters endometrium to prevent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Efficacy decreased with time (e.g. less effective at 72 h than 24 h)</td>
<td>implantation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Affects sperm/ova transport</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nausea (due to estrogen; treat with Gravol®)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Irregular spotting</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pre-existing pregnancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(although not teratogenic)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Caution in women with</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>contraindications to OCP (although NO absolute contraindications)</td>
<td></td>
</tr>
<tr>
<td>“Plan B”</td>
<td>• Consists of levonorgestrel 750 µg q12h for 2 doses (can also take 2 doses together); taken within 72 h of intercourse</td>
<td>• Can substitute with any OCP as well as OCP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Greater efficacy (75-95% if used within 24 h) and better side effect profile than Yuzpe method but efficacy decreases with time; 1st line if &gt;24 h</td>
<td>• No estrogen thus very few contraindications/side effects (less nausea)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No estrogen thus very few contraindications/side effects (less nausea)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NON-HORMONAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postcoital IUD (Copper)</td>
<td>• Insert up to 7 d postcoitus</td>
<td>• See Table 11</td>
<td>• See Table 11</td>
</tr>
<tr>
<td></td>
<td>• Prevents implantation</td>
<td>• See Table 11</td>
<td>• See Table 11</td>
</tr>
<tr>
<td></td>
<td>• 1% failure rate</td>
<td>• Can use for short duration in</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Can use for short duration in higher risk individuals</td>
<td>higher risk individuals</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mirena® IUD cannot be used as EPC</td>
<td>• Mirena® IUD cannot be used as</td>
<td></td>
</tr>
</tbody>
</table>

Follow-up
- 3-4 wk post treatment to confirm efficacy (confirmed by spontaneous menses or pregnancy test)
- contraception counseling

Infertility

Epidemiology
- 10-15% of couples
- must investigate both members of the couple

Female Factors

Etiology
- ovulatory dysfunction (15-20%)
  - hypotalamic (hypothalamic amenorrhea)
  - pituitary (prolactinoma, hypopituitarism)
  - ovarian
    - PCOS
    - premature ovarian failure
    - luteal phase defect (poor follicle production, premature corpus luteum failure, failed uterine lining response to progesterone), poorly understood
- systemic diseases (thyroid, Cushing’s syndrome, renal/hepatic failure)
- congenital (Turner’s syndrome, gonadal dysgenesis or gonadotropin deficiency)
- stress, poor nutrition, excessive exercise (even with presence of menstruation)

- outflow tract abnormality (15-20%)
  - tubal factors (20-30%)
    - PID
  - adhesions (previous surgery, peritonitis, endometriosis)
  - ligation/occlusion (e.g. previous ectopic pregnancy)
  - uterine factors (<5%)
    - congenital anomalies, bicornuate uterus, septate uterus, prenatal DES exposure
  - intrauterine adhesions (e.g. Asherman's syndrome)
  - infection (endometritis, pelvic TB)
  - fibroids/polyps (particularly intrauterine)
  - endometrial ablation
  - cervical factors (5%)
    - hostile or acidic cervical mucus
    - anti-sperm antibodies
    - structural defects (cone biopsies, laser or cryotherapy)
• endometriosis (15-30%)
• multiple factors (30%), see GY22
• unknown factors (10-15%)

**Investigations**

- **ovulatory**
  - day 3: FSH, LH, TSH, prolactin ± DHEA, free testosterone (if hirsute)
  - day 21-23: serum progesterone to confirm ovulation
  - initiate basal body temperature monitoring (biphasic pattern)
  - postcoital test: evaluate mucus for clarity, pH, spinnbarkeit/fibrosity (rarely done)
- **tubal factors**
  - HSG (can be therapeutic – opens fallopian tube)
  - SHG (can be therapeutic – opens fallopian tube)
  - laparoscopy with dye insufflation (or tubal dye test)
- **peritoneal/uterine factors**
  - HSG/SHG, hysteroscopy
- **other**
  - karyotype

**Treatment**

- education: timing of intercourse in relation to ovulation (from 2 d prior to 2 d following presumed ovulation), every other day
- **medical**
  - ovulation induction
    - clomiphene citrate (Clomid®): estrogen antagonist that causes a perceived decreased estrogen state, resulting in increased pituitary gonadotropins; causes increased FSH and LH, leading to ovulation induction (works much better if anovulatory)
    - human menopausal gonadotropin – HMG (Pergonal®), urofollitropin – FSH (Metrodin®)
      - FSH and LH extracted from urine of postmenopausal women
      - followed by β-hCG for stimulation of ovum release
    - may add
      - bromocriptine (dopamine agonist) if elevated prolactin
      - dexamethasone for hyperandrogenism (adult onset congenital adrenal hyperplasia)
      - metformin (for PCOS)
      - luteal phase progestrone supplementation for luteal phase defect (mechanism not completely understood)
      - ASA (81 mg PO OD) for women with a history of recurrent spontaneous abortions (for antiphospholipid antibody syndrome)
- **surgical/procedural**
  - tubuloplasty
  - lysis of adhesions
  - artificial insemination: intracervical insemination (ICI), intrauterine insemination (IUI), intrauterine tuboperitoneal insemination (IUTPI), intratubal insemination (ITI)
  - sperm washing
  - IVF (in vitro fertilization)
  - IFF (intrafallopian transfer)
  - GIFT* (gamete intrafallopian transfer): immediate transfer with sperm after oocyte retrieval
  - ZIFT* (zygote intrafallopian transfer): transfer after 24 h culture of oocyte and sperm
  - TET* (tubal embryo transfer): transfer after >24 h culture
  - ICSI (intracytoplasmic sperm injection)
  - IVM (in vitro maturation)
  - ± oocyte or sperm donors
  - ± pre-genetic screening for single gene defects in karyotype of zygote
  - *Not performed in Canada

### Male Factors

- see Urology, U33

**Etiology**

- varicocele (>40%)
- idiopathic (>20%)
- obstruction (~15%)
- cryptorchidism (~8%)
- immunologic (~3%)

**Investigations**

- semen analysis and culture
- post-coital (Hühner) test: rarely done

---

**When Should Investigations Begin?**

- <35 yr: after 1 yr of unprotected intercourse
- 35-40 yr: after >6 mo
- >40 yr: immediately

**Earlier if:**

- History of PID
- History of infertility in previous relationship
- Prior pelvic surgery
- Chemotherapy/radiation in either partner
- Recurrent pregnancy loss
- Moderate-severe endometriosis

**Controversial and Evolving Ethical Issues**

- Infertility demands non-judgmental discussion
- Ethical issues surrounding therapeutic donor insemination in same sex couples, surrogacy, donor gametes and other advanced reproductive technologies are still evolving and remain controversial
- If the doctor finds that certain treatment options lie outside of their moral boundaries, the infertile couple should be referred to another physician

**Summary of Current Legislation in Canada**

**Bill C-13 Assisted Human Reproduction Act 2004:**

- **What is allowed**
  - Cloning people
  - Cloning stem cells
  - Growing human embryos for research
  - Sex selection
  - Making changes to human DNA that would pass from one generation to the rest
  - Creating people who have animal DNA
  - Buying or selling embryos, sperm, eggs or other human reproductive material
- **What is not allowed**
  - Surrogate mothers
  - Donating sperm, eggs and other reproductive material
  - Using embryos, sperm, eggs, etc., to assist conception
  - Using human embryos and stem cells in research
  - Sex selection in X-linked genetic diseases

**Normal Semen Analysis (WHO lower reference limits)**

- Must be obtained after 2-7 d of abstinence
- **Volume** 1.5 cc
- **Count** 15 million/cc
- **Motility** 58% live
- **Motility** 32% progressive, 40% total (progressive + non-progressive)
- **Morphology** 4.0% normal
Gynecological Infections

Physiologic Discharge

- clear, white, flocculent, odourless discharge; pH 3.8-4.2
- smear contains epithelial cells, Lactobacilli
- increases with increased estrogen states: pregnancy, OCP, mid-cycle, PCOS or premenarchal
- if increased in perimenopausal/postmenopausal woman, consider investigation for other effects of excess estrogen (e.g. endometrial cancer)

Vulvovaginitis

PREPUBERTAL VULVOVAGINITIS

- clinical features
  - irritation, pruritus
  - discharge
  - vulvar erythema
  - vaginal bleeding (specifically due to Group A Streptococci and Shigella)
- differential diagnosis
  - non-specific vulvovaginitis (25-75%)
  - infections (respiratory, enteric, systemic, sexually acquired)
  - foreign body (toilet paper most common)
  - Candida (if using diapers)
  - pinworms
  - polyps, tumour (ovarian malignancy)
  - vulvar skin disease (lichen sclerosis, condyloma acuminata)
  - trauma (accidental straddle injury, sexual abuse)
  - psychosomatic vaginal complaints (specific to vaginal discharge)
  - endocrine abnormalities (specific to vaginal bleeding)
  - blood dyscrasia (specific to vaginal bleeding)
- etiology
  - infectious:
    - poor hygiene, proximity of vagina to anus
    - recent infection (respiratory, enteric, systemic)
    - STI: investigate sexual abuse
  - nonspecific:
    - lack of protective hair and labial fat pads
    - lack of estrogenization
    - susceptible to chemicals, soaps (bubble baths), medications and clothing
    - enuresis
- investigations
  - vaginal swab for culture (specifically state that it is a pre-pubertal specimen)
- treatment
  - enhanced hygiene and local measures (handwashing, white cotton underwear, no nylon tights, no tight fitting clothes, no sleeper pajamas, sitz baths, avoid bubble baths, use mild detergent, eliminate fabric softener, avoid prolonged exposure to wet bathing suits, urination with legs spread apart)
  - A&D® dermatological ointment (vitamin A/D) to protect vulvar skin
  - infectious: treat with antibiotics for organism identified

Table 13. Other Common Causes of Vulvovaginitis in Prepubertal Girls

<table>
<thead>
<tr>
<th>Pinworms</th>
<th>Lichen Sclerosis</th>
<th>Foreign Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Collophane tape test</td>
<td>Area of white patches and thinning of skin</td>
</tr>
<tr>
<td>Treatment</td>
<td>Empirical treatment with mebendazole</td>
<td>Topical steroid creams</td>
</tr>
</tbody>
</table>

Most common gynecological problem in prepubertal girls is non-specific vulvovaginitis, not yeast!

There is no high quality evidence showing a link between vulvovaginal candidiasis and hygienic habits or wearing tight or synthetic clothing.

Prepubertal and Adolescent Gynecological Infections: Legal Aspects of Confidentiality

- Clinicians who treat adolescents must be aware of federal, state and provincial laws related to adolescent consent and confidentiality
- They must be aware of guidelines governing funding sources for particular services and be familiar with the consent and confidentiality policies of the facility in which they practice
POSTMENOPAUSAL VAGINITIS/ATROPHIC VAGINITIS

- clinical features
  - dyspareunia
  - post-coital spotting
  - mild pruritus
- investigations
  - atrophy is usually a visual diagnosis: thinning of tissues, erythema, petechiae, bleeding points, dryness on speculum exam
  - rule out malignancy: especially endometrial cancer
- treatment
  - local estrogen replacement (ideal): Premarin® cream, VagiFem® tablets, or Estring®
  - oral or transdermal hormone replacement therapy (if treatment for systemic symptoms is desired)
  - good hygiene

INFECTIOUS VULVOVAGINITIS

Table 14. Infectious Vulvovaginitis

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Candidiasis (Moniliasis)</th>
<th>Bacterial Vaginosis (BV)</th>
<th>Trichomoniasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Candida albicans (90%)</td>
<td>Gardnerella vaginalis</td>
<td>Trichomonas vaginalis (flagellated protozoan)</td>
</tr>
<tr>
<td></td>
<td>Candida glabrata (&lt;5%)</td>
<td>Mycoplasma hominis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Candida tropicalis (&lt;5%)</td>
<td>Anaerobes: Prevotella, Mobiluncus, Bacteroides</td>
<td></td>
</tr>
<tr>
<td>Pathophysiology or Transmission</td>
<td>Predisposing factors include:</td>
<td>Replacement of vaginal Lactobacillus with organisms above</td>
<td>Sexual transmission</td>
</tr>
<tr>
<td></td>
<td>- Immunosuppressed host (diabetes, AIDS, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Recent antibiotic use</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Increased estrogen levels (e.g. pregnancy, OCP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>Whitish, “cottage cheese,” minimal</td>
<td>Grey, thin, diffuse</td>
<td>Yellow-green, malodorous, diffuse, frothy</td>
</tr>
<tr>
<td>Other</td>
<td>20% asymptomatic</td>
<td>50-75% asymptomatic</td>
<td>25% asymptomatic</td>
</tr>
<tr>
<td>Signs/Symptoms</td>
<td>Intense pruritus</td>
<td>Fishy odour, esp. after coitus</td>
<td>Petechiae on vagina and cervix</td>
</tr>
<tr>
<td></td>
<td>Swollen, inflamed genitals</td>
<td>Absence of vulvar/vaginal irritation</td>
<td>Occasionally irritated tender vulva</td>
</tr>
<tr>
<td></td>
<td>Vulvar burning, dysuria, dyspareunia</td>
<td></td>
<td>Dysuria, frequency</td>
</tr>
<tr>
<td>pH</td>
<td>≤4.5</td>
<td>≥4.5</td>
<td>2≥4.5</td>
</tr>
<tr>
<td>Saline Wetmount</td>
<td>KOH wetmount reveals hyphae and spores</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• &gt; 20% clue cells = squamous epithelial cells dotted with coccobacilli (Gardnerella)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Paucity of WBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Paucity of Lactobacilli</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Positive whiff test: fishy odour with addition of KOH to slide (due to formation of amines)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Clotrimazole, butoconazole, micinazole, terconazole suppositories and/or creams for 1, 3 or 7 d treatments</td>
<td>No treatment if non-pregnant and asymptomatic, unless scheduled for pelvic surgery or procedure</td>
<td>Treat even if asymptomatic</td>
</tr>
<tr>
<td></td>
<td>• Treatment in pregnancy is usually topical</td>
<td>• Oral</td>
<td>• Metronidazole 2 g PO single dose or 500 mg bid x 7 d (alternative)</td>
</tr>
<tr>
<td></td>
<td>• Fluconazole 150 mg PO in single dose (can be used in pregnancy)</td>
<td>• Topical</td>
<td>• Symptomatic pregnant women should be treated with 2 g metronidazole once</td>
</tr>
<tr>
<td></td>
<td>• Associated with recurrent preterm labour, preterm birth and postpartum endometritis</td>
<td>• Clindamycin 2% g intravaginally at bedtime for 7 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Need to warn patients on metronidazole not to consume alcohol (disulfiram-like action)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Routine treatment of partner(s) not recommended (not sexually transmitted)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Warnings accompanying metronidazole use</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Treat partner(s)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sexually Transmitted Infections (STIs)

- see Family Medicine, FM46

TRICHOMONIASIS
- see Infectious Vulvovaginitis, Table 14, GY25

CHLAMYDIA

Etiology
- Chlamydia trachomatis

Epidemiology
- most common bacterial STI in Canada
- often associated with N. gonorrhoeae

Clinical Features
- asymptomatic (80% of women)
- muco-purulent endocervical discharge
- urethral syndrome: dysuria, frequency, pyuria, no bacteria on culture
- pelvic pain
- post-coital bleeding or intermenstrual bleeding (particularly if on OCP and prior history of good cycle control)
- symptomatic sexual partner

Investigations
- cervical culture or nucleic acid amplification test
- obligate intracellular parasite: tissue culture is the definitive standard
- urine and vaginal tests now available, which are equally or more effective than cervical culture

Treatment
- doxycycline 100 mg PO bid for 7d or azithromycin 1 g PO in a single dose (may use in pregnancy)
- also treat gonorrhea because of high rate of co-infection
- treat partners
- reportable disease
- test of cure for chlamydia required in pregnancy (cure rates lower in pregnant patients) → retest 3-4 wk after initiation of therapy

Screening
- high risk groups
- during pregnancy
- with initiation of OCP (independent risk factor)
Complications
• acute salpingitis, PID
• Fitz-Hugh-Curtis syndrome (liver capsule inflammation)
• reactive arthritis (male predominance; HLA-B27 associated), conjunctivitis, urethritis
• infertility; tubal obstruction from low grade salpingitis
• ectopic pregnancy
• chronic pelvic pain
• perinatal infection: conjunctivitis, pneumonia

GONORRHEA
Etiology
• Neisseria gonorrhoeae
• symptoms and risk factors same as with chlamydia

Investigations
• Gram stain shows Gram-negative intracellular diplococci
• cervical, rectal and throat culture (if clinically indicated)

Treatment
• single dose of ceftriaxone 250 mg IM, or cefixime 800 mg PO
• if pregnant: above regimen or 2 g spectinomycin IM (avoid quinolones)
• also treat chlamydia, because of high rate of co-infection
• treat partners
• reportable disease
• screening as with Chlamydia

HUMAN PAPILLOMAVIRUS (HPV)
Etiology
• most common viral STI in Canada
• >200 subtypes, of which >30 are genital subtypes
• HPV types 6 and 11 are classically associated with anogenital warts/condylomata acuminata
• HPV types 16 and 18 are the most oncogenic (classically associated with cervical HSIL)
• types 16, 18, 31, 33, 35, 36, 45 (and others) associated with increased incidence of cervical and vulvar intraepithelial hyperplasia and carcinoma

Clinical Features
• latent infection
  • no visible lesions, asymptomatic
  • only detected by DNA hybridization tests
• subclinical infection
  • visible lesion found during colposcopy or on Pap test
• clinical infection
  • visible wart-like lesion without magnification
  • hyperkeratotic, verrucous or flat, macular lesions
  • vulvar edema

Investigations
• cytology (see Cervical Screening Pap Test, GY43)
  • koilocytosis: nuclear enlargement and atypia with perinuclear halo
• biopsy of lesions at colposcopy
• detection of HPV DNA subtype using nucleic acid probes (not routinely done but can be done in presence of abnormal Pap test to guide treatment)

Treatment
• patient administered:
  • podofilox 0.5% solution or gel bid x 3 d in a row (4 d off) then repeat x 4 wk
  • imiquimod (Aldara®) 5% cream 3x/wk qhs x 16 wk
• provider administered:
  • cryotherapy with liquid nitrogen: repeat q1-2wk
  • podophyllin resin in tincture of benzoin: weekly
  • trichloroacetic acid (TCA) or bichloroacetic acid weekly (80-90%); safe in pregnancy
  • surgical removal/laser
  • intralesional interferon

Prevention
• vaccination: Gardasil®, Cervarix® see Table 25, GY44
• condoms may not fully protect (areas not covered, must be used every time throughout entire sexual act)
HERPES SIMPLEX VIRUS (HSV) OF VULVA

Etiology
- 90% are HSV-2, 10% are HSV-1

Clinical Features
- may be asymptomatic
- initial symptoms: present 2-21 d following contact
- prodromal symptoms: tingling, burning, pruritus
- multiple, painful, shallow ulcerations with small vesicles appear 7-10 d after initial infection (absent in many infected persons); lesions are infectious
- inguinal lymphadenopathy, malaise, and fever often with first infection
- dysuria and urinary retention if urethral mucosa affected
- recurrent infections: less severe, less frequent and shorter in duration (especially with HSV-1)

Investigations
- viral culture preferred in patients with ulcer present, however decreased sensitivity as lesions heal
- cytologic smear (Tzanck smear)
  - multinucleated giant cells, acidophilic intranuclear inclusion bodies
- type specific serologic tests for antibodies to HSV-1 and HSV-2 (not available routinely in Canada)
- HSV DNA PCR

Treatment
- first episode
  - acyclovir 400 mg PO tid x 7-10 d, or famciclovir 250 mg PO tid x 7-10 d, or valacyclovir 1 g PO bid x 7-10 d
- recurrent episode
  - acyclovir 400 mg PO tid x 3-5 d, or famciclovir 125 mg PO bid x 3-5 d, or valacyclovir 500 mg PO bid x 3 d
- daily suppressive therapy
  - consider if 6-8 recurrences per year
  - acyclovir 400 mg PO bid, or famciclovir 250 mg bid, or valacyclovir 0.5-1 g PO OD
- severe disease
  - consider IV therapy acyclovir 5-10 mg/kg IV q8h x 5-7 d
- education regarding transmission
- avoid contact from onset of prodrome until lesions have cleared
- use barrier contraception

SYPHILIS

Etiology
- Treponema pallidum

Classifications
- primary syphilis
  - 3-4 wk after exposure
  - painless chancre on vulva, vagina or cervix
  - painless inguinal lymphadenopathy
  - serological tests usually negative, local infection only
- secondary syphilis (can resolve spontaneously)
  - 2-6 mo after initial infection
  - nonspecific symptoms: malaise, anorexia, headache, diffuse lymphadenopathy
  - generalized maculopapular rash: palms, soles, trunk, limbs
  - condylomata lata: anogenital, broad-based fleshy grey lesions
  - serological tests usually positive
- latent syphilis
  - no clinical manifestations; detected by serology only
- tertiary syphilis
  - may involve any organ system
  - neurological: tabes dorsalis, general paresis
  - cardiovascular: aortic aneurysm, dilated aortic root
  - vulvar gumma: nodules that enlarge, ulcerate and become necrotic (rare)
- congenital syphilis
  - may cause fetal anomalies, stillbirths or neonatal death
Investigations
- aspiration of ulcer serum or node
- darkfield microscopy (most sensitive and specific diagnostic test for syphilis)
  - spirochetes
- non-treponemal screening tests (VDRL, RPR); nonreactive after treatment, can be positive with other conditions
- specific anti-treponemal antibody tests (FTA-ABS, MHA-TP, TP-PA)
  - confirmatory tests; remain reactive for life (even after adequate treatment)

Treatment
- treatment of primary, secondary, latent syphilis of <1 yr duration
  - benzathine penicillin G 2.4 million units IM single dose
  - treat partners, reportable disease
- treatment of latent syphilis >1 yr duration
  - benzathine penicillin G 2.4 million units IM q1wk x 3 wk
- treatment of neurosyphilis
  - IV aqueous penicillin G 3-4 million units IM q4h x 10-14 d
- screening
  - high risk groups
  - in pregnancy (see Obstetrics, Table 13, OB21)

Complications
- if untreated, 1/3 will experience late complications

HIV
- see Infectious Diseases, ID41

Bartholinitis/Bartholin Gland Abscess
Etiology
- often anaerobic and polymicrobial
  - U. urealyticum, N. gonorrhoeae, C. trachomatis, E. coli, P. mirabilis, Streptococcus spp., S. aureus (rare)
  - blockage of duct
Clinical Features
- unilateral swelling and pain in inferior lateral opening of vagina
  - sitting and walking may become difficult and/or painful
Treatment
- sitz baths, warm compresses
  - antibiotics: cephalaxin x 1 wk
  - incision and drainage using local anesthesia with placement of Word catheter (10 French latex catheter) for 2-3 wk
  - marsupialization under general anesthetic – more definitive treatment
  - rarely treated by removing gland

Pelvic Inflammatory Disease (PID)
- up to 20% of all gynecology-related hospital admissions

Etiology
- causative organisms (in order of frequency)
  - C. trachomatis
  - N. gonorrhoeae
  - gonorrhea and chlamydia often co-exist
  - endogenous flora: anaerobic, aerobic, or both
    - E. coli, Staphylococcus, Streptococcus, Enterococcus, Bacteroides, Peptostreptococcus, H. influenzae, G. vaginalis
  - cause of recurrent PID
  - associated with instrumentation
  - Actinomyces israelii (Gram-positive, non acid-fast anaerobe)
  - 1-4% of PID cases associated with IUDs
  - others (TB, Gram-negatives, CMV, U. urealyticum, etc.)

Risk Factors
- age <30 yr
- risk factors as for chlamydia and gonorrhea
  - vaginal douching
  - IUD (within first 10 d after insertion)
  - invasive gynecologic procedures (D&C, endometrial biopsy)
**Clinical Presentation**
- up to 2/3 asymptomatic: many subtle or mild symptoms
- common
  - fever >38.3°C
  - lower abdominal pain and tenderness
  - abnormal discharge: cervical or vaginal
- uncommon
  - nausea and vomiting
  - dysuria
  - AUB
- chronic disease (often due to chlamydia)
  - constant pelvic pain
  - dyspareunia
  - palpable mass
  - very difficult to treat, may require surgery

**Investigations**
- bloodwork
  - β-hCG (must rule out ectopic pregnancy), CBC, blood cultures if suspect septicemia
- urine R&M
- speculum exam, bimanual exam
  - vaginal swab for Gram stain, C&S
  - cervical cultures for *N. gonorrhoea, C. trachomatis*
  - endometrial biopsy will give definitive diagnosis (rarely done)
- ultrasound
  - may be normal
  - free fluid in cul-de-sac
  - pelvic or tubo-ovarian abscess
  - hydrosalpinx (dilated fallopian tube)
- laparoscopy (gold standard)
  - for definitive diagnosis: may miss subtle inflammation of tubes or endometritis

**Treatment**
- must treat with polymicrobial coverage
- inpatient if:
  - moderate to severe illness
  - atypical infection
  - adnexal mass, tubo-ovarian or pelvic abscess
  - unable to tolerate oral antibiotics or failed oral therapy
  - immunocompromised
  - pregnant
  - adolescent – first episode
  - surgical emergency cannot be excluded (e.g. ovarian torsion)
  - PID is secondary to instrumentation
- recommended treatment
  - cefoxitin 2 g IV q6h (no longer available in U.S.A.) or cefotetan 2 g IV q12h + doxycycline 100 mg IV/PO q12h or
  - clindamycin 900 mg IV q8h + gentamicin 2 mg/kg IV loading dose then gentamicin 1.5 mg/kg q8h maintenance dose
  - continue IV antibiotics for 24 h after symptoms have improved then doxycycline 100 mg PO bid to complete 14 d
  - percutaneous drainage of abscess under U/S guidance
  - when no response to treatment, laparoscopic drainage
  - if failure, treatment is surgical (salpingectomy, TAH/BSO)
- outpatient if:
  - typical findings
  - mild to moderate illness
  - oral antibiotics tolerated
  - compliance ensured
  - follow-up within 48-72 h (to ensure symptoms not worsening)
- recommended treatment:
  - ofloxacin 400 mg PO bid x 14 d or levofloxacin 500 mg PO bid x 14 d ± metronidazole 500 mg PO bid x 14 d (if suspect abscess)
  - ceftriaxone 250 mg IM x 1 + doxycycline 100 mg PO bid x 14 d or cefoxitin 2 g IM x 1 + probenecid 1 g PO + doxycycline 100 mg PO bid ± metronidazole 500 mg PO bid x 14 d
  - consider removing IUD after a minimum of 24 h of treatment
  - reportable disease
  - treat partners
  - consider re-testing for *C. trachomatis* and *N. gonorrhoea* 4-6 wk after treatment if documented infection

---

**PID Complications**
**FACE PID**
- *Infertility*
- *Fitz-Hugh-Curtis syndrome*
- *Abscesses*
- *Chronic pelvic pain*
- *Ectopic pregnancy*
- *Peritonitis*
- *Intestinal obstruction*
- *Disseminated infection* (sepsis, endocarditis, arthritis, meningitis)

**PID Diagnosis**
- **Must have:**
  - Lower abdominal pain
- **Plus one of:**
  - Cervical motion tenderness
  - Adnexal tenderness
- **Plus one or more of:**
  - High risk partner
  - Temperature >38°C
  - Mucopurulent cervical discharge
  - Positive culture for *N. gonorrhoea, C. trachomatis, E. coli, or other vaginal flora*
  - Cul-de-sac fluid, pelvic abscess or inflammatory mass on U/S or bimanual
  - Leukocytosis
  - Elevated ESR or CRP (not commonly used)

**Alternative PID Treatments**
For patients with contraindications to treatment with cephalosporins or quinolones, recent evidence suggests that a short course of azithromycin at a dose of either 250 mg PO daily for 1 wk or 1 g PO weekly for 2 wk combined with metronidazole is effective in achieving a clinical cure for acute PID.

**Source:** Update to the Canadian Guidelines on Sexually Transmitted Infections. January 2010.
Complications of Untreated PID

- chronic pelvic pain
- abscess, peritonitis
- adhesion formation
- ectopic pregnancy
- infertility
  - 1 episode of PID → 13% infertility
  - 2 episodes of PID → 36% infertility
- bacteremia
- septic arthritis, endocarditis

Toxic Shock Syndrome

- see Infectious Diseases, ID26

Risk Factors

- tampon use
- diaphragm, cervical cap or sponge use (prolonged use, i.e. >24 h)
- wound infections
- post-partum infections
- early recognition and treatment of syndrome is imperative as incorrect diagnosis can be fatal

Clinical Presentation

- sudden high fever
- sore throat, headache, diarrhea
- erythroderma
- signs of multisystem organ failure
- refractory hypotension
- exfoliation of palmar and plantar surfaces of the hands and feet 1-2 wk after onset of illness

Treatment

- remove potential sources of infection (foreign objects and wound debris)
- debride necrotic tissues
- adequate hydration
- penicillinase-resistant antibiotics, e.g. cloxacillin
- steroid use controversial but if started within 72 h, may reduce severity of symptoms and duration of fever

Surgical Infections

Post-Operative Infections in Gynecological Surgery

- pelvic cellulitis
  - common post hysterectomy, affects vaginal vault
  - erythema, induration, tenderness, discharge involving vaginal cuff
  - treat if fever and leukocytosis with broad spectrum antibiotics, i.e. clindamycin and gentamicin
  - drain if excessive purulence or large mass
  - can result in intra-abdominal and pelvic abscess
- see General Surgery, Post-Operative Fever, GS7

Sexual Abuse

- see Family Medicine, FM28, Emergency Medicine, ER29

Sexuality and Sexual Dysfunction

SEXUAL RESPONSE

1. desire: energy that allows an individual to initiate or respond to sexual stimulation
2. arousal: physical and emotional stimulation leading to breast and genital vasodilatation and clitoral engorgement
3. orgasm: physical and emotional stimulation is maximized, allowing the individual to relinquish their sense of control
4. resolution: most of the congestion and tension resolves within seconds, complete resolution may take up to 60 min

SEXUAL DYSFUNCTION

Etiology

- intrapsychic: patient's life experiences, value system
- relationship/interpersonal issues
- physical/organic
**Classification**
- lack of desire (60-70% of women)
- lack of arousal
- anorgasmia (5-10%)
  - primary anorgasmia: never before achieved orgasm under any circumstances
  - secondary anorgasmia: was able to achieve orgasms before but now unable to
- dyspareunia (3-6%): painful intercourse, superficial or deep
  - vaginismus (15%)
  - vulvodynia
  - vaginal atrophy
  - vulvar vestibulitis: associated with history of frequent yeast infections
  - PID

**Treatment**
- lack of desire: assess factors, rule out organic causes, relationship therapy, sensate focus exercises
- anorgasmia: self-exploration/pleasuring, relationship therapy if needed, bridging techniques (different sexual positions, clitoral stimulation during intercourse)
- dyspareunia
  - Kegel and reverse Kegel exercises
  - dilator treatment
  - comfort with self-exam
  - psychotherapy, other behavioural techniques
  - female on top position: allows for control of speed and duration
  - vestibulitis: remove local irritants, change in contraceptive methods, and dietary changes (increased citrate, decreased oxalate), vestibulectomy (rare)
  - vulvodynia: local moisturization, cold compresses, systemic nerve blocking therapy (amitriptyline, gabapentin), topical anesthetics, estrogen cream
  - pain clinic

**Menopause**
- see Family Medicine, FM42

**Definitions**
- lack of menses for 1 yr
- types of menopause
  - physiological; average age 51 yr (follicular atresia)
  - premature ovarian failure; before age 40 (autoimmune disorder, infection, Turner’s syndrome)
  - iatrogenic (surgical/radiation/chemotherapy)

**Clinical Features**
- associated with estrogen deficiency
  - vasomotor instability (tends to dissipate with time)
    - hot flushes/flashes, night sweats, sleep disturbances, formication, nausea, palpitations
  - urogenital atrophy involving vagina, urethra, bladder
    - dyspareunia, pruritus, vaginal dryness, bleeding, urinary frequency, urgency, incontinence
  - skeletal
    - osteoporosis, joint and muscle pain, back pain
  - skin and soft tissue
    - decreased breast size, skin thinning/loss of elasticity
  - psychological
    - mood disturbance, irritability, fatigue, decreased libido, memory loss

**Investigations**
- increased levels of FSH (>35 IU/L) on day 3 of cycle (if still cycling) and LH (FSH>LH). But FSH level not always predictive due to monthly variation. Use absence of menses for 1 yr to diagnose
- decreased levels of estradiol (later)

**Treatment**
- goal is for individual symptom management
  - vasomotor instability
    - HRT (first line), SSRI, venlafaxine, gabapentin, propranolol, clonidine
    - acupuncture
  - vaginal atrophy
    - local estrogen: cream (Premarin®), vaginal suppository (VagiFem®), ring (Estring®)
    - lubricants (Replens®)
  - urogenital health
    - lifestyle changes (weight loss, bladder re-training), local estrogen replacement, surgery

**Menopause Definitions**
- Occurrence of last spontaneous menstrual period, resulting from loss of ovarian function (loss of oocyte response to gonadotropins).
  - "Being in menopause" Lack of menses for 1 yr.
- Perimenopause
  - Period of time surrounding menopause (2-8 yr preceding + 1 yr after last menses) characterized by fluctuating hormone levels, irregular menstrual cycles, and symptom onset.

**Menopause Investigations**
- 85% of women experience hot flashes
- 20-30% seek medical attention
- 10% are unable to work
- Osteoporosis is the single most important health hazard associated with menopause
- Cardiovascular disease is the leading cause of death post-menopause
- Increased risk of breast cancer (RR 1.3) is associated with estrogen + progesterone HRT, but not with estrogen-only HRT
- All women taking HRT should have periodic surveillance and counseling regarding its benefits and risks
osteoporosis
- 1000-1500 mg calcium OD, 800-1000 IU vitamin D, weight-bearing exercise, quit smoking
- bisphosphonates (e.g. alendronate)
- selective estrogen receptor modifiers (SERMs): raloxifene (Evista®) – mimics estrogen effects on bone, avoids estrogen-like action on breast and uterine cancer; does not help hot flashes
- HRT: second-line treatment (unless for vasomotor instability as well)
- decreased libido
- vaginal lubrication, counseling, androgen replacement (testosterone cream or the oral form Andriol®)
- cardiovascular disease
- management of cardiovascular risk factors
- mood and memory
- antidepressants (first line), HRT (augments effect)
- alternative choices (not evidence-based, safety not established)
  - black cohosh, phytoestrogens, St. John's wort, gingko biloba, valerian, evening primrose oil, ginseng, Don Quai

Hormone Replacement Therapy (HRT)

- see Family Medicine, FM42
- primary indication is treatment of menopausal symptoms (vasomotor instability)
- keep doses low (e.g. 0.3 mg Premarin®) and duration of treatment short (<5 yr)

**HRT Components**

- estrogen
  - oral or transdermal (e.g. patch, gel)
  - transdermal preferred for women with hypertriglyceridemia or impaired hepatic function, smokers and women who suffer from headaches associated with oral HRT
  - low-dose (preferred dose: 0.3 mg Premarin®/25 µg Estradot® patch, can increase if necessary)
- progestin
  - given in combination with estrogen for women with an intact uterus to prevent development of endometrial hyperplasia/cancer

**Table 15. Examples of HRT Regimens**

<table>
<thead>
<tr>
<th>HRT Regimen</th>
<th>Estrogen Dose</th>
<th>Progestin Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unopposed Estrogen</td>
<td>CEE 0.625 mg PO OD</td>
<td>None</td>
<td>If no intact uterus</td>
</tr>
<tr>
<td>Standard-dose</td>
<td>CEE 0.625 mg PO OD</td>
<td>MPA 2.5 mg PO OD or micronized progestrone 100 mg PO OD</td>
<td>Withdrawal bleeding may occur in a spotty, unpredictable manner. Usually abates after 6-8 mo due to endometrial atrophy. Once patient has become amenorrheic on HRT, significant subsequent bleeding episodes require evaluation (endometrial biopsy)</td>
</tr>
<tr>
<td>Standard-dose Cyclic</td>
<td>CEE 0.625 mg PO OD</td>
<td>MPA 5-10 mg PO days 1-14 only or micronized progestrone 200 mg PO OD days 1-14 only</td>
<td>Bleeding occurs monthly after day 14 of progestin. Can continue for years. PMS-like symptoms (breast tenderness, fluid retention, headache, nausea) are more prominent with cyclic HRT</td>
</tr>
<tr>
<td>Pulsatile</td>
<td>CEE 0.625 mg PO OD</td>
<td>MPA low-dose</td>
<td>3 d on, 3 d off</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Estroderm®-Estradiol 0.05 mg/d or 0.1 mg/d</td>
<td>Estroderm®-MPA 2.5 mg PO OD</td>
<td>Use patch twice weekly. Can use oral progestins (Estroderm®)</td>
</tr>
<tr>
<td></td>
<td>Estalis®-Estradiol 140 µg/d or 250 µg/d</td>
<td>Estalis®-NEA 50 µg/d</td>
<td>Combined patches available (Estalis®)</td>
</tr>
</tbody>
</table>

CEE = conjugated equine estrogen (e.g. Premarin®); MPA = medroxyprogesterone acetate (e.g. Provera®); NEA = norethindrone acetate
Consider lower dose regimens, PREMPRO® 0.45/1.5 (Premarin® 0.45 mg and Provera® 1.5 mg)

**Side Effects of HRT**

- abnormal uterine bleeding
- mastodynia – breast tenderness
- edema, bloating, heartburn, nausea
- mood changes (progesterone)
- can be worse in progestrone phase of combined therapy

**Contraindications to HRT**

- absolute
  - acute liver disease
  - undiagnosed vaginal bleeding
  - known or suspected uterine cancer/breast cancer
  - acute vascular thrombosis or history of severe thrombophlebitis or thromboembolic disease
  - cardiovascular disease

Menopause Pathophysiology

- Degenerating theca cells fail to react to endogenous gonadotropins (FSH, LH)
- Less estrogen is produced
- Decreased negative feedback on hypothalamic-pituitary-adrenal axis
- Increased FSH and LH
- Stromal cells continue to produce androgens as a result of increased LH stimulation

Absolute Contraindications to HRT

ABCD
- Acute liver disease
- Undiagnosed vaginal bleeding
- Cancer (breast/uterine, Cardiovascular disease)
- DVT (thromboembolic disease)
• relative
  ▪ pre-existing uncontrolled hypertension
  ▪ uterine fibroids and endometriosis
  ▪ familial hyperlipidemias
  ▪ migraine headaches
  ▪ family history of estrogen-dependent cancer
  ▪ chronic thrombophlebitis
  ▪ diabetes mellitus (with vascular disease)
  ▪ gallbladder disease, hypertriglyceridemia, impaired liver function (consider transdermal estrogen)
  ▪ fibrocystic disease of the breasts

**WOMEN’S HEALTH INITIATIVE (WHI)** (launched in 1991)
• two non-randomized studies investigating health risks and benefits of HRT in healthy postmenopausal women 50-79 yr old
  ▪ continuous combined HRT (CEE 0.625 mg + MPA 2.5 mg OD) in 16,608 women with an intact uterus
  ▪ estrogen-alone (CEE 0.625 mg) in 10,739 women with a previous hysterectomy
• both arms of the trial were stopped early because of evidence of increased risk of breast cancer, stroke, PE and CHD in the combined HRT arm, and increased risk of stroke with no CHD benefits in the estrogen-alone arm
• the apparent increase in CHD was in disagreement with results of previous observational trial
• results of the WHI study have since been challenged and revision of how CHD was diagnosed led to loss of statistical significance of the results
• benefits and risks reported as number of cases per 10,000 women each year

**Table 16. HRT Benefits versus Risks**

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasomotor Symptoms:</strong> less frequent and severe with use of either combined or estrogen-alone HRT</td>
<td><strong>Stroke:</strong> 8 additional cases with combined HRT, and 12 additional cases for estrogen alone (WHI)</td>
</tr>
<tr>
<td><strong>Osteoporosis:</strong> 5 fewer cases of hip fractures and 47 fewer cases of all fractures with combined HRT. 6 fewer cases of hip fractures with estrogen alone</td>
<td><strong>DVT/PE:</strong> 18 additional cases with combined HRT, and 9 additional cases for estrogen-alone (WHI)</td>
</tr>
<tr>
<td><strong>Colon Cancer:</strong> 6 fewer cases with combined HRT (WHI). One additional case with estrogen-alone</td>
<td><strong>CHD:</strong> 7 additional MIs with combined HRT (WHI). Secondary analysis suggests greater absolute risk for women aged &gt;70 yr and for women who start HRT &gt;10 yr post-menopause</td>
</tr>
<tr>
<td><strong>Breast Cancer:</strong> 8 additional cases with combined HRT (WHI). Risk only increased after &gt;5 yr of combined HRT use. No increased risk for estrogen-alone</td>
<td><strong>Dementia and Mild Cognitive Impairment:</strong> 50% greater risk of developing dementia in women taking estrogen-alone after age 65. Risk is greater for women taking combined HRT. Risk of developing dementia was reduced for women taking HRT before age 65</td>
</tr>
</tbody>
</table>

**Urogynecology**

**Pelvic Relaxation/Prolapse**

**Etiology**
• relaxation, weakness, or defect in the cardinal and uterosacral ligaments which normally maintain the uterus in an anteflexed position and prevent it from descending through the urogenital diaphragm (i.e. levator ani muscles)
• related to:
  ▪ vaginal childbirth
  ▪ aging
  ▪ decreased estrogen (post-menopause)
  ▪ following pelvic surgery
  ▪ increased intra-abdominal pressure (obesity, chronic cough, constipation, ascites, heavy lifting)
  ▪ congenital (rarely)
  ▪ ethnicity (Caucasian women > Asian or African women)
  ▪ collagen disorders

**GENERAL CONSERVATIVE TREATMENT**
(for pelvic relaxation/prolapse and urinary incontinence)
• Kegel exercises
• local vaginal estrogen therapy
• vaginal pessary (intravaginal suspension disc)
### Table 17. Pelvic Prolapse

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Uterine Prolapse (protrusion of cervix and uterus into vagina) | • Groin/back pain (stretching of uterosacral ligaments)  
  • Feeling of heaviness/pressure in the pelvis  
  • Worse with standing, lifting  
  • Worse at the end of the day  
  • Relieved by lying down  
  • Ulceration/bleeding (particularly if hypoestrogenic)  
  • ± urinary incontinence | • See General Conservative Treatment, GY34  
  • Vaginal hysterectomy ± surgical prevention of vault prolapse  
  • Consider additional surgical procedures if urinary incontinence, cystocele, rectocele, and/or enterocele are present |
| Vault Prolapse (protrusion of apex of vaginal vault into vagina, post-hysterectomy) | | • See General Conservative Treatment, GY34  
  • Sacralcolpopexy (vaginal vault suspension), sacrospinous fixation, or uterosacral ligament suspension |
| Cystocele (protrusion of bladder into the anterior vaginal wall) | • Frequency, urgency, nocturia  
  • Stress incontinence  
  • Incomplete bladder emptying ± associated increased incidence of urinary tract infections – may lead to renal impairment | • See General Conservative Treatment, GY34  
  • Anterior colporrhaphy (“anterior repair”)  
  • Consider additional/alternative surgical procedure if documented urinary stress incontinence |
| Rectocele (protrusion of rectum into posterior vaginal wall) | • Straining/digitation to evacuate stool  
  • Constipation | • See General Conservative Treatment, GY34  
  • Also laxatives and stool softeners  
  • Posterior colporrhaphy (“posterior repair”), plication of endopelvic fascia and perineal muscles approximated in midline to support rectum and perineum (can result in dyspareunia) |
| Enterocele (prolapse of small bowel in upper posterior vaginal wall) | | • Similar to hernia repair  
  • Contents reduced, neck of peritoneal sac ligated, uterosacral ligaments, and levator ani muscles approximated |

### Grading of Pelvic Organ Prolapse
- **0** = no descent during straining  
- **1** = distal portion of prolapse > 1 cm above level of hymen  
- **2** = distal portion of prolapse ≤ 1 cm above or below level of hymen  
- **3** = distal portion of prolapse > 1 cm below level of hymen but without complete vaginal eversion  
- **4** = complete eversion of total length of lower genital tract  

**Procidentia:** Failure of genital supports and complete protrusion of uterus through the vagina.

The only true hernia of the pelvis is an **ENTEROCELE** because peritoneum herniates with the small bowel.

---

**Figure 14. Pelvic anatomy**

**Figure 15. Rectocele, cystocele, uterine prolapse, enterocele**
Urinary Incontinence

- see Urology, U6

STRESS INCONTINENCE

Risk Factors for Stress Incontinence in Women
- pelvic prolapse
- pelvic surgery
- vaginal delivery
- hypoestrogenic state (post-menopause)
- age
- smoking
- neurological/pulmonary disease

Treatment
- see General Conservative Treatment, GY34
- surgical
  - tension-free vaginal tape (TVT), tension-free obturator tape (TOT), prosthetic/fascial slings or retropubic bladder suspension (Burch or Marshall-Marchetti-Krantz procedures)

URGE INCONTINENCE

Definition
- urine loss associated with an abrupt, sudden urge to void
- “overactive bladder”
- diagnosed based on symptoms

Etiology
- idiopathic (90%)
- detrusor muscle overactivity (“detrusor instability”)

Associated Symptoms
- frequency, urgency, nocturia, leakage

Treatment
- behaviour modification (reduce caffeine/liquid, smoking cessation, regular voiding schedule)
- Kegel exercises
- medications
  - anticholinergics: oxybutinin (Ditropan®), tolterodine (Detrol®), solifenacin (VESIcare®)
  - tricyclic antidepressants: imipramine

Gynecological Oncology

Uterus

ENDOMETRIAL CARCINOMA

Epidemiology
- most common gynecological malignancy in North America (40%); 4th most common cancer in women
- 2-3% of women develop endometrial carcinoma during lifetime
- mean age is 60 yr
- majority are diagnosed in early stage due to detection of symptoms
- 85-90% 5-yr survival for stage I disease
- 70-80% overall 5-yr survival for all stages

Risk Factors
- Type I: excess estrogen (estrogen unopposed by progesterone)
  - obesity
  - PCOS
  - unbalanced HRT (balanced HRT is protective)
  - nulliparity
  - late menopause
  - estrogen-producing ovarian tumours (e.g. granulosa cell tumours)
  - HNPCC (hereditary non-polyposis colorectal cancer)/Lynch II syndrome
  - tamoxifen

Incidence of Malignant Gynecological Lesions in North America
- endometrium > ovary > cervix > vulva > vagina > fallopian tube

Complications of Therapy:
- Surgical site infection
- Lymphedema
- Radiation fibrosis
- Cystitis
- Proctitis
• Type II: not estrogen-related
  • possibly tamoxifen

Classification and Clinical Features
• Type I (well-differentiated endometrioid adenocarcinoma) ~80% of cases:
  • postmenopausal bleeding in majority, abnormal uterine bleeding in majority of affected premenopausal women (menorrhagia, intermenstrual bleeding)
• Type II (serous, clear cell carcinoma, grade 3 endometrioid, undifferentiated, carcinosarcoma) ~15% of cases:
  • may not present with bleeding in early stage, more likely to present with advanced stage disease with symptoms like ovarian cancer (i.e. bloating, bowel dysfunction, pelvic pressure)

Investigations
• endometrial sampling:
  • office endometrial biopsy
  • D&C ± hysteroscopy
  • pelvic ultrasound (in women where adequate endometrial sampling not feasible without invasive methods)
  • not acceptable as alternative to pelvic exam or endometrial sampling to rule out cancer

Table 18. FIGO Staging of Endometrial Cancer (2009)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Confined to corpus</td>
<td>IIIC</td>
<td>Metastasis to pelvic ± para-aortic LNs</td>
</tr>
<tr>
<td>IA</td>
<td>No or less than half myometrial invasion</td>
<td>IIIC1</td>
<td>Positive pelvic LN</td>
</tr>
<tr>
<td>IB</td>
<td>Invades through ≥½ of myometrium</td>
<td>IIIC2</td>
<td>Positive para-aortic LN ± positive pelvic LNs</td>
</tr>
<tr>
<td>II</td>
<td>Tumour invades cervical stroma, but does not extend beyond uterus*</td>
<td>IV</td>
<td>Invasion of bladder ± bowel mucosa ± distant metastases</td>
</tr>
<tr>
<td>III</td>
<td>Local and/or regional spread of the tumour</td>
<td>IVB</td>
<td>Invasion of bladder ± bowel mucosa</td>
</tr>
<tr>
<td>IIIA</td>
<td>Invasion of serosa, corpus uterus ± adnexae</td>
<td>IVB</td>
<td>Distant mets, including intra-abdominal mets ± inguinal LNs</td>
</tr>
<tr>
<td>IIIB</td>
<td>Vaginal ± parametral involvement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: endocervical glandular involvement is now considered as Stage I (previously Stage II)

Spread
• direct extension is most common
• lymphatic spread to pelvic and para-aortic nodes
• transtubal dissemination to peritoneal cavity
• hematogenous spread (usually to lungs, liver)

Treatment
• surgical: hysterectomy/bilateral salpingo-oophorectomy (BSO) and pelvic washings ± pelvic and para-aortic node dissection ± omentectomy
• goals: diagnosis, staging, treatment, defining optimal adjuvant treatment
• laparoscopic approach associated with improved quality of life (optimal for most patients)
• adjuvant radiotherapy (for improved local control in patients at risk for local recurrence) and adjuvant chemotherapy (in patients at risk for distant recurrence or with metastatic disease): based on presence of poor prognostic factors in definitive pathology
• chemotherapy: often used for recurrent disease (especially if high grade or aggressive histology)
• hormonal therapy: progestins can be used for recurrent disease (especially if low grade)

UTERINE SARCOMA
• rare; 2-6% of all uterine malignancies
• arise from stromal components (endometrial stroma, mesenchymal or myometrial tissues)
• behave more aggressively and are associated with worse prognosis than endometrial carcinoma; 5-yr survival is 35%
• vaginal bleeding is most common presenting symptom
### Table 19. Summary of Uterine Sarcoma Subtypes and Features

<table>
<thead>
<tr>
<th>Type</th>
<th>Epidemiology</th>
<th>Features</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PURE TYPE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Leiomyosarcoma</td>
<td>• Accounts for 40%</td>
<td>• Histologic distinction from leiomyoma</td>
<td>• Often postoperatively after uterus removed for presumed fibroids</td>
<td>• Hysterectomy/BSO usually</td>
</tr>
<tr>
<td></td>
<td>• Average age of presentation is 55 yr but may present in pre-menopause</td>
<td>1. Increased mitotic count (&gt;10 mitoses/10 high power fields)</td>
<td>• Staging using FIGO 2009 staging for Leimyosarcomas</td>
<td>• No routine pelvic lymphadenectomy</td>
</tr>
<tr>
<td></td>
<td>• Often coexists with benign leiomyomata (fibroids)</td>
<td>2. Tumour necrosis</td>
<td></td>
<td>• Adjuvant chemotherapy may be used if tumour has spread beyond uterus, for palliation</td>
</tr>
<tr>
<td></td>
<td>• 50% arise within a fibroid (&quot;sarcomatous degeneration&quot;)</td>
<td>3. Cellular atypia</td>
<td></td>
<td>• Radiation therapy does not improve local control or survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rapidly enlarging fibroids in a pre-menopausal woman</td>
<td></td>
<td>• Poor outcomes overall, even for early stage disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• enlarging fibroids in a postmenopausal woman</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Endometrial Stromal Sarcoma (ESS)</td>
<td>• Accounts for 10-15%</td>
<td>• Abnormal uterine bleeding</td>
<td>• Diagnosed by histology of endometrial biopsy or D&amp;C</td>
<td>• Hysterectomy/BSO (remove ovaries as ovarian hormones may stimulate growth)</td>
</tr>
<tr>
<td></td>
<td>• Usually presents in perimenopausal or postmenopausal women with abnormal uterine bleeding</td>
<td>• Good prognosis</td>
<td></td>
<td>• No routine pelvic lymphadenectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Adjuvant therapy based on stage and histologic features (hormones and/or radiation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Hormonal therapy (progestins) may be used for metastatic disease</td>
</tr>
<tr>
<td>3. Undifferentiated Sarcoma</td>
<td>• Accounts for 5-10%</td>
<td>• Severe nuclear pleomorphism, high mitotic activity, tumour cell necrosis and lack smooth muscle or endometrial stromal differentiation</td>
<td>• Often found incidentally for abnormal bleeding</td>
<td>• Treatment primarily surgical</td>
</tr>
<tr>
<td></td>
<td>• Mixed tumour of low malignant potential</td>
<td>• Poor prognosis</td>
<td></td>
<td>• Radiation and/or chemotherapy for advanced diseased or unresectable disease</td>
</tr>
<tr>
<td><strong>MIXED TYPE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Adenosarcoma</td>
<td>• The rarest of the uterine sarcoma</td>
<td>• Present with abnormal vaginal bleeding</td>
<td>• Mixture of benign epithelium with malignant low-grade sarcoma</td>
<td>• Treatment is surgical with TAH/BSO</td>
</tr>
<tr>
<td></td>
<td>• Mixed tumour of low malignant potential</td>
<td>• Polypoid mass in uterine cavity</td>
<td>• Often found incidentally at time of hysterectomy for PMB</td>
<td></td>
</tr>
<tr>
<td><strong>RECLASSIFIED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Carcinosarcoma</td>
<td>• Most common (43%)</td>
<td>• Both epithelial and stromal malignant elements present</td>
<td>• Diagnosed by histology of endometrial biopsy or D&amp;C</td>
<td>• Usually treated as “high grade endometrial carcinoma” since behaviour and treatment similar (i.e. surgical staging and resection of any gross metastatic disease, adjuvant chemotherapy and radiation)</td>
</tr>
<tr>
<td></td>
<td>• Recently reclassified as high grade endometrioid carcinoma with associated metaplasia of the mesenchyme, rather than arising separately from stroma</td>
<td>• Tend to form bulky polypoid masses that often fill uterine cavity and extend into or through the endocervical canal – often have extraterine disease at presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Surgical staging using FIGO 2009 staging for endometrial cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 20. FIGO Staging of Uterine Sarcoma (2009)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumour limited to uterus</td>
<td>III</td>
<td>Tumour invades abdominal tissues, one site</td>
</tr>
<tr>
<td>IA</td>
<td>&lt;5 cm</td>
<td>IIIA</td>
<td>Metastasis to pelvic and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td>IB</td>
<td>&gt;5 cm</td>
<td>IIIB</td>
<td>Tumour invades bladder and/or rectum</td>
</tr>
<tr>
<td>II</td>
<td>Tumour extends beyond uterus</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>To the pelvis, adrenal involvement</td>
<td>IVA</td>
<td>Tumour invades bladder and/or rectum</td>
</tr>
<tr>
<td>IIB</td>
<td>To extra-uterine pelvic tissue</td>
<td>IVB</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

### Ovary

**BENIGN OVARIAN TUMOURS**

- see Table 21
- many are asymptomatic
- usually enlarge slowly, if at all
- may rupture or undergo torsion, causing pain
  - pain associated with torsion of an adnexal mass usually originates in the iliac fossa and radiates to the flank
  - peritoneal irritation may result from an infarcted tumour – rare
MALIGNANT OVARIAN TUMOURS

• see Table 21

Epidemiology
• lifetime risk 1.4% (1/70)
• in women >50 yr, more than 50% of ovarian tumours are malignant
• causes more deaths in North America than all other gynecologic malignancies combined
• 4th leading cause of cancer death in women
• 65% epithelial; 35% non-epithelial
• 5-10% of epithelial ovarian cancers are related to hereditary predisposition

Risk Factors (for epithelial ovarian cancers)
• excess estrogen:
  ▫ nulliparity
  ▫ early menarche/late menopause
• age
• family history of breast, colon, endometrial, ovarian cancer
• race: Caucasian

Protective Factors (for epithelial ovarian cancers)
• OCP: likely due to ovulation suppression (significant reduction in risk even after 1 yr of use)
• pregnancy/breastfeeding
• tubal ligation (recently questioned)
• hysterectomy (without removal of ovaries)
• BSO (prophylactic surgery performed for this reason in high risk women – i.e. BRCA mutation carriers)

Screening
• no effective method of mass screening
• routine CA-125 level measurements or U/S not recommended
  ▫ high false positive rates
• controversial in high risk groups: transvaginal U/S and CA-125, starting age 30 (no consensus on interval)
  ▫ familial ovarian cancer (>1 first degree relative affected, BRCA-1 mutation)
  ▫ other cancers (e.g. endometrial, breast, colon)
• BRCA-1 or BRCA-2 mutation: may recommend prophylactic bilateral oophorectomy after age 35 or when child-bearing is completed

Clinical Features
• most women with epithelial ovarian cancer present with advanced stage disease since often “asymptomatic” until disseminated disease (symptoms with early stage disease are vague and non-specific)
• when present, symptoms may include:
  ▫ abdominal symptoms (nausea, bloating, dyspepsia, anorexia, early satiety)
  ▫ symptoms of mass effect
    ▪ increased abdominal girth – from ascites or tumour itself
    ▪ urinary frequency
    ▪ constipation
  ▫ postmenopausal bleeding; irregular menses if pre-menopausal (rare)

Low Malignant Potential (also called “Borderline”) Tumours
• pregnancy, OCP and breastfeeding are protective factors
• ~15% of all epithelial ovarian tumours
• tumour cells display malignant characteristics histologically, but no invasion is identified
• able to metastasize, but not commonly
• treated primarily with surgery (BSO/omental biopsy ± hysterectomy)
• NO proven benefit of chemotherapy
• generally slow growing, excellent prognosis
  ▫ 5-yr survival >99%
  ▫ recurrences tend to occur late, may be associated with low grade serous carcinoma

Effects of screening on ovarian cancer mortality: The prostate, lung, colorectal and ovarian cancer screening randomized controlled trial JAMA 2011;305:2295-2303

Objective: To evaluate the effect of screening for ovarian cancer with CA-125 and transvaginal ultrasound on mortality in the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial.

Participants: 78,216 women aged 55-74 yr.

Study Groups: Intervention group – annual screening with CA-125 for 6 yr, transvaginal ultrasound for 4 yr; control group – no CA-125 or transvaginal ultrasound screening, received usual medical care.

Follow-up: Maximum 13 yr (median, 12.4 yr).

Outcome Measures: Mortality from ovarian cancer, including primary fallopian tube cancers. Secondary outcomes included ovarian cancer incidence and complications associated with screening, examinations and diagnostic procedures.

Results: Of those diagnosed with ovarian cancer in the intervention and usual care group, the mortality was 3.1% and 2.6% respectively. 15% of women undergoing diagnostic evaluation following a false positive screening test suffered a complication of the procedure.

Conclusions: Simultaneous screening with CA-125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality. Diagnostic evaluation following a false positive screening test was associated with complications.
### Table 21. Ovarian Tumours

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Presentation</th>
<th>Ultrasound/Cytology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FUNCTIONAL TUMOURS (all benign)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular cyst</td>
<td>Follicle fails to rupture during ovulation</td>
<td>Usually asymptomatic</td>
<td>4-8 cm mass, unilocular, lined with granulosa cells</td>
<td>Symptomatic or suspicious masses warrant surgical exploration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May rupture, bleed, tort, infarct causing pain ± signs of peritoneal irritation</td>
<td></td>
<td>Otherwise if &lt; 6 cm, wait 6 wk then re-examine as cyst usually regresses with next cycle</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OCP (ovarian suppression) – will prevent development of new cysts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment usually laparoscopic (cystectomy vs. oophorectomy, based on fertility choice)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lutein cyst</td>
<td>Corpus luteum fails to regress after 14 d, becoming cystic or hemorrhagic</td>
<td>More likely to cause pain than follicular cyst</td>
<td>Larger (10-15 cm) and firmer than follicular cysts</td>
<td>Same as for follicular cysts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May delay onset of next period</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theca-lutein cyst</td>
<td>Due to atretic follicles stimulated by abnormal β-HCG levels</td>
<td>Associated with molar pregnancy, ovulation induction with clomiphene</td>
<td></td>
<td>Conservative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cyst will regress as β-HCG levels fall</td>
</tr>
<tr>
<td>Luteoma of pregnancy</td>
<td>Usually bilateral</td>
<td>Associated with multiple pregnancy</td>
<td></td>
<td>Same as for theca-lutein (conservative)</td>
</tr>
<tr>
<td></td>
<td>Due to prolonged elevation of β-HCG</td>
<td></td>
<td></td>
<td>Regresses postpartum</td>
</tr>
<tr>
<td>Endometrioma</td>
<td>See Endometriosis, GY16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycystic Ovaries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BENIGN GERM-CELL TUMOURS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign cystic teratoma (dermoid)</td>
<td>Single most common ovarian germ cell neoplasm</td>
<td>May rupture, twist, infarct 20% bilateral</td>
<td>Smooth-walled, mobile, unilocular Ultrasound may show calcification which is pathognomonic</td>
<td>Treatment usually laparoscopic cystectomy; may recur</td>
</tr>
<tr>
<td></td>
<td>Elements of all 3 cell lines; contains dermal appendages (sweat and sebaceous glands, hair follicles, teeth)</td>
<td>20% occur outside of reproductive yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MALIGNANT GERM-CELL TUMOURS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Information</td>
<td>Rapidly growing, 2-3% of all ovarian cancers</td>
<td>Usually children and young women (&lt;30 yr)</td>
<td>Surgical resection (often conservative unilateral salpingo-oophorectomy ± nodes) ± chemo</td>
<td></td>
</tr>
<tr>
<td>Dysgerminoma</td>
<td>Produces lactate dehydrogenase (LDH)</td>
<td>10% bilateral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immature teratoma</td>
<td>No tumour marker identified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yolk sac tumour</td>
<td>Produces fetoprotein (AFP)</td>
<td>Unilateral</td>
<td>More aggressive subtype, often need chemo (bleomycin, etoposide, cisplatin, BEP)</td>
<td></td>
</tr>
<tr>
<td>Embryonal</td>
<td>Produces AFP and β-HCG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoma</td>
<td>Rare</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>Produces β-HCG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed Germ Cell</td>
<td>Depends on type of tumour involved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EPITHELIAL OVARIAN TUMOURS (malignant or borderline)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Information</td>
<td>Derived from mesothelial cells lining peritoneal cavity</td>
<td>Varies depending on subtype</td>
<td>Borderline</td>
<td>Cystectomy vs. unilateral salpingo-oophorectomy</td>
</tr>
<tr>
<td></td>
<td>Classified based on histologic type 80-85% of all ovarian neoplasms (includes malignant)</td>
<td></td>
<td></td>
<td>Malignant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. Early stage (stage I): Hysterectomy/BSO/staging (omentectomy, peritoneal biopsies, washings, pelvic and para-aortic lymphadenectomy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Advanced stage: Upfront cytoreductive (debulking) followed by adjuvant chemotherapy consisting of IV carboplatin/paclitaxel versus Intraperitoneal chemotherapy (stage III)Neoadjuvant chemotherapy with IV carboplatin/paclitaxel followed by delayed debulking with further adjuvant IV chemotherapy</td>
</tr>
<tr>
<td>Serous</td>
<td>Most common ovarian tumour</td>
<td>20-30% bilateral</td>
<td>Lining similar to fallopian tube epithelium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50% of all ovarian cancers</td>
<td></td>
<td>Often multicellular Histologically contain Psammoma bodies (calcified concentric concretions)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75% of epithelial tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70% benign</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 21. Ovarian Tumours (continued)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Presentation</th>
<th>Ultrasound/Cytology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPITHELIAL OVARIAN TUMOURS (malignant or borderline)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucinous</td>
<td>20% of epithelial tumours</td>
<td>85% benign</td>
<td>Resembles endocervical epithelium</td>
<td>Poor response to chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Rarely complicated by Pseudomyxoma peritonei: implants seed abdominal cavity and produce large quantities of mucin</td>
<td></td>
<td></td>
<td>If mucinous, remove appendix as well to rule out possible source of primary disease</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>20% of epithelial ovarian Ca</td>
<td>High malignant potential</td>
<td>Histology resembles endometrium</td>
<td></td>
</tr>
<tr>
<td>Clear cell</td>
<td>≤1% of epithelial ovarian Ca</td>
<td>High malignant potential</td>
<td>Histology resembles mesonephric cells</td>
<td></td>
</tr>
<tr>
<td>Brenner tumour</td>
<td>≤1% of epithelial ovarian Ca</td>
<td>Majority benign</td>
<td>Fibrotic tumour with transitional cell–like epithelial core</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SEX CORD STROMAL OVARIAN TUMOURS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Information</td>
<td>Surgical resection of tumour</td>
<td></td>
<td></td>
<td>Chemotherapy may be used for unresectable metastatic disease</td>
</tr>
<tr>
<td>Fibroma/thecoma (benign)</td>
<td>From mature fibroblasts in ovarian stroma</td>
<td>Non-functioning</td>
<td>Firm, smooth rounded tumour with interlacing fibrocytes</td>
<td></td>
</tr>
<tr>
<td>(benign)</td>
<td>Occasionaly associated with Meig’s syndrome (benign ovarian tumour and ascites and pleural effusion)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulosa-theca cell tumours (benign or malignant)</td>
<td>Can be associated with endometrial cancer</td>
<td>Estrogen-producing (\rightarrow) feminizing effects (precocious puberty, menorrhagia, postmenopausal bleeding)</td>
<td>Histologic hallmark of cancer (\rightarrow) is small groups of cells known as Call-Exner bodies</td>
<td></td>
</tr>
<tr>
<td>Sertoli-Leydig cell tumour</td>
<td>Can measure elevated androgens as tumour markers</td>
<td>Androgen-producing (\rightarrow) virilizing effects (hirsutism, deep voice, recession of front hairline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(benign or malignant)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>METASTATIC OVARIAN TUMOURS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From GI tract, breast, endometrium, lymphoma</td>
<td>4-8% of ovarian malignancies</td>
<td>Kroenkeberg tumour – metastatic ovarian tumour (usually GI tract, commonly stomach or colon, breast) with “signet-ring” cells</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Investigation of Suspicious Ovarian Mass

- women with suspected ovarian cancer based on history, physical, or investigations should be referred to a gynecologic oncologist
  - bimanual examination
  - solid, irregular, or fixed pelvic mass is suggestive of ovarian cancer
  - RMI (Risk of Malignancy Index) is best tool available to assess likelihood of ovarian malignancy and need for pre-operative gynecologic oncology referral (see sidebar)
- bloodwork: CA-125 for baseline, CBC, liver function tests, electrolyte, creatinine
- radiology:
  - bone scan or PET scan not indicated
  - transvaginal ultrasound best to visualize ovaries
  - CT scan abdomen and pelvis to look for metastatic disease
- try to rule out other primary source if suspected, based on:
  - occult blood per rectum: endoscopy ± barium enema
  - gastric symptoms, gastroscopy ± upper GI series
  - abnormal vaginal bleeding, endometrial biopsy: rule out concurrent endometrial cancer, colposcopy ± ECC to rule out cervical cancer if abnormal cervix
  - breast lesion identified or risk factors present: mammogram

A Risk of Malignancy Incorporating CA125, Ultrasound and Menopausal Status for the Accurate Preoperative Diagnosis of Ovarian Cancer
BJOG 1990;97:922-929
RMI = U x M x CA-125

Ultrasound Findings (1 pt for each)
- Multilocular cyst
- Evidence of solid areas
- Evidence of metastases
- Presence of ascites
- Bilateral lesions
- 
  - U = 1 (for U/S scores of 0 or 1)
  - U = 4 (for U/S scores of 2-5)

Menopausal Status
- Postmenopausal: M = 4
- Pre-menopausal: M = 1

Absolute Value of CA-125 Serum Level
- For RMI > 200: Gynecologic oncology referral is recommended
Table 22. FIGO Staging for Primary Carcinoma of the Ovary (Surgical Staging) (2009)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Growth limited to the ovaries</td>
</tr>
<tr>
<td>IA</td>
<td>1 ovary, no ascites, no tumour on external surface, capsule intact</td>
</tr>
<tr>
<td>IB</td>
<td>2 ovaries, no ascites, no tumour on external surface, capsule intact</td>
</tr>
<tr>
<td>IC</td>
<td>1 or 2 ovaries with any of the following: capsule ruptured, tumour on ovarian surface or malignant cells in ascites</td>
</tr>
<tr>
<td>II</td>
<td>Growth involving one or both ovaries with pelvic extension</td>
</tr>
<tr>
<td>IIA</td>
<td>Extension to uterus/tubes</td>
</tr>
<tr>
<td>IIB</td>
<td>Extension to other pelvic structures</td>
</tr>
<tr>
<td>IIC</td>
<td>A/B with malignant cells in ascites or positive peritoneal washings</td>
</tr>
<tr>
<td>III</td>
<td>Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver mets is Stage III</td>
</tr>
<tr>
<td>IIIA</td>
<td>Microscopic peritoneal metastasis beyond pelvis, LNs negative</td>
</tr>
<tr>
<td>IIIB</td>
<td>Macroscopic peritoneal metastasis beyond pelvis &lt;2 cm, LNs negative</td>
</tr>
<tr>
<td>IIIC</td>
<td>Implant &gt;2 cm and/or retroperitoneal or inguinal nodes</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastasis beyond peritoneal cavity</td>
</tr>
</tbody>
</table>

FIGO: International Federation of Gynecology and Obstetrics

Cervix

BENIGN CERVICAL LESIONS
- Nabothian cyst/inclusion cyst
  - no treatment required
- endocervical polyps
  - treatment is polypectomy (office procedure)

MALIGNANT CERVICAL LESIONS

Epidemiology
- majority are squamous cell carcinomas (95%); adenocarcinomas increasing (5%); rare subtypes include small cell, adenosquamous
- 8,000 deaths annually in North America
- annual Pap test reduces a woman’s chance of dying from cervical cancer from 0.4% to 0.05%
- average age at presentation: 52 yr old

Etiology
- at birth, vagina is lined with squamous epithelium; columnar epithelium lines only the endocervix and the central area of the ectocervix (original squamocolumnar junction)
- during puberty, estrogen stimulates eversion of a single columnar layer (ectopy), thus exposing it to the acidic pH of the vagina, leading to metaplasia (change of exposed epithelium from squamous to columnar)
  - a new squamocolumnar junction forms as a result
- the transformation zone (TZ) is the area located between the original and the current squamocolumnar junction
- the majority of dysplasias and cancers arise in the TZ of the cervix
- must have active metaplasia in presence of inducing agent (HPV) to get dysplasia
- dysplasia → carcinoma in situ (CIS) → invasion
- slow process (~10 yr on average)
- growth is by local extension
- metastasis occurs late

Risk Factors
- HPV infection
  - see Sexually Transmitted Infections, GY27
  - high risk of neoplasia associated with types 16, 18
  - low risk of neoplasia associated with types 6, 11
  - >99% of cervical cancers contain one of the high risk HPV types
- high risk behaviours (risk factors for HPV infection)
  - multiple partners
  - other STIs (HSV, trichomonas)
  - early age at first intercourse
  - high risk male partner
- smoking
- poor screening uptake is the most important risk factor for cervical cancer in Canada
- at-risk groups include:
  - immigrant Canadians
  - First Nations Canadians
  - geographically isolated Canadians
  - sex-trade workers
  - low socioeconomic status

Malignant Ovarian Tumour Prognosis
5-yr Survival
- Stage I 75-95%
- Stage II 60-75%
- Stage III 23-41%
- Stage IV 11%

Figure 16. The cervix

Original squamous epithelium

Squamous metaplasia

Columnar epithelium

Gland opening

External os

New squamo-columnar junction

Transformation zone

Original squamocolumnar junction

© Ayalah Hutchins

Figure 16. The cervix

Causes of Elevated CA-125
- Age influences reliability of test as a tumour marker
- 50% sensitivity in early stage ovarian cancer (poor) — therefore not good for screening

Malignant
- Gyne: ovary, uterus
- Non-Gyne: pancreas, stomach, colon, rectum

Non Malignant
- Gyne: benign ovarian neoplasm, endometriosis, pregnancy, fibroids, PID
- Non-Gyne: cirrhosis, pancreatitis, renal failure
Cervical Cancer Screening Guidelines (Pap Test)
• see Family Medicine, FM4

Clinical Features
• squamous cell carcinoma (SCC): exophytic, fungating tumour
• adenocarcinoma: endophytic, with barrel-shaped cervix
• early
  • asymptomatic
  • discharge: initially watery, becoming brown or red
  • post-coital bleeding
• late
  • 80-90% present with bleeding: either post-coital, postmenopausal or irregular bleeding
  • pelvic or back pain (extension of tumour to pelvic walls)
  • bladder/bowel symptoms
• signs
  • friable, raised, reddened or ulcerated area visible on cervix

Table 23. Cytological Classification: Terminology Used to Describe Lesions

<table>
<thead>
<tr>
<th>Bethesda Grading System (Pap Test Cytology)</th>
<th>Classic System/Cervical Intraepithelial Neoplasia (CIN) Grading System (Biopsy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within normal limits</td>
<td>Normal</td>
</tr>
<tr>
<td>Infection</td>
<td>Inflammatory atypia (organism)</td>
</tr>
<tr>
<td>Reactive and reparative changes</td>
<td></td>
</tr>
<tr>
<td>Squamous cell abnormalities</td>
<td></td>
</tr>
<tr>
<td>Atypical squamous cells of undetermined significance (ASCUS)</td>
<td>Squamous atypia of uncertain significance</td>
</tr>
<tr>
<td>Atypical squamous cells, cannot exclude HSIL (ASC-H)</td>
<td>Squamous cell carcinoma (SCC)</td>
</tr>
<tr>
<td>Low grade squamous intraepithelial lesion (LSIL)</td>
<td>HPV atypia or mild dysplasia (CIN I)</td>
</tr>
<tr>
<td>High grade squamous intraepithelial lesion (HSIL)</td>
<td>Moderate dysplasia (CIN II)</td>
</tr>
<tr>
<td></td>
<td>Severe dysplasia (CIN III)</td>
</tr>
<tr>
<td></td>
<td>Carcinoma in situ (CIS)</td>
</tr>
<tr>
<td>Squamous cell carcinoma (SCC)</td>
<td></td>
</tr>
<tr>
<td>Glandular cell abnormalities</td>
<td></td>
</tr>
<tr>
<td>Atypical glandular cells of undetermined significance (AGUS)</td>
<td>Glandular atypia of uncertain significance</td>
</tr>
<tr>
<td>Endocervical adenocarcinoma</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Endometrial adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Extratubal adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma, not otherwise specified (NOS)</td>
<td></td>
</tr>
</tbody>
</table>

The Bethesda Classification System is based on cytological results of a Pap test that permits the examination of cells but not tissue structure. The diagnosis of cervical intraepithelial neoplasia (CIN) or cervical carcinoma requires a tissue sample, obtained by biopsy of suspicious lesions (done during colposcopy), to make a histologic diagnosis.

Figure 17. Decision making chart for Pap test (not applicable for adolescents)
Adapted from Ontario Cervical Screening Practice Guidelines. May 2012. Cervical screening guidelines unique to each province.
Diagnosis
- see Colposcopy, GY9
- apply acetic acid and identify acetowhite lesions, punctation, mosaicism, and abnormal blood vessels to guide cervical biopsy
- endocervical curettage (ECC) if entire lesion is not visible or no lesion visible
- diagnostic excision (loop electrosurgical excision procedure, LEEP) if:
  - lesion extends into endocervical canal
  - positive ECC
  - discrepancy between Pap test results and colposcopy
  - microinvasive carcinoma
- consider cold knife conization (in OR) if glandular abnormality suspected based on cytology or colposcopic findings due to concern for margin interpretation
- tests permitted for FIGO clinical staging include: physical exam (including EUA), cervical biopsy (including cone biopsy), proctoscopy/cystoscopy, IVF, ultrasound liver/kidneys, CXR, LFTs
- MRI and/or CT and/or PET scan often done to facilitate planning of radiation therapy, results do not influence clinical stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Confined to cervix</td>
</tr>
<tr>
<td>IIA</td>
<td>Microinvasive (diagnosed only by microscopy)</td>
</tr>
<tr>
<td>IAB</td>
<td>Stromal invasion not &gt;3 mm deep, not &gt;7 mm wide</td>
</tr>
<tr>
<td>IIB</td>
<td>Clinically visible lesion confined to cervix, or microscopic lesion &gt;IAB</td>
</tr>
<tr>
<td>IIB</td>
<td>Clinically visible lesion ≤4 mm in greatest dimension</td>
</tr>
<tr>
<td>IIB</td>
<td>Clinically visible lesion &gt;4 mm in greatest dimension</td>
</tr>
<tr>
<td>II</td>
<td>Beyond uterus but not to the pelvic wall or lower 1/3 of vagina</td>
</tr>
<tr>
<td>II A</td>
<td>No obvious parametrial involvement</td>
</tr>
<tr>
<td>IIB</td>
<td>Clinically visible lesion ≤4 mm in greatest dimension</td>
</tr>
<tr>
<td>IIB</td>
<td>Clinically visible lesion &gt;4 mm in greatest dimension</td>
</tr>
<tr>
<td>III</td>
<td>Extends to pelvic wall, and/or involves lower 1/3 of vagina and/or causes hydronephrosis or non-functioning kidney</td>
</tr>
<tr>
<td>IIIA</td>
<td>Involves lower 1/3 vagina but no extension into pelvic side wall</td>
</tr>
<tr>
<td>IIIB</td>
<td>Extension into pelvic side wall and/or hydronephrosis or non-functioning kidney</td>
</tr>
<tr>
<td>IV</td>
<td>Carcinoma has extended beyond true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum</td>
</tr>
<tr>
<td>IVA</td>
<td>Spread of the growth to adjacent organs</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>

Treatment: Prevention and Management

Prevention: HPV Vaccine
- two vaccines currently approved (Gardasil®, Cervarix®)

| Table 25. Comparison of Two Vaccines against Human Papillomavirus (HPV) |
|-----------------|-----------------|
| Gardasil®  | Cervarix®  |
| Viral strains covered | 6, 11, 16, 18 | 16, 18 |
| Route of administration | IM | IM |
| Schedule of dosing | 0, 2, 6 mo | 0, 1, 6 mo |
| Side effects | Local: redness, pain, swelling | Local: redness, pain, swelling |
|               | General: headache, low grade fever, GI upset | General: headache, low grade fever, GI upset |
| Approved age | Females age 9-45, males age 9-26 | Females age 10-25 |
| Contraindications | Pregnant women and women who are nursing (limited data) |

- for optimal benefit of vaccination, should be administered before onset of sexual activity (i.e. before exposure to virus)
- may be given at the same time as Hep B or other vaccines using a different injection site
- not for treatment of active infections
- most women will not be infected with all four types of the virus at the same time, therefore vaccine is still indicated for sexually active females or those with a history of previous HPV infection or HPV-related disease
- conception should be avoided until 30 d after last dose of vaccination
Table 26. Management of Patients Abnormal Cervical Histology and Cervical Cancer

<table>
<thead>
<tr>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN I</td>
</tr>
<tr>
<td>• Preferred option for biopsy-proven CIN I is observation</td>
</tr>
<tr>
<td>• Repeat assessment and cytology in 12 mo</td>
</tr>
<tr>
<td>• Management according to cytology results</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>• If HSIL or AGC</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>• Cytology and histology should be reviewed</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>• If discrepancy remains, excisional biopsy may be considered</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>CIN II and CIN III</td>
</tr>
<tr>
<td>Women over 25 yr</td>
</tr>
<tr>
<td>• CIN II or III should be treated</td>
</tr>
<tr>
<td>• Excisional procedures preferred for CIN III</td>
</tr>
<tr>
<td>• Those with + margins should have follow-up with colposcopy and directed biopsies and/or endocervical curettage</td>
</tr>
<tr>
<td>• Treatment for recurrent CIN II or III should be by excision</td>
</tr>
<tr>
<td>Women less than 25 yr</td>
</tr>
<tr>
<td>• Pathologist should be asked to clarify whether lesion is CIN II or CIN III</td>
</tr>
<tr>
<td>• CIN II: observe with colposcopy at 8-mo intervals for up to 24 mo before treatment considered</td>
</tr>
<tr>
<td>• CIN III: should be treated</td>
</tr>
</tbody>
</table>

During pregnancy:
- CIN II or III suspected or diagnosed during pregnancy, repeat colposcopy and treatment delayed until 8-12 wk after delivery

<table>
<thead>
<tr>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA2 (no LVSI)</td>
</tr>
<tr>
<td>• Trachelectomy (removal of only the cervix) if future fertility desired (and lesion ≤2 cm)</td>
</tr>
<tr>
<td>• Simple hysterectomy if future fertility is not desired</td>
</tr>
<tr>
<td>Stage IA2, IB1</td>
</tr>
<tr>
<td>• Typically treated with radical hysterectomy and pelvic lymphadenectomy (sentinel nodes under study)</td>
</tr>
<tr>
<td>• Equal cure rates may be obtained with primary radiation therapy; advantage of surgery: may accurately stage and grade and more targeted adjuvant therapy</td>
</tr>
<tr>
<td>• Advantage is that ovaries can be spared if pre-menopausal</td>
</tr>
<tr>
<td>• For fertility preservation, may have radical trachelectomy (removal of cervix and parametria) and nodes instead of radical hysterectomy for early-stage disease</td>
</tr>
<tr>
<td>• Concurrent chemoradiation therapy if adverse high risk prognostic factors on radical surgical specimen, such as: positive pelvic lymph nodes, positive parametria and/or positive margins</td>
</tr>
<tr>
<td>Stages IB2 (&gt;4 cm), II, III, IV</td>
</tr>
<tr>
<td>• Primary chemoradiation therapy</td>
</tr>
<tr>
<td>• PET/CT to grade: evaluate pelvic and para-aortic nodes</td>
</tr>
<tr>
<td>• For positive nodes on PET: primary chemoradiation with extended field RT</td>
</tr>
<tr>
<td>• Hysterectomy generally not suggested following primary treatment with curative intent</td>
</tr>
</tbody>
</table>

Abnormal Pap Tests in Pregnancy
- incidence: 1/2,200
- Pap test at all initial prenatal visits
  - if abnormal Pap or suspicious lesion, refer to colposcopy
  - if diagnostic conization required, should be deferred until second trimester (T2) to minimize risk of pregnancy loss
- if invasive cancer ruled out, management of dysplasia deferred until completion of pregnancy (may deliver vaginally)
- if invasive cancer present, management depends on prognostic factors, degree of fetal maturity, and patient wishes
  - general recommendations in T1: consider pregnancy termination, management with either radical surgery (hysterectomy vs. trachelectomy if desires future fertility) or concurrent chemoradiation therapy
  - recommendations in T2/T3: delay of therapy until viable fetus and C/S for delivery with concurrent radical surgery or subsequent concurrent chemoradiation therapy

Vulva

BENIGN VULVAR LESIONS

Non-Neoplastic Disorders of Vulvar Epithelium
- biopsy is necessary to make diagnosis and/or rule out malignancy
- hyperplastic dystrophy (squamous cell hyperplasia)
  - surface thickened and hyperkeratotic
  - pruritus most common symptom
  - typically postmenopausal women
  - treatment: 1% fluorinated corticosteroid ointment bid for 6 wk
- lichen sclerosis
  - subepithelial fat becomes diminished, labia become thin and atrophic, membrane-like epithelium, labial fusion
  - pruritus, dyspareunia, burning
  - figure of 8’ distribution
  - most common in postmenopausal women but can occur at any age
  - treatment: ultrapotent topical steroid 0.05% clobetasol x 2-4 wk then taper down
• mixed dystrophy (lichen sclerosis with epithelial hyperplasia)
  ▪ hyperkeratotic areas with areas of thin, shiny epithelium
  ▪ treatment: fluorinated corticosteroid ointment

Tumours
• papillary hidradenoma, nevus, fibroma, hemangioma

MALIGNED VULVAR LESIONS

Epidemiology
• 5% of genital tract malignancies
• 90% squamous cell carcinoma; remainder melanomas, basal cell carcinoma, Paget’s disease, Bartholin’s gland carcinoma
  ▪ Type I disease: HPV-related (50-70%)
    • more likely in younger women
  ▪ 90% of vulvar intraepithelial neoplasia (VIN) contain HPV DNA (usually types 16, 18)
  ▪ Type II disease: not HPV-related, associated with current or previous vulvar dystrophy
    • usually postmenopausal women

Risk Factors
• HPV infection (see above)
• VIN (vulvar intraepithelial neoplasia): precancerous change which presents as multicentric white or pigmented plaques on vulva (may only be visible at colposcopy)
  ▪ progression to cancer rarely occurs with appropriate management
  ▪ treatment: local excision (i.e. superficial vulvectomy ± split thickness skin grafting to cover defects if required) vs. ablative therapy (i.e. laser, cauterization) vs. local immunotherapy (imiquimod)

Clinical Features
• many patients asymptomatic at diagnosis (many also deny or minimize symptoms)
• most lesions occur on the labia majora, followed by the labia minora (less commonly on the clitoris or perineum)
• localized pruritus or lesion most common
• less common: raised red, white or pigmented plaque, ulcer, bleeding, discharge, pain, dysuria
• patterns of spread
  ▪ local
  ▪ groin lymph nodes (usually inguinal → pelvic nodes)
  ▪ hematogenous

Investigations
• ± colposcopy
• ALWAYS biopsy any suspicious lesion

Table 27. FIGO Staging Classification and Treatment of Vulvar Cancer (Surgical Staging)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Intraepithelial neoplasia (VIN), carcinoma in situ</td>
<td>Local excision/superficial vulvectomy, Laser ablation, Local immunotherapy (imiquimod)</td>
</tr>
<tr>
<td>I</td>
<td>Tumour confined to vulva</td>
<td>Radical local excision + groin node dissection if &gt;1 mm invasion, Sentinel node dissection acceptable if lesion &lt;4 cm and no suspicious nodes on examination</td>
</tr>
<tr>
<td>IA</td>
<td>&lt;2 cm lesion, confined to vulva, perineum ± stromal invasion ≤1 mm, no LN involvement</td>
<td>Radical local excision</td>
</tr>
<tr>
<td>IB</td>
<td>&gt;2 mm lesion or stromal invasion &gt;1 mm, confined to vulva or perineum, no LNs</td>
<td>Sentinel node dissection</td>
</tr>
<tr>
<td>II</td>
<td>Tumour any size with adjacent extension (1/3 lower urethra, 1/3 lower vagina or anus) with negative LN</td>
<td>Individualized, Radical surgical excision ± chemoradiation, Neoadjuvant chemoradiation followed by surgical resection, Assessment of regional nodes</td>
</tr>
<tr>
<td>III</td>
<td>Tumour any size with or without extension to perineal structures plus positive inguino-femoral LNs</td>
<td>Individualized, Primary resection versus neoadjuvant chemoradiation followed by surgical resection, Chemoradiation ± radical surgical excision</td>
</tr>
<tr>
<td>IIIA</td>
<td>LN met (≤5 mm) or 1-2 LN mets (&lt;5 mm)</td>
<td>Individualized, Primary resection versus neoadjuvant chemoradiation followed by surgical resection</td>
</tr>
<tr>
<td>IIIB</td>
<td>2 or more LN mets (≤5 mm) or &gt;3 LNs mets (&lt;5 mm)</td>
<td>Individualized, Chemoradiation ± radical surgical excision</td>
</tr>
<tr>
<td>IIC</td>
<td>Positive LNs with extracapsular spread</td>
<td>Individualized, Primary resection versus neoadjuvant chemoradiation</td>
</tr>
<tr>
<td>IV</td>
<td>Regional Invasion (2/3 upper urethra, 2/3 upper vagina or distal structures)</td>
<td>Individualized, Palliative therapy, Individualized, Chemoradiation ± radical surgical excision</td>
</tr>
<tr>
<td>IVA</td>
<td>1. Spread to upper urethra ± vaginal mucosa, bladder, rectal mucosa or fixed to pelvic bone</td>
<td>Individualized, Palliative therapy</td>
</tr>
<tr>
<td>IVB</td>
<td>2. Fixed or ulcerated inguino-femoral LN</td>
<td>Individualized, Palliative therapy</td>
</tr>
<tr>
<td></td>
<td>Distant mets including pelvic LN</td>
<td>Individualized, Palliative therapy</td>
</tr>
</tbody>
</table>
Prognosis
- depends on stage – particularly nodal involvement (single most important predictor followed by tumour size)
- lesions >4 cm associated with poorer prognosis
- overall 5 yr survival rate: 79%

Vagina

BENIGN VAGINAL LESIONS
- inclusion cysts
  - cysts form at site of abnormal healing of laceration (e.g. episiotomy)
  - no treatment required
- endometriosis
  - dark lesions that tend to bleed at time of menses
  - treatment: excision
- Gartner’s duct cysts
  - remnants of Wolffian duct, seen along side of cervix
  - treatment: conservative unless symptomatic
- urethral diverticulum
  - can lead to recurrent urethral infection, dyspareunia
  - treatment: surgical correction if symptomatic

MALIGNANT VAGINAL LESIONS

Epidemiology
- primary carcinomas of the vagina represent 2-3% of malignant neoplasms of the female genital tract
- 80-90% are squamous cell carcinoma
- more than 50% diagnosed between 70-90 yr old

Risk Factors
- associated with HPV infection (analogous to cervical cancer)
- increased incidence in patients with prior history of cervical and vulvar cancer

Investigations
- cytology
  - significant false negative rate for existing malignancy (i.e. if gross lesion present, biopsy!)
- colposcopy
- Schiller test (normal squamous epithelium takes up Lugol’s iodine)
- biopsy, partial vaginectomy (wide local excision for diagnosis)
- rule out disease on cervix, vulva, or anus (most vaginal cancers are actually metastatic from one of these sites)
- staging (see Table 29)

Clinical Features

Table 28. Clinical Features of Malignant Vaginal Lesions

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal Intra-Epithelial Neoplasia (VAIN)</td>
<td>Grades: analogous to cervical dysplasia</td>
</tr>
</tbody>
</table>
| Squamous Cell Carcinoma (SCC) | Most common site is upper 1/3 of posterior wall of vagina
|                               | Asymptomatic                                                                     |
|                               | Painless discharge and bleeding                                                   |
|                               | Vaginal discharge (often foul-smelling)                                          |
|                               | Vaginal bleeding especially during/after coitus                                   |
|                               | Urinary or/and rectal symptom 2° to compression                                  |
| Adenocarcinoma                | Most are metastatic, usually from cervix, endometrium, ovary or colon
|                               | Most primaries are clear cell adenocarcinomas                                    |
|                               | 2 types: non-DES and DES syndrome                                                 |

Diethylstilbestrol (DES) Syndrome
- fetal exposure to DES (due to maternal use) predisposes to cervical or vaginal clear cell carcinoma: occurs in 30-95% of exposed females
- if exposed, <1 in 1,000 risk of developing clear cell adenocarcinoma
- clinical features
  - adenosis is persistent Müllerian type glandular epithelium in vagina
  - malformations of upper vagina, cervix, and interior of uterus (T-shaped); cockscomb or hooded cervix, cervical collar and pseudopolyps of cervix
- patients with DES exposure should have annual Pap tests (cervix and vagina) and digital vaginal exam for subepithelial masses
  - if any abnormality, refer for colposcopy
Table 29. FIGO Staging Classification of Vaginal Cancer (Clinical Staging) and Treatment

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| 0     | Intraepithelial neoplasia (VAIN), carcinoma in situ | • Must rule out invasive cancer via biopsies and colposcopy prior to conservative treatment  
• Laser ablation vs. surgical excision vs. local immunotherapy (e.g. imiquimod) |
| I     | Limited to the vaginal wall | • Radiation is mainstay of therapy: combination of brachytherapy and external beam radiation  
• In certain situations where surgery has a role in management:  
1. Stage I disease involving upper posterior vagina  
2. Young patients who require radiation therapy  
3. Stage IVA disease, particularly if rectovaginal or vesicovaginal fistula is present  
4. In patients with a central recurrence after radiation therapy  
• Limited reported evidence with chemoradiation |
| II    | Involves subvaginal tissue, NO pelvic wall extension | |
| III   | Pelvic wall extension | |
| IV    | Extension beyond true pelvis OR bladder/rectum involvement | |
| IVA   | Bladder + rectal mucosal spread = extension beyond true pelvis | 1. Stage I disease involving upper posterior vagina  
2. Young patients who require radiation therapy  
3. Stage IVA disease, particularly if rectovaginal or vesicovaginal fistula is present  
4. In patients with a central recurrence after radiation therapy |
| IVB   | Spread to distant organs | |

Fallopian Tube

- least common site for carcinoma of female reproductive system (0.3%)  
- usually serous epithelial carcinoma  
- recently considered to be origin of serous ovarian cancer  
- more common in fifth and sixth decade

Clinical Features

- classic triad present in minority of cases, but very specific  
  - watery discharge (most specific) = "hydrops tubae profluens"  
  - vaginal bleeding or discharge in 50% of patients  
  - crampy lower abdominal/pelvic pain  
- most patients present with a pelvic mass (see Ovarian Cancer, GY39 for guidelines regarding diagnosis/investigation)

Treatment

- as for malignant epithelial ovarian tumours

Gestational Trophoblastic Disease/Neoplasia (GTD/GTN)

- refers to a spectrum of proliferative abnormalities of the trophoblast

Epidemiology

- 1/1000 pregnancies  
- marked geographic variation – as high as 1/125 in Taiwan  
- 80% benign, 15% locally invasive, 5% metastatic  
- cure rate >95%

HYDATIDIFORM MOLE (Benign GTD)

Complete Mole

- most common type of hydatidiform mole  
- diffuse trophoblastic hyperplasia, hydropic swelling of chorionic villi, no fetal tissues or membranes present  
- 46XX or 46XY, chromosomes completely of paternal origin (90%)  
- 2 sperm fertilize empty egg or 1 sperm with reduplication  
- 15-20% risk of progression to malignant sequelae  
- risk factors  
  - geographic (South East Asia most common)  
  - others (maternal age >40 yr, β-carotene deficiency, vitamin A deficiency) – not proven  
- clinical features  
  - often present during apparent pregnancy with abnormal symptoms/findings:  
    - vaginal bleeding (97%)  
    - excessive uterine size for LMP (51%)  
    - theca-lutein cysts >6 cm (50%)  
    - preeclampsia (27%)  
    - hyperemesis gravidarum (26%)  
    - hyperthyroidism (7%)  
    - β-hCG >100,000 IU/L  
    - no fetal heart beat detected

Prognosis

5-yr Survival Rates

- Stage I: 70%  
- Stage II: 40%  
- Stage III: 30%  
- Stage IV: 15-20%

With development of hypertension early in pregnancy (i.e. <20 wk), think gestational trophoblastic disease!
Partial (or Incomplete) Mole
- focal trophoblastic hyperplasia and hydropic villi are associated with fetus or fetal parts
- often triploid (XXX, XYY, XXX) with chromosome complement from both parents
  - usually related to single ovum fertilized by two sperm
- low risk of progression to malignant sequelae (<4%)
- associated with fetus, which may be growth-restricted and/or have multiple congenital malformations
- clinical features
  - typically present similar to threatened/spontaneous/missed abortion
  - pathological diagnosis often made after D&C

Investigations
- quantitative β-hCG levels (tumour marker) abnormally high for gestational age
  - U/S findings:
    - if complete: no fetus (classic “snow storm” due to swelling of villi)
    - if partial: molar degeneration of placenta ± fetal anomalies, multiple echogenic regions corresponding to hydropic villi, and focal intrauterine hemorrhage
  - CXR (may show metastatic lesions)
  - features of molar pregnancies at high risk of developing persistent GTN post-evacuation
    - local uterine invasion as high as 31%
    - β-hCG >100,000 IU/L
    - excessive uterine size
    - prominent theca-lutein cysts

Treatment
- suction D&C with sharp curettage and oxytocin
  - Rhogam® if Rh negative
- consider hysterectomy (if patient no longer desires fertility)
- prophylactic chemotherapy of no proven benefit
- chemotherapy for GTN if develops after evacuation

Follow-up
- contraception required to avoid pregnancy during entire follow-up period
- serial β-hCGs (as tumour marker) every week until negative x 3 (usually takes several wk), then monthly for 6-12 mo prior to trying to conceive again
- increase or plateau of β-hCG indicates GTN → patient needs chemotherapy

GTN (MALIGNANT GTD)

Invasive Mole or Persistent GTN
- diagnosis made by rising or plateau in β-hCG, development of metastases following treatment of documented molar pregnancy (see sidebar)
- histology: molar tissue from D&C
- metastases are rare (4%)

Choriocarcinoma
- often present with symptoms from metastases
- highly anaplastic, highly vascular
- no chorionic villi, elements of syncytiotrophoblast and cytotrophoblast
- may follow molar pregnancy, abortion, ectopic, or normal pregnancy

Placental-site Trophoblastic Tumour
- rare aggressive form of GTN
- abnormal growth of intermediate trophoblastic cells
- low β-hCG, production of human placental lactogen (hPL), relatively insensitive to chemotherapy

CLASSIFICATION of GTN
- non-metastatic
  - ~15% of patients after molar evacuation
  - may present with abnormal bleeding
  - all have rising or plateau of β-hCG
  - negative metastases on staging investigations
- metastatic
  - 4% patients after treatment of complete molar pregnancy
  - metastasis more common with choriocarcinoma which tends toward early vascular invasion and widespread dissemination
  - if signs or symptoms suggest hematogenous spread, do not biopsy (they bleed)
    - lungs (80%): cough, hemoptysis, CXR lesion(s)
    - vagina (30%): vaginal bleeding, “blue lesions” on speculum exam
    - pelvis (20%): rectal bleeding (if invades bowel), U/S lesion(s)
    - liver (10%): elevated LFTs, U/S or CT findings
    - brain (10%): headaches, dizziness, seizure (symptoms of space-occupying lesion), CT/MRI findings
highly vascular tumour → bleeding → anemia
• all have rising or plateau of β-hCG  
• classification of metastatic GTN  
  • divided into good prognosis and bad prognosis  
  • features of bad prognosis  
    – long duration (>4 mo from antecedent pregnancy)  
    – high pre-treatment β-hCG titre: >100,000 IU/24 h urine or >40,000 IU/L of blood  
    – brain or liver metastases  
    – prior chemotherapy  
    – metastatic disease following term pregnancy  
• good prognosis characterized by the absence of each of these features

Investigations – For Staging
• bloodwork: CBC, electrolytes, creatinine, β-hCG, TSH, LFTs  
• imaging: CXR, U/S pelvis, CT abdo/pelvis, CT brain  
• if suspect brain metastasis but CT brain negative, consider lumbar puncture for CSF β-hCG  
  • ratio of plasma β-hCG:CSF β-hCG <60 indicates metastases

<table>
<thead>
<tr>
<th>Stage</th>
<th>Findings</th>
<th>Management</th>
</tr>
</thead>
</table>
| I     | Disease confined to uterine corpus | Single agent chemotherapy for low risk disease (WHO score ≤6)  
  1st line: pulsed – actinomycin D (Act-D) IV q2wk  
  Alternatives: MTX-based regimen  
  20% of patients need to switch to alternate single-agent regimen due to failure of β-hCG to return to normal  
  Combination chemotherapy (EMA-CO: etoposide, MTX, ACT-D, cyclophosphamide, vincristine) if high risk (WHO score ≥7) or if resistant to single agent chemotherapy  
  Can consider hysterectomy if fertility not desired or placental-site trophoblastic tumour |
| II    | Metastatic disease to genital structures | As above |
| III   | Metastatic disease to lungs with or without genital tract involvement | As above |
| IV    | Distant metastatic sites including brain, liver, kidney, GI tract | Usually high risk (EMA-CO) with surgical resection of sites of disease  
  Persistence/resistance to chemotherapy  
  Consider radiation for brain mets |

Table 30. FIGO Staging and Management of Malignant GTN

<table>
<thead>
<tr>
<th>Stage</th>
<th>Findings</th>
<th>Management</th>
</tr>
</thead>
</table>
| I     | Disease confined to uterine corpus | Single agent chemotherapy for low risk disease (WHO score ≤6)  
  1st line: pulsed – actinomycin D (Act-D) IV q2wk  
  Alternatives: MTX-based regimen  
  20% of patients need to switch to alternate single-agent regimen due to failure of β-hCG to return to normal  
  Combination chemotherapy (EMA-CO: etoposide, MTX, ACT-D, cyclophosphamide, vincristine) if high risk (WHO score ≥7) or if resistant to single agent chemotherapy  
  Can consider hysterectomy if fertility not desired or placental-site trophoblastic tumour |
| II    | Metastatic disease to genital structures | As above |
| III   | Metastatic disease to lungs with or without genital tract involvement | As above |
| IV    | Distant metastatic sites including brain, liver, kidney, GI tract | Usually high risk (EMA-CO) with surgical resection of sites of disease  
  Persistence/resistance to chemotherapy  
  Consider radiation for brain mets |

Table 31. WHO Prognostic Score for GTD (2011)

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td>AP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40</td>
</tr>
<tr>
<td>Interval (end of AP to chemotherapy in months)</td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>4-6</td>
</tr>
<tr>
<td></td>
<td>7-13</td>
</tr>
<tr>
<td></td>
<td>&gt;13</td>
</tr>
<tr>
<td>HCG IU/1</td>
<td></td>
</tr>
<tr>
<td>&lt;103</td>
<td>103-104</td>
</tr>
<tr>
<td></td>
<td>104-105</td>
</tr>
<tr>
<td></td>
<td>&gt;105</td>
</tr>
<tr>
<td>Number of metastases</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1-4</td>
</tr>
<tr>
<td></td>
<td>5-8</td>
</tr>
<tr>
<td></td>
<td>&gt;8</td>
</tr>
<tr>
<td>Site of metastases</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>Splen, kidney</td>
</tr>
<tr>
<td></td>
<td>GI tract</td>
</tr>
<tr>
<td></td>
<td>Brain, liver</td>
</tr>
<tr>
<td>Largest tumour mass</td>
<td></td>
</tr>
<tr>
<td>3-5 cm</td>
<td>&gt;5 cm</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Single drug</td>
<td>Two drug</td>
</tr>
</tbody>
</table>

Follow-up (for GTN)
• contraception for all stages to avoid pregnancy during entire follow-up period  
• stage I, II, III  
  • weekly β-hCG until 3 consecutive normal results  
  • then monthly x 12 mo  
• stage IV  
  • weekly β-hCG until 3 consecutive normal results  
  • then monthly x 24 mo
### Table 32. Common Medications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Action</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>acyclovir (Zovirax&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Antiviral; inhibits DNA synthesis and viral replication</td>
<td>First Episode: 400 mg PO tid x 7-10 d Recurrence: 400 mg PO tid x 5 d</td>
<td>Genital herpes</td>
<td>S/E: headache, GI upset D/I: zidovudine, probenecid</td>
</tr>
<tr>
<td>bromocriptine (Parlodel&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Dopaminomimetic Agonist at D&lt;sub&gt;2&lt;/sub&gt;R Antagonist at D&lt;sub&gt;1&lt;/sub&gt;R Acts directly on anterior pituitary cells to inhibit synthesis and release of prolactin</td>
<td>Initial: 1.25-2.5 mg PO qhs with food Then: increase by 2.5 mg every 2-7 d as needed until optimal therapeutic response</td>
<td>Galactorrhea + amenorrhea 2° to hyperprolactinemia Prolactin-dependent menstrual disorders and infertility Prolactin-secreting adenomas (microadenomas, prior to surgery of macroadenomas)</td>
<td>S/E: nausea, vomiting, headache, postural hypotension, somnolence C/I: uncontrolled hypertension, pregnancy-induced hypertension, CAD, breastfeeding D/I: domperidone, macrolides, octreotide</td>
</tr>
<tr>
<td>clomiphene citrate (Clomid&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Increases output of pituitary gonadotropins which induces ovulation</td>
<td>50 mg OD x 5 d Try 100 mg or 160 mg OD if ineffective 3 courses = adequate trial</td>
<td>Patients with persistent ovulatory dysfunction (e.g. amenorrhea, PCOS) who desire pregnancy</td>
<td>S/E: Common – hot flashes, abdominal discomfort, exacerbated cyclic ovarian enlargement, accentuation of Mittelschmerz Rare – ovarian hyperstimulation syndrome, multiple pregnancy, visual blurring, birth defects C/I: pregnancy, liver disease, hormone-dependent tumours, ovarian cyst, undiagnosed vaginal bleeding</td>
</tr>
<tr>
<td>danazol (Cyclomen&lt;sup&gt;®&lt;/sup&gt; – CAN) (Danocrine&lt;sup&gt;®&lt;/sup&gt; – US)</td>
<td>Synthetic steroid that inhibits pituitary gonadotropin output and ovarian steroid synthesis Has mild androgenic properties</td>
<td>200-800 mg in 2-3 divided doses Used for 3-6 mo Biannual hepatic U/S required if &gt;6 mo use</td>
<td>Endometriosis 1° menorrhagia/DUB</td>
<td>S/E: weight gain, acne, mild hirsutism, hepatic dysfunction C/I: pregnancy, undiagnosed vaginal bleeding, breastfeeding, severely impaired renal/hepatic/cardiac function, porphyria, genital neoplasia, thromboembolic disease D/I: warfarin, carbamazepine, cyclosporine, tacrolimus, anti-hypertensives</td>
</tr>
<tr>
<td>doxycycline</td>
<td>Tetracycline derivative; inhibit protein synthesis</td>
<td>100 mg PO bid x ≥7 d</td>
<td>Chlamydia, gonococcal infection, syphilis</td>
<td>S/E: GI upset, hepatotoxicity C/I: pregnancy, severe hepatic dysfunction D/I: warfarin, digoxin</td>
</tr>
<tr>
<td>fluconazole (Diflucan&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Antifungal; disrupt fungal cell membrane</td>
<td>150 mg PO x 1 dose</td>
<td>Vulvovaginal candidiasis unsensitive to clotrimazole</td>
<td>S/E: headache, rash, nausea, vomiting, abdominal pain, diarrhea D/I: terfenadine, cisapride, astemizole, hydrochlorothiazide, phenytoin, warfarin, ritampin</td>
</tr>
<tr>
<td>leuprolide (Lupron&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Synthetic GnRH analog Induces reversible hypoestrogenic state</td>
<td>3.75 mg IM q1mo or 11.25 mg IM q3mo Usually ≤6 mo, check bone density if &gt;6 mo Retreatment with Lupron&lt;sup&gt;®&lt;/sup&gt; alone not recommended because of effects on bone density</td>
<td>Endometriosis Leiomymoma DUB Precocious puberty</td>
<td>S/E: hot flashes, sweats, headache, vaginitis, reduction in bone density, acne, GI upset C/I: pregnancy, undiagnosed vaginal bleeding, breastfeeding</td>
</tr>
<tr>
<td>menotropin (Pergonal&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Human Gonadotropin with FSH and LH effects; induce ovulation and stimulate ovarian follicle development</td>
<td>75-150 U of FSH and LH IM OD x 7-12 d, then 10,000 U hCG one day after last dose</td>
<td>Infertility</td>
<td>S/E: bloating, irritation at injection site, abdominal/pelvic pain, headache, nausea and vomiting, multiple pregnancy C/I: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, undiagnosed uterine bleeding</td>
</tr>
<tr>
<td>metronidazole (Flagyl&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Bactericidal; forms toxic metabolites which damage bacterial DNA</td>
<td>2 g PO x 1 dose or 500 mg PO bid x 7 d</td>
<td>Bacterial vaginosis, trichomonas vaginitis</td>
<td>S/E: headache, dizziness, nausea, vomiting, diarrhea, disulfiram-like reaction (flushing, tachycardia, nausea and vomiting) C/I: pregnancy (1&lt;sup&gt;st&lt;/sup&gt; trimester) D/I: cisapride, warfarin, cinetidine, lithium, alcohol, amiodarone, milk thistle, carbamazepine</td>
</tr>
</tbody>
</table>
### Table 32. Common Medications/References

<table>
<thead>
<tr>
<th>Drug Name (Brand Name)</th>
<th>Action</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxybutinin (Ditropan®)</td>
<td>Anticholinergic – relaxes bladder smooth muscle, inhibits involuntary detrusor contraction</td>
<td>5 or 10 mg/d PO May increase doses by 5 mg weekly to a max of 30 mg/d</td>
<td>Overactive bladder (urge incontinence)</td>
<td>S/E: dry mouth/eyes, constipation, palpitations, urinary retention, dizziness, headache C/I: glaucoma, GI ileus, severe colitis, obstructive uropathy, use with caution if impaired hepatic/renal function</td>
</tr>
<tr>
<td>tolterodine (Detrol®)</td>
<td>Anticholinergic</td>
<td>1-2 mg PO bid</td>
<td>Overactive bladder (urge incontinence)</td>
<td>S/E: anaphylaxis, psychosis, tachycardia, dry mouth/eyes, headache, constipation, uriinary retention, chest pain, abdominal pain C/I: glaucoma, gastric/urinary retention, use with caution if impaired hepatic/renal function</td>
</tr>
<tr>
<td>tranexamic acid (Cyklokapron®)</td>
<td>Anti-fibrinolytic, reversibly inhibits plasminogen activation</td>
<td>1-1.5 g tid-qid for first 4 d of cycle Max 4 g/d</td>
<td>Ovarian enlargement or cysts, edema and pain at injection site, arterial thromboembolism, fever, abdominal pain, headache, multiple pregnancy C/I: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, abnormal uterine bleeding</td>
<td></td>
</tr>
<tr>
<td>urofolitropin (Metrodin®)</td>
<td>FSH</td>
<td>75 Unit SC x 7-12d</td>
<td>Ovulation induction in PCOS</td>
<td>Menorrhagia</td>
</tr>
<tr>
<td>combined oral contraceptive pill (OCP)</td>
<td>Ovulatory suppression by inhibiting LH and FSH Decidualization of endometrium Thickening of cervical mucus to prevent sperm penetration</td>
<td></td>
<td>Contraception Disorders of menstruation</td>
<td></td>
</tr>
<tr>
<td>intrauterine device (IUD)</td>
<td>Copper IUD: mild foreign body reaction in endometrium which is toxic to sperm and alters sperm motility Progesterone-releasing IUD: decidualization of endometrium and thickening of cervical mucus, may suppress ovulation</td>
<td></td>
<td>Same as above</td>
<td></td>
</tr>
</tbody>
</table>

### References

**Books/Manuals**
- Berek JS, Hacker NF, Gynecologic oncology. 5th ed. Lippincott Williams & Wilkins, 2010.
- Cunningham FG, MacDonald PC, Gant NF. Williams obstetrics, 14th ed. Appleton and Lange, 1993.

**Guidelines**
- Davis V, Dunn S. Emergency postcoital contraception. SOGC Clinical Practice Guidelines July 2000;82.

**Journal Articles**


Woolston E. Medroxyprogesterone acetate (Provera) and bone mineral density loss. JAMA 2000;283:749-752.

Acronyms .................................................. 2

Basics of Hematology .................................. 2
Complete Blood Count (CBC)
Blood Film Interpretation
Bone Marrow Aspiration and Biopsy

Common Presenting Problems ....................... 5
Anemia
Erythrocytosis
Thrombocytopenia
Thrombocytosis
Pancytopenia
Neutrophilia
Neutropenia
Lymphocytosis
Lymphopenia
Eosinophilia
Agranulocytosis
Leukemoid Reactions

Approach to Lymphadenopathy ..................... 11

Approach to Splenomegaly ............................ 12

Microcytic Anemia: ................................. 12
Iron Metabolism
Iron Deficiency Anemia
Anemia of Chronic Disease
Sideroblastic Anemia
Lead Poisoning
Thalassemia

Normocytic Anemia: ................................. 16
Aplastic Anemia

Hemolytic Anemia (HA): ........................... 17
Thalassemia
β-Thalassemia Minor (Thalassemia Trait)
β-Thalassemia Major
α-Thalassemia
Sickle Cell Disease
Autoimmune Hemolytic Anemia (AIHA)
Microangiopathic Hemolytic Anemia (MAHA)
Hereditary Spherocytosis
Hereditary Elliptocytosis
G6PD Deficiency

Macrocytic Anemia: ................................. 22
Vitamin B12 Deficiency
Folate Deficiency

Hemostasis: ............................................ 24
Three Phases of Hemostasis
Disorders of Primary Hemostasis .................. 25
Immune Thrombocytopenic Purpura (ITP)
Heparin-Induced Thrombocytopenia (HIT)
Thrombotic Thrombocytopenic Purpura (TTP)
and Hemolytic Uremic Syndrome (HUS)
Von Willebrand Disease (vWD)

Disorders of Secondary Hemostasis .............. 29
Hemophilia A (Factor VIII Deficiency)
Hemophilia B (Factor IX Deficiency)
Factor XI Deficiency
Liver Disease
Vitamin K Deficiency
Disseminated Intravascular Coagulation (DIC)

Venous Thromboembolism ........................... 31
Approach to Treatment of Venous Thromboembolism

Hypercoagulable Disorders: ....................... 34

Hematologic Malignancies and Related Disorders ........................... 35
Myeloid Malignancies: .............................. 35
Acute Myeloid Leukemia (AML)
Myelodysplastic Syndromes (MDS)

Myeloproliferative Neoplasms (MPNs) ........... 37
Chronic Myeloid Leukemia (CML)
Polycythemia Vera (PV)
Idiopathic Myelofibrosis (IMF)
Essential Thrombocythemia (ET)

Lymphoid Malignancies: ............................ 41
Acute Lymphoblastic Leukemia (ALL)

Lymphomas: ........................................... 42
Hodgkin Lymphoma
Non-Hodgkin Lymphoma (NHL)

Malignant Clonal Proliferations of Mature B-Cells .................... 46
Chronic Lymphocytic Leukemia (CLL)
Multiple Myeloma (MM)
Monoclonal Gammapathy of Unknown Significance (MGUS)
Lymphoplasmacytic Lymphoma
(Waldenstrom’s Macroglobulinemia)

Complications of Hematologic Malignancies .. 49
Hyperviscosity Syndrome
Tumour Lysis Syndrome

Blood Products and Transfusions ................... 50
Blood Products
Red Blood Cells
Platelets
Coagulation Factors
Acute Blood Transfusion Reactions
Delayed Blood Transfusion Reactions

Common Medications: .............................. 54
Antiplatelet Therapy
Anticoagulant Therapy
Chemotherapeutic and Biological Agents used in Oncology

Landmark Hematology Trials ....................... 57

References ............................................ 58
Basics of Hematology

- over $10^{11}$ blood cells are produced daily
- sites of hematopoiesis in adults: pelvis, sternum, vertebral bodies
- lifespan of mature cells in blood:
  - erythrocytes (120 d), neutrophils (~1 d), platelets (10 d), lymphocytes (varies – memory cells persist for years)
- role of lymphoid organs
  - spleen: part of reticuloendothelial system, removes aged RBCs, removes antibody-coated bacteria/cells, site of antibody production
  - thymus: site of T-cell maturation, involutes with age
  - lymph nodes: sites of B and T-cell activation (adaptive immune response)

Figure 1. Hematopoiesis

- over $10^{11}$ blood cells are produced daily
- sites of hematopoiesis in adults: pelvis, sternum, vertebral bodies
- lifespan of mature cells in blood:
  - erythrocytes (120 d), neutrophils (~1 d), platelets (10 d), lymphocytes (varies – memory cells persist for years)
- role of lymphoid organs
  - spleen: part of reticuloendothelial system, removes aged RBCs, removes antibody-coated bacteria/cells, site of antibody production
  - thymus: site of T-cell maturation, involutes with age
  - lymph nodes: sites of B and T-cell activation (adaptive immune response)
Complete Blood Count (CBC)

Table 1. Common Terms Found on CBC

<table>
<thead>
<tr>
<th>Test</th>
<th>Definition</th>
<th>Normal Values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cell (RBC) count</td>
<td>The number of RBCs per volume of blood</td>
<td>4.2-6.9 x 10^6/mm³</td>
</tr>
<tr>
<td>Hemoglobin (Hb)</td>
<td>Amount of oxygen-carrying protein in the blood</td>
<td>130-180 g/L (13-18 g/dL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(male)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120-160 g/L (12-16 g/dL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(female)</td>
</tr>
<tr>
<td>Hematocrit (Hct)</td>
<td>Percentage of a given volume of whole blood</td>
<td>45%-62% (male)</td>
</tr>
<tr>
<td></td>
<td>occupied by packed RBCs</td>
<td>37%-48% (female)</td>
</tr>
<tr>
<td>Mean corpuscular volume (MCV)</td>
<td>Measurement of size of RBCs</td>
<td>80-100 µm³</td>
</tr>
<tr>
<td>Mean corpuscular Hb (MCH)</td>
<td>Amount of oxygen-carrying Hb inside RBCs</td>
<td>27-32 pg/cell</td>
</tr>
<tr>
<td>Mean corpuscular Hb concentration (MCHC)</td>
<td>Average concentration of Hb inside RBCs</td>
<td>32%-36%</td>
</tr>
<tr>
<td>RBC distribution width (RDW)</td>
<td>Measurement of variance in RBC size</td>
<td>11.0%-15.0%</td>
</tr>
<tr>
<td>White blood cell (WBC) count</td>
<td>The number of WBCs per volume of blood</td>
<td>4.3-10.8 x 10^9/mm³</td>
</tr>
<tr>
<td>WBC differential</td>
<td>Includes neutrophils, eosinophils, basophils,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lymphocytes and monocytes</td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td>The number of platelets per volume of blood</td>
<td>150-400 x 10^9/mm³</td>
</tr>
<tr>
<td>Mean platelet volume (MPV)</td>
<td>Measurement of platelet size</td>
<td></td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>Immature RBCs that contain no nucleus but have</td>
<td>Normally make up 1% of total</td>
</tr>
<tr>
<td></td>
<td>residual RNA</td>
<td>RBC count</td>
</tr>
</tbody>
</table>

*Normal values may vary depending on site and age

Approach to Interpreting a CBC
1. Consider values in the context of individual's baseline
   - up to 5% of population without disease may have values outside “normal” range
   - an individual may display a clinically significant change from their baseline without violating “normal” reference range
2. Is one cell line affected or are several?
   - if all lines are low: pancytopenia (see Pancytopenia, H7)
   - if RBCs and platelets are low: consider a microangiopathic hemolytic anemia (MAHA) (see H21)
   - if single cell line affected: see corresponding section in Common Presenting Problems, H5

Blood Film Interpretation

RED BLOOD CELLS

Size
- microcytic (MCV<80), normocytic (MCV=80-100), macrocytic (MCV>100)
- anisocytosis: RBCs with increased variability in size (increased RDW)
- iron deficiency anemia, hemolytic anemias, myelofibrosis, blood transfusion

Colour
- hypochromic: increase in size of central pallor (normal = less than 1/3 of RBC diameter)
- iron deficiency anemia, anemia of chronic disease, sideroblastic anemia
- polychromasia: increased reticulocytes (pinkish-blue cells)
- increased RBC production by bone marrow

Shape
- poikilocytosis: increased proportion of RBCs of abnormal shape
- iron deficiency anemia, myelofibrosis

Table 2. Common Erythrocyte Shapes

<table>
<thead>
<tr>
<th>Shape</th>
<th>Definition</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discocyte</td>
<td>Biconcave disc</td>
<td>Normal RBC</td>
</tr>
<tr>
<td>Spherocyte</td>
<td>Spherical RBC (due to loss of membrane)</td>
<td>Hereditary spherocytosis, immune hemolytic anemia, post-transfusion</td>
</tr>
<tr>
<td>Elliptocyte/Ovalcyte</td>
<td>Oval-shaped, elongated RBCs</td>
<td>Hereditary elliptocytosis, megaloblastic anemia, megaloblastic anemia, myelofibrosis, iron-deficiency, MDS (myelodysplastic syndrome)</td>
</tr>
<tr>
<td>Schistocyte (helmet cell)</td>
<td>Fragmented cells (due to traumatic disruption of membrane)</td>
<td>Microangiopathic hemolytic anemia (HUS/ TTP DIC, preeclampsia, HELLP, malignant HTN), vasculitis, glomerulonephritis, prosthetic heart valve</td>
</tr>
<tr>
<td>Sickle cell</td>
<td>Sickle-shaped RBC (due to polymerization of hemoglobin S)</td>
<td>Sickle cell disorders: HbSC, HbSS</td>
</tr>
<tr>
<td>Codocyte (target cell)</td>
<td>“Bull’s eye” on dried film</td>
<td>Liver disease, hemoglobin SC, thalassemia, Fe deficiency, anemia</td>
</tr>
<tr>
<td>Dacrocyte (teardrop cell)</td>
<td>Single pointed end, looks like a teardrop</td>
<td>Myelofibrosis, thalassemia major, megaloblastic anemia</td>
</tr>
</tbody>
</table>

Clinical Use of RDW
- To distinguish the etiologies of microcytosis:
  - Iron deficiency: increased RDW (anisocytosis) as cells are of varying sizes in iron deficiency.
  - Thalassemia major: normal RDW (also expect a high RBC count) as cells are of similar size due to genetic defect in Hb.
Table 2. Common Erythrocyte Shapes (continued)

<table>
<thead>
<tr>
<th>Shape</th>
<th>Definition</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthocyte (spur cell)</td>
<td>Distorted RBC with irregularly distributed thorn-like projections (due to abnormal membrane lipids)</td>
<td>Severe liver disease (spur cell anemia), starvation/anorexia, post-splenectomy</td>
</tr>
<tr>
<td>Echinocyte (burr cell)</td>
<td>RBC with numerous regularly spaced, small spiny projections</td>
<td>Uremia, HUS, burns, cardiopulmonary bypass, post-transfusion, storage artifact</td>
</tr>
<tr>
<td>Rouleaux formation</td>
<td>Aggregates of RBC resembling stacks of coins (due to increased plasma concentration of high molecular weight proteins)</td>
<td>Pregnancy: most common cause; due to physiological increase in fibrinogen Inflammatory conditions: due to polyclonal immunoglobulins Plasma cell dyscrasias: due to monoclonal paraproteinaemia, e.g. multiple myeloma, macroglobulinaemia Storage artifact</td>
</tr>
</tbody>
</table>

HUS = Hemolytic uremic syndrome; TTP = Thrombotic thrombocytopenic purpura; DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver enzymes and low platelets

Table 3. RBC Inclusions (see Figure 2)

<table>
<thead>
<tr>
<th>Inclusions</th>
<th>Definition</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear</td>
<td>Present in erythroblasts (immature RBCs)</td>
<td>Hyperplastic erythropoiesis (seen in hypoxia, hemolytic anemia), BM infiltration disorders, MPNs (MF)</td>
</tr>
<tr>
<td>Heinz bodies</td>
<td>Denatured and precipitated hemoglobin</td>
<td>GPA deficiency (post-exposure to oxidant), thalassemia, unstable hemoglobins</td>
</tr>
<tr>
<td>Howell-Jolly</td>
<td>Small nuclear remnant resembling a pyknotic nucleus</td>
<td>Post-splenectomy, hyposplenism (sickle cell disease), neonates, megaloblastic anemia</td>
</tr>
<tr>
<td>Basophilic stippling</td>
<td>Deep blue granulations indicating ribosome aggregation</td>
<td>Thalassemia, heavy metal (Pb, Zn, Ag, Hg) poisoning, megaloblastic anemia, hereditary (pyrimidine 5' nucleotidase deficiency)</td>
</tr>
<tr>
<td>Sideroblasts</td>
<td>Erythrocytes with Fe containing granules in the cytoplasm</td>
<td>Hereditary, idiopathic, drugs, hypothyroidism (see Sideroblastic Anemia, H15), myelodysplastic syndrome</td>
</tr>
</tbody>
</table>

BM = bone marrow; MPN = myeloproliferative neoplasm; MF = myelofibrosis

WHITE BLOOD CELLS
- lymphocytes: comprise 30–40% of WBCs; great variation in “normal” lymphocyte morphology
  - Reed-Sternberg cell: giant, multinucleated B-lymphocyte, only seen with bone marrow specimens
    - associations: primarily Hodgkin lymphoma, also seen in some non-Hodgkin lymphoma, CLL and EBV infection
  - smudge cells: lymphocytes damaged during blood film preparation indicating cell fragility
    - associations: chronic lymphocytic leukemia (CLL) and other lymphoproliferative disorders – pathognomonic in EBV infection
- neutrophils
  - normally only mature neutrophils (with 3-4 lobed nucleus) and band neutrophils (immediate precursor with horseshoe-shaped nucleus) are found in circulation
  - hypersegmented neutrophil: >5 lobes suggests megaloblastic process (B12 or folate deficiency)
  - left shift (increased granulocyte precursors)
    - seen in leukemoid reactions: acute infections, pregnancy, neonates, hypoxia, shock, myeloproliferative neoplasms (CML, MF)
- blasts
  - immature, undifferentiated precursors; associated with acute leukemia, MDS, G-CSF (growth factor that stimulates neutrophil production) use
  - Auer rods: clumps of granular material that form long needles in the cytoplasm of myeloblasts
    - pathognomonic for acute myeloid leukemia (AML)

PLATELETS
- small, purple, anuclear cell fragments

Bone Marrow Aspiration and Biopsy
- sites: posterior iliac crest, sternum
- possible analyses
  - aspiration: takes a fluid marrow sample for cellular morphology, flow cytometry, cytogenticities, molecular studies, microbiology (C&S, AFB, PCR)
  - biopsy: takes a sample of intact bone marrow to assess histology and immunohistochemistry

Indications
- unexplained CBC abnormalities
- diagnosis and evaluation of infiltrating cancers: plasma cell disorders, leukemias, solid tumours
- diagnosis and staging of lymphoma or solid tumours
- evaluate iron metabolism and stores (gold standard, but rarely done)
evaluate suspected deposition and storage disease (e.g. amyloidosis, Gaucher’s disease)
evaluate fever of undetermined origin, suspected mycobacterial, fungal or parasitic infections,
or granulomatous disease
unexplained splenomegaly
confirm normal bone marrow in potential allogenic hematopoietic cell donor

Contraindications
• absolute: untreated hemophilia, severe DIC, infection over skin site
• relative: platelet count <10, recent warfarin use with INR >2.0, liver disease with associated
coaagulopathy
• thrombocytopenia is not a contraindication; may need platelet transfusion prior to procedure

Common Presenting Problems

Anemia
Definition
• a decrease in red blood cell (RBC) mass that can be detected by hemoglobin (Hb) concentration, hematocrit (Hct), and RBC count
  • adult males: Hb <130 g/L or Hct <0.41
  • adult females: Hb <120 g/L or Hct <0.36

Clinical Features
• history
  • symptoms of anemia: fatigue, malaise, weakness, dyspnea, decreased exercise tolerance, palpitations, headache, dizziness, tinnitus, syncope
  • acute vs. chronic, bleeding, systemic illness, diet, alcohol, family history
  • menstrual history: menorrhagia, menometrorrhagia, dysfunctional uterine bleeding
  • rule out pancytopenia (recurrent infection, mucosal bleeding/easy bruising)
• physical signs
  • HEENT: pallor in mucous membranes, palmar creases and conjunctiva at Hb <90 g/L (<9 g/dL), ocular bruits at Hb <55 g/dL (<5.5 g/dL), angular cheilosis, jaundice
  • cardiac: tachycardia, orthostatic hypotension, systolic flow murmur, wide pulse pressure, signs of CHF
  • dermatologic: pallor in palmar skin creases at Hb <75 g/L, jaundice (if due to hemolysis), nail changes, glossitis

Investigations
• rule out dilutional anemia (low Hb due to increased effective circulating volume)
• CBC with differential (MCV, RDW, RBC count)
• reticulocyte count
• blood film
• rule out nutritional deficit, gastrointestinal and genitourinary disease in iron deficiency anemia
• additional laboratory investigations as indicated (see Microcytic Anemia, H12, Normocytic Anemia, H17 and Macrocytic Anemia, H22)
**Erythrocytosis**

**Definition**
- an increase in the number of RBCs: Hb >185 g/L or Hct >52% (males); Hb >165 or Hct >47% (females and African males)

**Etiology**
- relative/spurious erythrocytosis (decreased plasma volume): diuretics, severe dehydration, burns, "stress" (Gaisböck’s syndrome)
- absolute erythrocytosis

<table>
<thead>
<tr>
<th>Table 4. Etiology of Erythrocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
</tr>
<tr>
<td>------------------------------------</td>
</tr>
<tr>
<td>Polycythemia Vera (PV) (see H39)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Pulmonary disease:</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease:</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Clinical Features**
- secondary to high red cell mass and hyperviscosity
  - headache, dizziness, tinnitus, visual disturbances, hypertensive symptoms
  - symptoms of angina, congestive heart failure, aquagenic pruritis
  - thrombosis (venous or arterial) or bleeding (abnormal platelet function)
  - physical findings
    - splenomegaly ± hepatomegaly, facial plethora/ruddy complexion (70%) and/or palms, gout

**Investigations**
- serum erythropoietin (EPO): increased EPO suggests autonomous production or hypoxia, and is used to rule out PV
  - search for tumour as source of EPO as indicated (e.g. abdominal U/S, CT head)
  - JAK-2 mutation analysis: positive in >96% of cases of PV
    - only send if low/normal EPO level
  - ferritin (iron deficiency can mask the diagnosis)

**Treatment**
- if primary: see PV, H39
- if secondary: treat underlying cause
  - O$_2$ for hypoxemia, CPAP for sleep apnea, surgery for EPO-secreting tumours
  - often cardiologists will not treat high HCT in cyanotic patients (or will have high threshold)

---

**Thrombocytopenia**

**Definition**
- platelet count <150 x10$^9$/L

**Clinical Features**
- history: bleeding gums, epistaxis, bleeding post-surgical procedures, metromenorrhagia
- physical exam: bruising, petechiae, ecchymoses, non-palpable purpura
  - hemarthrosis and deep muscle hematomas are rarely initial signs in patients with primary hemostatic disorders
- see Disorders of Primary Hemostasis, H25, for complications

**Investigations**
- CBC and differential
- blood film
  - decreased production: other cell line abnormalities, blasts, hypersegmented PMNs, leukoerythroblastic changes
  - increased destruction: large platelets, schistocytes (seen in MAHA)
  - rule out platelet clumping
- work-up for nutritional deficiencies: B$_{12}$, RBC folate
- PT/INR, aPTT and fibrinogen if DIC suspected
- LFTs

**Must rule out factitious thrombocytopenia**: platelet clumping (secondary to EDTA antibodies from collection tube). This can be seen on blood film and confirmed by repeating in a citrated sample (i.e. using a sodium citrate tube to collect blood, rather than EDTA).
**Thrombocytopenia**

**Definition**
- platelet count >400 x10^9/L
- primary thrombocytopenia: due to myeloproliferative neoplasms [e.g. CML, polycythemia vera (PV), primary myelofibrosis, essential thrombocytosis (ET). Rarely associated with MDS]
- reactive/secondary thrombocytopenia: acute phase reactant (e.g. surgery, inflammation, infection, trauma, bleeding, iron deficiency, neoplasms, ischemic injury); much more common than primary

**Clinical Features**
- history: trauma, surgery, splenectomy, infection, inflammation, bleeding, iron deficiency, prior diagnosis of chronic hematologic disorder, constitutional symptoms (malignancy)
- vasomotor symptoms: headache, visual disturbances, lightheadedness, atypical chest pain, acral dysesthesia, erythromelalgia, livedo reticularis, aquagenic pruritus
- clotting risk, bleeding risk (rare)
- physical exam: splenomegaly can be seen in myeloproliferative neoplasms (MPNs)

**Investigations**
- CBC, peripheral blood film, serum ferritin concentration
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
- if reactive process has been ruled out, bone marrow biopsy may be required to rule out MPN/MDS

**Treatment**
- primary: ASA ± cytoreductive agents
- secondary: treat underlying cause

**Pancytopenia**

**Definition**
- a decrease in all hematopoietic cell lines

**Clinical Features**
- anemia: fatigue
- leukopenia: recurrent infections
- thrombocytopenia: mucosal bleeding and ecchymoses

**Investigations**
- CBC and differential, blood film
- reticulocyte count
- investigate secondary causes as per history: HIV test, serum B12, RBC folate, ANA
- on history, inquire about drug (including OTC/herbal) and environmental exposures
- often requires bone marrow biopsy to determine cause
Neutrophilia

**Definition**
- different guidelines, but absolute neutrophil count (ANC) >7.7 x 10⁹/L

**Etiology**
- primary neutrophilia
  - chronic myeloid leukemia (CML)
    - other myeloproliferative disorders: PV, essential thrombocytosis (ET), myelofibrosis
    - hereditary neutrophilia (autosomal dominant)
  - chronic idiopathic neutrophilia in otherwise healthy patients
- secondary neutrophilia
  - smoking: most common cause of mild neutrophilia
  - infection: leukocytosis with left shift ± toxic granulation, Döhle bodies (intra-cytoplasmic structures composed of agglutinated ribosomes)
  - inflammation: e.g. rheumatoid arthritis (RA), IBD, chronic hepatitis, MI, PE, burns
  - malignancy: hematologic (i.e. marrow invasion by tumour) and non-hematologic (especially large cell lung cancer)
  - stress/exercise/epinephrine: movement of neutrophils from marginated pool into circulating pool
  - medications: glucocorticoids, β-agonists (e.g. epinephrine), lithium

**Clinical Features**
- look for signs and symptoms of fever, inflammation, malignancy to determine appropriate further investigations
  - including lymph nodes and organomegaly
- examine oral cavity, teeth, peri-rectal area, genitals and skin for signs of infection

**Investigations**
- CBC and differential: mature neutrophils or bands >20% of total WBC suggests infection/inflammation
- blood film: Döhle bodies, toxic granulation, cytoplasmic vacuoles in infection
- review other blood counts
- may require bone marrow biopsy if MPN suspected

**Treatment**
- directed at underlying cause

Neutropenia

**Definition**
- mild: ANC 1.0-1.5 x 10⁹/L
- moderate: ANC 0.5-1.0 x 10⁹/L (risk of infection starts to increase)
- severe: ANC <0.5 x 10⁹/L
- profound: ANC <0.1 x 10⁹/L for >7 d

**Absolute Neutrophil Count (ANC) =**
WBC count x (%PMNs + %bands)

**Beware of fever + ANC <0.5 x10⁹/L = FEBRILE NEUTROPENIA**
Etiology

Table 5. Etiology of Neutropenia

<table>
<thead>
<tr>
<th>Decreased Production</th>
<th>Peripheral Destruction</th>
<th>Excessive Margination (Transient Neutropenia)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral hepatitis, EBV, HIV, TB, typhoid, malaria</td>
<td>Anti-neutrophil antibodies</td>
<td>Idiopathic (most common)</td>
</tr>
<tr>
<td>hematological diseases:</td>
<td>Spleen or lung trapping</td>
<td>Overwhelming bacterial infection</td>
</tr>
<tr>
<td>idiopathic, aplastic anemia, myelofibrosis, BM infiltration</td>
<td>Autoimmune disorders: RA, SLE</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td>Drug-induced:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkylating agents, antimitobolites, anticonvulsants, antidepressants, anti-inflammatory agents, anti thyroid drugs</td>
<td>Granulomatosis with polyangiitis (formerly Wegener’s)</td>
<td>Racial variation (e.g. African or Ashkenazi Jewish descent)</td>
</tr>
<tr>
<td>Toxins/Chemicals:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose radiation, benzene, DDT</td>
<td>Drugs: haptens (e.g. α-methyldopa)</td>
<td></td>
</tr>
<tr>
<td>Nutritional Deficiency:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B12, folate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constitutional neutropenia, benign cyclic neutropenia, cyclical</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features
- fever, chills (only if infection present)
- infection by endogenous bacteria (e.g. S. aureus, gram negatives from GI and GU tract)
- painful ulceration on skin, anus, mouth and throat following colonization by opportunistic organisms
- avoid digital rectal exam

Investigations
- dependent on degree of neutropenia, history, and symptoms
- ranges from observation with frequent CBCs to bone marrow aspiration and biopsy

Treatment
- regular dental care: chronic gingivitis and recurrent stomatitis major sources of morbidity
- febrile neutropenia (see Infectious Diseases, ID39)
- in severe immune-mediated neutropenia, G-CSF may increase neutrophil counts
  - if no response to G-CSF, consider immunosuppression (e.g. steroids, cyclosporine, methotrexate)

**Lymphocytosis**

Definition
- absolute lymphocyte count >4 x 10^9/L

Etiology
- infection
  - viral infections (majority); particularly mononucleosis
  - TB, pertussis, brucellosis, toxoplasmosis
  - physiologic response to stress (e.g. trauma, status epilepticus)
  - hypersensitivity (e.g. drugs, serum sickness)
  - autoimmune (e.g. rheumatoid arthritis)
  - neoplasm (e.g. ALL, CLL, lymphoma)

Investigations
- peripheral smear

Treatment
- treat underlying cause

**Lymphopenia**

Definition
- absolute lymphocyte count <1.5 x 10^9/L

Etiology
- idiopathic CD4+ lymphocytopenia
- radiation
- HIV/AIDS, hepatitis B, hepatitis C
- malignancy/chemotherapeutic agents
- malnutrition, alcoholism
- autoimmune disease (e.g. SLE)

### Prophylactic Hematopoietic Colony-Stimulating Factors on Mortality and Infection

**Ann Intern Med 2007;147:400-411**

**Purpose:** To review the effects of colony-stimulating factor (CSF) on mortality, infections, and febrile neutropenia in patients undergoing chemotherapy or stem-cell transplant (SCT).

**Study Selection:** 148 RCTs comparing the effects of CSFs to either placebo or no therapy were included. Prophylactic CSFs were given concurrently with or after initiation of chemotherapy.

**Results:** There were no differences in all-cause mortality or infection-related death between CSF and placebo groups. Compared to placebo or no therapy, CSFs reduced infection rate (median rate 38.8% vs. 43.1%; rate ratio 0.85), microbiologically documented infections (MR 23.5% vs. 28.6%; rate ratio 0.86), and febrile neutropenia (MR 25.3% vs. 44.2%; rate ratio 0.71).

**Conclusions:** Prophylactic CSFs decrease infection rates and episodes of febrile neutropenia in patients undergoing chemotherapy or SCT, but have no effect on mortality.

**G-CSF = Neupogen® = Filgrastim**

Presence of smudge cells suggests a lymphoproliferative disorder if persistently elevated above 5.0 x10^9/L for >3 mo. Consider flow cytometry.

Presence of atypical lymphocytes suggests viral infection.
Clinical Features
• opportunistic infections (see Infectious Diseases, ID39)

Treatment
• treat underlying cause
• treat opportunistic infections aggressively and consider antimicrobial prophylaxis (see Infectious Diseases, ID47)

Eosinophilia

Definition
• absolute eosinophil count >0.5 x 10⁹/L

Etiology
• primary: due to clonal bone marrow disorder
  ▪ if no primary etiology identified, classified as hypereosinophilic syndrome
  ▪ 6 mo of eosinophilia with no other detectable causes
  ▪ can involve heart, bone marrow, CNS
• secondary:
  ▪ most common causes are parasitic (usually helminth) infections and allergic reactions
  ▪ less common causes:
  ▪ polyarteritis nodosa, see Rheumatology, RH19
  ▪ respiratory causes (asthma, eosinophilic pneumonia, Churg-Strauss)
  ▪ cholesterol emboli
  ▪ hematologic malignancy: CML, Hodgkin lymphoma, see H38, H43
  ▪ adrenal insufficiency, see Endocrinology, E35
  ▪ medications (penicillins)

Treatment
• treat underlying cause

Agranulocytosis

Definition
• severe depletion of granulocytes (neutrophils, eosinophils, basophils) from the blood and granulocyte precursors from bone marrow

Etiology
• associated with medications in 70% of cases: e.g. chemotherapy, clozapine, thionamides (antithyroid drugs), sulfasalazine and ticlopidine
  ▪ immune-mediated destruction of circulating granulocytes by drug-induced antibodies or direct toxic effects upon marrow granulocytic precursors

Clinical Features
• abrupt onset of fever, chills, weakness, and oropharyngeal ulcers

Prognosis
• high fatality without vigorous treatment

Investigations/Treatment
• discontinue offending drug
• pan-culture and screen for infection if patient is febrile (blood cultures x2, urine culture and chest x-ray as minimum, initiate broad-spectrum antibiotics)
• consider bone marrow aspirate and biopsy if cause unclear
• consider G-CSF

Leukemoid Reactions

• blood findings resembling those seen in certain types of leukemia which reflect the response of healthy BM to cytokines released due to infection or trauma
• leukocytosis >50 x 10⁹/L, marked left shift (myelocytes, metamyelocytes, bands in peripheral blood smear)

Etiology
• important to rule out CML
• differential diagnosis:
  ▪ myeloid progenitors: pneumonia, other acute bacterial infections, intoxications, burns, malignant disease, severe hemorrhage or hemolysis
  ▪ lymphoid progenitors: pertussis, TB, infectious mononucleosis
• monocytic progenitors: TB
Approach to Lymphadenopathy

History
- constitutional/B-symptoms: seen in TB, lymphoma, other malignancies
- exposures: cats (cat scratch – Bartonella henselae), ticks (Lyme disease – Borrelia burgdorferi), high risk behaviors (HIV)
- joint pain/swelling, rashes (connective tissue disorder)
- pruritus (seen in Hodgkin lymphoma)
- medications (can cause serum sickness → lymphadenopathy)

Physical Exam
- basic assessment: occipital, preauricular, submandibular, cervical, supra/infra-clavicular, axillary, epitrochlear, inguinal, popliteal nodes
  - characteristics of lymph nodes (see Table 6)
  - look for signs of infection in regions which lymph nodes drain
- determine if lymphadenopathy is localized or generalized
  - localized: typically reactive or neoplastic
    - cervical (bacterial/mycobacterial infections, ENT malignancies, metastatic cancer)
    - supraclavicular
      - right (mediastinal, bronchogenic, esophageal cancer)
      - left (gastric, gall bladder, pancreas, renal, testicular/ovarian cancer)
    - axillary (cat scratch fever, breast cancer, metastatic cancer)
    - epitrochlear (infections, sarcoidosis, lymphoma)
    - lower/inguinal (STDs, skin, cervix, vulva/penis, rectum/anus cancer)
- generalized: see Table 7
  - thorough examination required to assess for systemic disease

Investigations
- CBC and differential, blood film
- ± tuberculin test, HIV RNA, RPR/VDRL, monospot/EBV serology, ANA, imaging as indicated
- if localized and no symptoms suggestive of malignancy, can observe 3-4 wk (if no resolution → biopsy)
- excisional biopsy is preferred as it preserves node architecture (essential for diagnosing lymphoma)
- in difficult to access areas (retroperitoneal, mediastinal/hilar) multiple core biopsies may be more practical/feasible
- FNA should NOT be used for diagnostic purposes in lymphoproliferative disease (use excisional biopsy instead)
  - helpful for recurrence of solid tumour malignancy

Table 6. Inflammatory vs. Neoplastic Lymph Nodes

<table>
<thead>
<tr>
<th>Feature</th>
<th>Inflammatory</th>
<th>Neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency</td>
<td>Rubbery</td>
<td>Firm/hard</td>
</tr>
<tr>
<td>Mobility</td>
<td>Mobile</td>
<td>Matted/Immobile</td>
</tr>
<tr>
<td>Tenderness</td>
<td>Tender</td>
<td>Non-tender</td>
</tr>
<tr>
<td>Size</td>
<td>&lt;2 cm</td>
<td>&gt;2 cm</td>
</tr>
</tbody>
</table>

*Note: these classifications are not absolute; lymphoma and CLL nodes can feel rubbery and are frequently mobile, non-tender

Table 7. Differential Diagnosis of Generalized Lymphadenopathy

<table>
<thead>
<tr>
<th>Reactive</th>
<th>Inflammatory</th>
<th>Neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial (TB, Lyme, brucellosis, cat-scratch disease, syphilis)</td>
<td>Collagen disease (RA, dermatomyositis, SLE, vasculitis, Sjögren)</td>
<td>Lymphoproliferative disorder/Lymphoma</td>
</tr>
<tr>
<td>Viral (EBV, CMV, HIV)</td>
<td>Drug hypersensitivity</td>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Parasitic (toxoplasmosis)</td>
<td>Sarcoidosis, amyloidosis</td>
<td>Histiocytosis X</td>
</tr>
<tr>
<td>Fungal (histoplasmosis)</td>
<td>Serum sickness</td>
<td></td>
</tr>
</tbody>
</table>

B-symptoms
- Unexplained temperature >38°C
- Unexplained weight loss (>10% of body weight in 6 mo)
- Night sweats

Drugs That Can Cause Lymphadenopathy
- Allopurinol
- Atenolol
- Captopril
- Carbamazepine
- Cephalosporins
- Gold
- Hydralazine
- Penicillin
- Phenytoin
- Primidone
- Pyrimethamine
- Quinidine
- Sulfonamides
**Approach to Splenomegaly**

**Table 8. Differential Diagnosis of Splenomegaly**

<table>
<thead>
<tr>
<th>Increased Demand for Splenic Function</th>
<th>Congestive</th>
<th>Infiltrative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spherocytosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobinopathies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequestration crisis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elliptocytosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial endocarditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felty syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Still’s disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenic vein thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portal vein obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portal HTN (including right heart failure)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-malignant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign metaplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amyloidosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lysosomal storage diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Gaucher’s, Niemann-Pick)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycogen storage diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamartomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cysts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia (CML, CLL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoproliferative disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloproliferative disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic tumour</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The underlined conditions cause massive splenomegaly (spleen crosses midline or reaches pelvis).

**History**
- constitutional symptoms, feeling of fullness in LUQ
- signs or symptoms of infection or malignancy
- history of liver disease, hemolytic anemia or high-risk exposures

**Physical Exam**
- jaundice, petechiae
- signs of chronic liver disease
- percussion (Castell’s sign, Traube’s space, Nixon’s method) and palpation
- associated lymphadenopathy or hepatomegaly
- signs of CHF

**Investigations**
- CBC and differential, blood film
- as indicated: liver enzymes/liver function tests, reticulocyte count, Monospot®, haptoglobin, LDH, infectious and autoimmune workups
- imaging
  - ultrasound of abdomen/liver to rule out cirrhosis and portal vein thrombosis
  - echo for cardiac function
  - CT to rule out lymphoma

**Microcytic Anemia**
- MCV <80 fL
- see Figure 3, Approach to Anemia, H5

**Table 9. Iron Indices and Blood Film in Microcytic Anemia (MCV<80)**

<table>
<thead>
<tr>
<th>Lab Tests</th>
<th>Blood Film</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin</td>
<td>• Hypochromic, microcytic</td>
</tr>
<tr>
<td>Serum Iron</td>
<td>• Normocytic/microcytic</td>
</tr>
<tr>
<td>TIBC</td>
<td>• Dual population</td>
</tr>
<tr>
<td>RDW</td>
<td>• Basophilic stippling</td>
</tr>
<tr>
<td>Iron Deficiency Anemia</td>
<td></td>
</tr>
<tr>
<td>Anemia of Chronic Disease</td>
<td></td>
</tr>
<tr>
<td>Sideroblastic Anemia</td>
<td></td>
</tr>
<tr>
<td>Thalassemia</td>
<td></td>
</tr>
</tbody>
</table>

TIBC = total iron-binding capacity

**Iron Metabolism**

- average North American adult diet = 10-20 mg iron (Fe) daily
- absorption is 5-10% (0.5-2 mg/d); enhanced by citric acid, ascorbic acid (vitamin C) and reduced by polyphenols (e.g. in tea), phytate (e.g. in bran), dietary calcium, and soy protein
- males have positive Fe balance; up to 20% of menstruating females have negative Fe balance

**Causes of Splenomegaly**
- CHINA
  - Cirrhosis/Congestion (portal HTN)
  - Hematological
  - Infectious
  - Neoplasm (malignant, non-malignant)
  - Autoimmune

**Does this Adult Patient have Splenomegaly?**
From The Rational Clinical Examination JAMA 2009; http://www.jamaevidence.com/content/3487298

**Study:** Systematic review of articles assessing the sensitivity and specificity of clinical exam maneuvers for detecting splenomegaly.

**Results:** On percussion, Nixon sign had a positive likelihood ratio (+LR) of 3.6 (95% CI, 1.8-7.3) and a negative likelihood ratio (-LR) of 0.41 (95% CI, 0.26-0.64). Percussion of Traube’s space had a +LR of 2.3 (95% CI, 1.8-2.9) and -LR of 0.48 (95% CI, 0.39-0.60), while Castell sign had a +LR of 1.2 (95% CI, 0.86-1.6) and -LR of 0.45 (95% CI, 0.38-1.1). On palpation, supine 1-handed palpation had a +LR of 1.2 (95% CI, 0.8-1.5) and -LR of 0.45 (95% CI, 0.30-1.0). Middleton hooking maneuver had a +LR of 1.3 (95% CI, 1.3-2.6) and -LR of 0.60 (95% CI, 0.49-0.83).

**Conclusions:** Palpation may have greater accuracy than percussion, but may be best when both are used in tandem. Specifically, Nixon sign and supine 1-handed palpation are the most accurate, respectively.
Iron Indices (see Table 9 and Figure 6)
- bone marrow aspirate: gold standard test for iron stores (rarely done)
- serum ferritin: most important blood test for iron stores
  - decreased in iron deficiency anemia
  - elevated in:
    - infection, inflammation, malignancy
    - liver disease, hyperthyroidism and iron overload
- serum iron: measure of all non-heme iron present in blood
  - varies significantly daily
  - virtually all serum iron is bound to transferrin, only a trace is free or complexed in ferritin
- total iron binding capacity (TIBC): total amount of transferrin present in blood
  - normally, one third of TIBC is saturated with iron
  - high specificity for decreased iron, low sensitivity
- saturation:
  - serum Fe divided by TIBC, expressed as a proportion or a percentage
  - low in iron deficiency anemia
- soluble transferrin receptor (sTfR):
  - reflects the availability of iron at the tissue level
  - the transferrin receptor is expressed on the surface of erythroblasts and is responsible for iron uptake – some is cleaved off and is present in circulation as sTfR
  - in iron deficient states more transferrin receptor is expressed on erythroblasts leading to an increase in sTfR
  - low in reduced erythropoiesis and iron overload
  - useful in determining iron deficiency in the setting of chronic inflammatory disorders (see Iron Deficiency Anemia, H14)

Iron Absorption and Transport (see Figure 6)
- dietary iron is absorbed in the duodenum (impaired by IBD, celiac disease, etc.)
- in circulation the majority of non-heme iron is bound to transferrin which transfers iron from enterocytes and storage pool sites (macrophages and hepatocytes) to RBC precursors in the bone marrow

Iron Storage
- ferritin
  - ferric iron (Fe³⁺) complexed to a protein called apoferritin (hepatocytes are main ferritin storage site)
  - small quantities are present in plasma in equilibrium with intracellular ferritin
  - also an acute phase reactant – can be spuriously elevated despite low Fe stores in response to a stressor
- hemosiderin
  - aggregates or crystals of ferritin with the apoferritin partially removed
  - macrophage-monocyte system is main source of hemosiderin storage

Figure 6. Iron metabolism
Iron Deficiency Anemia

- see Pediatrics, P47
- most common cause of anemia in North America

**Etiology**
- increased demand
  - increased physiological need for iron in the body (e.g. pregnancy)
- decreased supply: dietary deficiencies (rarely the only etiology)
  - cow’s milk (infant diet)
  - “tea and toast” diet (elderly)
  - absorption imbalances
  - post-gastrectomy
  - malabsorption (IBD of duodenum, celiac disease, autoimmune atrophic gastritis)
- increased losses
  - hemorrhage
    - obvious causes: menorrhagia, abnormal uterine bleeding, frank GI bleed
    - occult: peptic ulcer disease, GI cancer
  - hemolysis
    - intravascular (e.g. paroxysmal nocturnal hemoglobinuria (PNH), cardiac valve RBC fragmentation)
    - extravascular (e.g. immune hemolytic anemias)

**Clinical Features**
- iron deficiency may cause fatigue before clinical anemia develops
- signs/symptoms of anemia: see Approach to Anemia, H5
- brittle hair, nail changes (brittle, koilonychia)
- Plummer-Vinson syndrome: dysphagia (esophageal webs), glossitis, angular stomatitis (inflammation and fissuring at the corners of the mouth)
- pica (appetite for non-food substances e.g. ice, paint, dirt)

**Investigations**
- iron indices, including soluble transferrin receptor (Figure 7)
  - low ferritin (<45 µg/L) is diagnostic of iron deficiency (Table 10)
  - ferritin is an acute phase reactant and is elevated in the setting of inflammatory conditions and liver disease; serum ferritin <100 µg/L in these settings is suggestive of iron deficiency, necessitating further workup (Figure 7)
- peripheral blood film
  - hypochromic microcytosis: RBCs have low Hb levels due to lack of iron
  - pencil forms, anisocytosis
  - target cells (thin)
- bone marrow (gold standard but rarely done)
  - iron stain (Prussian blue) shows decreased iron in macrophages and in erythroid precursors (sideroblasts)
  - intermediate and late erythroblasts show micronormoblastic maturation

**Table 10. The Utility of Ferritin in the Diagnosis of Iron Deficiency Anemia**

<table>
<thead>
<tr>
<th>Ferritin (µg/L)</th>
<th>Likelihood ratio for iron deficiency anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;100</td>
<td>0.13</td>
</tr>
<tr>
<td>45-100</td>
<td>0.46</td>
</tr>
<tr>
<td>18-45</td>
<td>3.12</td>
</tr>
<tr>
<td>≤18</td>
<td>41.47</td>
</tr>
</tbody>
</table>

**Treatment**
- treat underlying cause
- supplementation
  - oral (tablets, syrup)
    - ferrous sulphate 325 mg tid, ferrous gluconate 300 mg tid, or ferrous fumarate 300 mg tid
    - supplement until anemia corrects, then continue for 3+ mo until serum ferritin returns to normal
    - oral iron should be taken with citrus juice to enhance absorption
  - IV (iron sucrose or dextran) can be used if patient cannot tolerate or absorb oral iron
• monitoring response
  • reticulocyte count will begin to increase after one wk
  • Hb normalizes by 10 g/L per wk (if no blood loss)
  • iron supplementation required for 4-6 mo to replenish stores

### Anemia of Chronic Disease

- see Pediatrics, P48

#### Etiology
- infection, malignancy, inflammatory and rheumatologic disease, chronic renal and liver disease, endocrine disorders (e.g. diabetes mellitus, hypothyroidism, hypogonadism, hypopituitarism)

#### Pathophysiology
- an anemia of underproduction due to impaired iron utilization (hepcidin is a key regulatory peptide)
  - enterocyte trapping of iron → increased hepcidin inhibits ferroportin (→ iron into circulation)
  - macrophage trapping of iron → reduced plasma iron levels making iron relatively unavailable for new hemoglobin synthesis
  - marrow unresponsive to normal or slightly elevated EPO
- mild hemolytic component is often present
- RBC survival is modestly decreased

#### Investigations
- diagnosis of exclusion
- associated with elevation in acute phase reactants (ESR, CRP, fibrinogen)
- "classic" serum iron indices (see Table 9)
  - serum iron and TIBC low, % saturation normal
  - serum ferritin is normal or increased
- anemia of chronic disease often co-exists with iron deficiency (see sidebar)
- peripheral blood
  - mild: usually normocytic and normochromic
  - moderate: may be microcytic and normochromic
  - severe: may be microcytic and hypochromic
  - absolute reticulocyte count is frequently low, reflecting overall decrease in RBC production
- bone marrow
  - normal or increased iron stores
  - decreased or absent staining for iron in erythroid precursors

#### Treatment
- treat underlying disease
- only treat anemia in patients who can benefit from a higher hemoglobin
- IV iron if no benefit from PO iron
- erythropoietin indicated in chronic renal failure. Not to be used if patient has concommitant curative solid tumour malignancy. Ensure Hb target <110 g/L

### Sideroblastic Anemia

- uncommon compared to iron deficiency anemia or anemia of chronic disease

#### Sideroblasts
- erythrocytes with iron-containing (basophilic) granules in the cytoplasm
- "normal": granules are small, randomly spread in the cytoplasm
  - found in healthy individuals
- "ring": iron deposits in mitochondria, forming a ring around the nucleus
  - abnormal, large granules
  - the hallmark of sideroblastic anemia

#### Etiology
- due to defects in heme biosynthesis in erythroid precursors
- hereditary (rare): X-linked; median survival 10 yr
- idiopathic (acquired)
  - aka refractory anemia with ringed sideroblasts: a subtype of MDS (see Myelodysplastic Syndromes, H36)
  - may be a preleukemic phenomenon (10% transform to AML)
- reversible
  - drugs (isoniazid, chloramphenicol), alcohol, lead, copper deficiency, zinc toxicity, hypothyroidism
Clinical Features
- anemia symptoms (see Approach to Anemia, H5)
- hepatosplenomegaly, Fe²⁺ overload syndrome

Investigations
- serum iron indices
  ▪ increased serum Fe²⁺, normal TIBC, increased ferritin, increased sTR
- blood film/bone marrow biopsy
  ▪ ringed sideroblasts (diagnostic hallmark)
  ▪ RBCs are hypochromic; can be micro-, normo-, or macrocytic
  ▪ anisocytosis, poikilocytosis, basophilic stippling

Treatment
- depends on etiology
  ▪ X-linked: high dose pyridoxine (vitamin B₆) in some cases
  ▪ acquired: EPO and G-CSF
  ▪ reversible: remove precipitating cause
- supportive transfusions for severe anemia

Lead Poisoning

Definition/Etiology
- blood lead levels greater than 80 µg/dL, possible symptomatology at 50 µg/dL.

Clinical Features
- identify source: consider occupational history, exposures history
- abdominal pain, constipation, irritability, difficulty concentrating

Treatment
- chelation therapy: dimercaprol and EDTA are first line agents

Thalassemia
- see Hemolytic Anemia – Thalassemia, H18

Normocytic Anemia
- MCV 80-100 fl.
- see Figure 3, Approach to Anemia, H5

Aplastic Anemia

Definition
- destruction of hematopoietic cells of the bone marrow leading to pancytopenia and hypocellular bone marrow

Epidemiology
- occurs at any age
- slightly more common in males

Etiology

<table>
<thead>
<tr>
<th>Table 11. Etiology of Aplastic Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital</strong></td>
</tr>
<tr>
<td>Fanconi’s anemia</td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Dose-related (i.e. chemotherapeutics)</td>
</tr>
<tr>
<td>Idiosyncratic (chloramphenicol, phenylbutazone)</td>
</tr>
<tr>
<td>Toxins</td>
</tr>
<tr>
<td>Benzene/organic solvents</td>
</tr>
<tr>
<td>DDT, insecticides</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Clinical Features
- can present acutely or insidiously
- symptoms of anemia (see Approach to Anemia, H5), thrombocytopenia (see Thrombocytopenia, H6) and/or infection
- ± splenomegaly and lymphadenopathy (depending on the cause)
Investigations
- exclude other causes of pancytopenia (Figure 3)
- CBC
  - anemia or neutropenia or thrombocytopenia (any combination) ± pancytopenia
  - decreased reticulocytes (<1% of the total RBC count)
- blood film
  - decreased number of normal RBCs
- bone marrow
  - aplasia or hypoplasia of marrow cells with fat replacement
  - decreased cellularity

Treatment
- remove offending agents
- supportive care (red cell and platelet transfusions, antibiotics)
  - judicious use so as to not increase the risk of immune sensitization to blood products
- immunosuppression
  - anti-thymocyte globulin: 50-60% of patients respond
  - cyclosporine
- allogenic bone marrow transplant

Hemolytic Anemia (HA)

Classification
- hereditary
  - abnormal membrane (spherocytosis, elliptocytosis)
  - abnormal enzymes (pyruvate kinase deficiency, G6PD deficiency)
  - abnormal hemoglobin synthesis (thalassemias, hemoglobinopathies)
- acquired
  - immune
    - hemolytic transfusion reaction, autoimmune HA (AIHA), drugs (e.g. penicillin), cold agglutinins
    - alloimmune (transfusion reaction, hemolytic disease of the fetus/newborn)
  - non-immune
    - microangiopathic HA (MAHA): thrombus in blood vessel causes RBCs to be sheared – associated with DIC, HUS/TTP, preeclampsia/HELLP, vasculitides, malignant hypertension
    - other causes: paroxysmal nocturnal hemoglobinuria (PNH), hypersplenism, march hemoglobinuria (exertional hemolysis), infection (e.g. malaria), snake venoms, mechanical heart valves
  - also classified as intravascular or extravascular:
    - intravascular: G6PD deficiency, TTP, DIC and PNH
    - extravascular: AIHA and hereditary spherocytosis

Clinical Features Specific to HA
- jaundice
- dark urine (hemoglobinuria, bilirubin)
- cholelithiasis (pigment stones)
- potential for an aplastic crisis (i.e. BM suppression in overwhelming infection)
- iron overload with extravascular hemolysis
- iron deficiency with intravascular hemolysis

Investigations

<table>
<thead>
<tr>
<th>Screening Tests</th>
<th>Tests Specific For Intravascular Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased LDH</td>
<td>Schistocytes on blood film</td>
</tr>
<tr>
<td>Decreased haptoglobin</td>
<td>Free hemoglobin in serum</td>
</tr>
<tr>
<td>Increased unconjugated bilirubin</td>
<td>Methemalbuminemia (heme + albumin)</td>
</tr>
<tr>
<td>Increased urobilinogen</td>
<td>Hemoglobinuria (immediate)</td>
</tr>
<tr>
<td>Reticulocytosis</td>
<td>Hemosiderinuria (delayed)</td>
</tr>
<tr>
<td></td>
<td>Plasma hemoglobin</td>
</tr>
</tbody>
</table>

Tests Specific for Extravascular Hemolysis

<table>
<thead>
<tr>
<th>Tests Specific for Extravascular Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Coombs test (direct antiglobulin test)</td>
</tr>
<tr>
<td>- Detects IgG or complement on the surface of RBC</td>
</tr>
<tr>
<td>- Add anti-IgG or anti-complement Ab to patient's RBCs; positive if agglutination</td>
</tr>
<tr>
<td>- Indications: hemolytic disease of newborn, AIHA, hemolytic transfusion reaction</td>
</tr>
<tr>
<td>Indirect Coombs test (indirect antiglobulin test)</td>
</tr>
<tr>
<td>- Detects antibodies in serum that can recognize antigens on RBCs</td>
</tr>
<tr>
<td>- Mix patient's serum + donor RBCs + Coombs' serum (anti-human Ig Ab); positive if agglutination</td>
</tr>
<tr>
<td>- Indications: cross-matching donor RBCs, atypical blood group, blood group Ab in pregnant women, AIHA</td>
</tr>
</tbody>
</table>
Thalassemia

Definition
- defects in production of the α or β chains of hemoglobin
  - resulting imbalance in globin chains leads to ineffective erythropoiesis and hemolysis in the spleen or BM
- clinical manifestations and treatment depends on specific gene and number of alleles affected
- common features:
  - increasing severity with increasing number of alleles involved
  - hypochromic microcytic anemia
  - basophilic stippling, abnormally shaped RBCs on blood film

Pathophysiology
- defect may be in any of the Hb genes
  - normally 4α genes in total; 2 on each copy of chromosome 16
  - normally 2β genes in total; 1 on each copy of chromosome 11
  - fetal hemoglobin, HbF (αβγδ), switches to adult forms HbA (αβ2) and HbA2 (αδ2) at 3-6 mo of life
  - HbA constitutes 97% of adult hemoglobin
  - HbA2 constitutes 3% of adult hemoglobin

β-Thalassemia Minor (Thalassemia Trait)

Definition
- defect in single allele of β gene (heterozygous)
- common in people of Mediterranean and Asian descent

Clinical Features
- None; a palpable spleen is very rare

Investigations
- Hb 100-140 g/L or 9-14 g/dL, MCV<70, normal Fe, normal RBC count
- peripheral blood film – microcytosis basophilic stippling
- Hb electrophoresis
  - specific: HbA2 increased to 2.5-5% (normal 1.5-3.5%)
  - non-specific: 50% have slight increase in HbF

Treatment
- no treatment required
- genetic counselling for patient and family

β-Thalassemia Major

Definition
- defect in both alleles of β gene (homozygous, autosomal recessive)

Pathophysiology
- ineffective chain synthesis leading to ineffective erythropoiesis, hemolysis of RBCs and increase in HbF

Clinical Features
- initial presentation at age 6-12 mo when HbA normally replaces HbF
  - severe anemia, jaundice
  - stunted growth and development (hypogonadal dwarf)
  - gross hepatosplenomegaly (due to extramedullary hematopoiesis)
  - radiologic changes (due to expanded marrow cavity) and extramedullary hematopoietic masses (erythroid tissue tumours)
    - skull x-ray has “hair-on-end” appearance
    - pathologic fractures common
  - evidence of increased Hb catabolism (e.g. pigmented gallstones)
  - death can result from
    - untreated anemia (should transfuse)
    - infection (should identify and treat early)
    - iron overload: late complication secondary to repeated transfusions and ineffective erythropoiesis

Microcytosis in β-Thal Minor
Microcytosis is much more profound and the anemia is much milder than that of iron deficiency.
Hematology

Hemolytic Anemia (HA)

Investigations
- CBC: Hb 40-60 g/L (4-6 g/dL)
- Hb electrophoresis
  - HbA: 0-10% (normal >95%)  
  - HbA2 >2.5%  
  - HbF: 90-100%

Treatment
- lifelong regular transfusions to suppress endogenous erythropoiesis  
- iron chelation (e.g. deferoxamine, deferasirox, deferiprone) to prevent iron overload in organs and the formation of free radicals (which promote tissue damage and fibrosis)  
- folic acid supplementation if not transfused  
- allogenic bone marrow transplantation  
- splenectomy (now performed less frequently)

α-Thalassemia

Definition
- defect(s) in α genes  
- similar geographic distribution as β-thalassemia, but higher frequency among Asians and Africans

Clinical Features
- 1 defective α gene: clinically silent; normal Hb, normal MCV  
- 2 defective α genes: decreased MCV, normal Hb  
- 3 defective α genes: HbH (δ4) disease; presents in adults, decreased MCV, decreased Hb, splenomegaly  
- 4 defective α genes: Hb Barts (γ4) disease (hydrops fetalis); usually incompatible with life

Investigations
- peripheral blood film – screen for HbH inclusion bodies with special stain  
- Hb electrophoresis not diagnostic for α-thalassemia  
- DNA analysis using α gene probes is the only way to confirm the diagnosis

Treatment
- depends on degree of anemia:  
  - 1 or 2 defective α genes: no treatment required  
  - HbH disease: similar to β-thalassemia intermedia  
  - HbBarts: intrauterine transfusion

Sickle Cell Disease

Definition
- see Pediatrics, P48

Definition
- sickling disorders arise due to a mutant β-globin chain, most commonly caused by a Glu→Val substitution at position 6 (chromosome 11) resulting in HbS variant, rather than HbA (normal adult Hb)  
  - increased incidence of HbS allele with African or Mediterranean heritage (thought to be protective against malaria)  
- sickle cell disease occurs when an individual has two HbS genes (homozygous, HbSS) or one HbS gene + another mutant β-globin gene (compound heterozygote) – most commonly HbS-β-thal and HbSC disease

Pathophysiology (Figure 8)
- at low pO2, deoxy HbS polymerizes leading to rigid crystal-like rods that distort membranes  
  - ‘sickles’  
- the pO2 level at which sickling occurs is related to the percentage of HbS present  
  - heterozygotes (HbAS); sickling occurs at a pO2 of 40 mmHg  
  - homozygotes (HbSS); sickling occurs at a pO2 of 80 mmHg  
- sickling aggravated by acidemia, increased CO2, increased 2,3-DPG, fever and osmolality  
- fragile sickle cells hemolyze (nitric oxide depletion); they also occlude small vessels (ischemia-reperfusion injury)
Clinical Features
- HbAS (sickle cell trait): patient will be asymptomatic except during extreme hypoxia or infection
- increased risk of renal medullary carcinoma
- SCD-SS (HbSS)
  - chronic hemolytic anemia
  - jaundice in the first year of life
  - retarded growth and development ± skeletal changes
  - splenomegaly in childhood; splenic atrophy in adulthood
- SCD-SS often presents with acute pain episode:
  1. aplastic crises
  2. toxic crises (especially parvovirus B19) transiently suppress bone marrow
  3. vaso-occlusive crises (infarction)
  4. acute chest syndrome (see sidebar, H19)
- SCD-SC (most common compound heterozygote)
  1. 1,833 live births in African-Americans, common in West Africa
  2. milder anemia than HbSS
  3. similar complications as HbSS although typically milder and less frequent (exception is proliferative sickle retinopathy, glomerulonephritis and avascular necrosis)
  4. spleen not always atrophic in adults

Investigations
- sickle cell prep (detects sickling of RBCs under the microscope in response to O₂ lowering agent): determines the presence of a HbA allele, but does not distinguish HbAS from HbSS
- Hb electrophoresis distinguishes HbAS, HbSS, HbSC and other variants

### Table 13. Investigations for Sickle Cell Disease

<table>
<thead>
<tr>
<th></th>
<th>HbAS</th>
<th>HbSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Normal</td>
<td>Increased reticulocytes, decreased Hb, decreased Hct</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>Normal; possibly a few target cells</td>
<td>Sickled cells</td>
</tr>
<tr>
<td>Hb electrophoresis</td>
<td>HbA fraction of 0.65 (65%)</td>
<td>No HbA, only HbS and HbF (proportions change with age), Normal amount of HbA2.</td>
</tr>
</tbody>
</table>

Treatment
- genetic counselling
- HbAS: no treatment required
- HbSC: treatment as per HbSS, but is dictated by symptom severity
- HbSS
  1. folic acid to prevent folate deficiency
  2. hydroxyurea to enhance production of HbF
  3. treatment of vaso-occlusive crisis
  4. prevention of crises

Long-Term Harms: Birth defects in offspring of people receiving the drug, growth delays in children, and cancer in both children and adults who receive the drug.

Organ Affected by Vaso-Occlusive Crisis

<table>
<thead>
<tr>
<th>Organ</th>
<th>Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Seizures, stroke</td>
</tr>
<tr>
<td>Eye</td>
<td>Hemorrhage, blindness</td>
</tr>
<tr>
<td>Liver</td>
<td>Infarcts, RUQ syndrome</td>
</tr>
<tr>
<td>Lung</td>
<td>Chest syndrome, long-term pulmonary hypertension</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>Stones</td>
</tr>
<tr>
<td>Heart</td>
<td>Hyperdynamic flow murmurs</td>
</tr>
<tr>
<td>Spleen</td>
<td>Enlarged (child); atrophic (adult)</td>
</tr>
<tr>
<td>Kidney</td>
<td>Hematuria, loss of renal concentrating ability, proteinuria</td>
</tr>
</tbody>
</table>

### Table 11. Organs Affected by Vaso-Occlusive Crisis

<table>
<thead>
<tr>
<th>Organ Affected</th>
<th>Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Acute abdomen</td>
</tr>
<tr>
<td>Placenta</td>
<td>Stillbirths</td>
</tr>
<tr>
<td>Penis</td>
<td>Priapism</td>
</tr>
<tr>
<td>Genitalia</td>
<td>Dactylitis</td>
</tr>
<tr>
<td>Femoral and Humeral head</td>
<td>Avascular necrosis</td>
</tr>
<tr>
<td>Bone</td>
<td>Infarction, infection</td>
</tr>
<tr>
<td>Ankle</td>
<td>Leg ulcers</td>
</tr>
</tbody>
</table>

NIH Consensus Development Conference Statement: Hydroxyurea Treatment for Sickle Cell Disease

Am Intern Med 2008;148:932-938

Efficacy: Strong evidence for adolescents and adults and there is emerging data supporting its use in children. In the single RCT, the Hb level was higher in hydroxyurea recipients than placebo recipients after 2 yr (difference, 6 g/L), as was HbF (absolute difference, 3.2%). The median number of painful crises was 44% lower than in the placebo arm. The 12 observational studies that enrolled adults reported a relative increase in HbF of 4% to 20% and a relative reduction in crisis rates by 66% to 84%. Hospital admissions declined by 18% to 32%.

Effectiveness: Data is limited but seems to be highly effective but is currently underestimated.

Long-Term Harms: Birth defects in offspring of people receiving the drug, growth delays in children receiving the drug, and cancer in both children and adults who receive the drug.
Autoimmune Hemolytic Anemia (AIHA)

Table 14. Classification of AIHA

<table>
<thead>
<tr>
<th>Warm</th>
<th>Cold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody Allotype</td>
<td>IgG</td>
</tr>
<tr>
<td>Agglutination Temperature</td>
<td>37ºC</td>
</tr>
<tr>
<td>Direct Coombs’ Test (direct anti-globulin test)</td>
<td>Positive for IgG ± complement</td>
</tr>
<tr>
<td>Etiology</td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td>Secondary to lymphoproliferative disorder (e.g. CLL, Hodgkin)</td>
</tr>
<tr>
<td></td>
<td>Secondary to autoimmune disease (e.g. SLE)</td>
</tr>
<tr>
<td></td>
<td>Drug induced: Type I: hapten-mediated (e.g. penicillin)</td>
</tr>
<tr>
<td></td>
<td>Type II: immune-complex mediated (e.g. quinine)</td>
</tr>
<tr>
<td></td>
<td>Type III: “true” anti-RBC Ab (e.g. methyl dopa)</td>
</tr>
<tr>
<td>Blood Film</td>
<td>Spherocytes</td>
</tr>
<tr>
<td>Management</td>
<td>Treat underlying cause</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Immunosuppression</td>
</tr>
<tr>
<td></td>
<td>Splenectomy</td>
</tr>
<tr>
<td></td>
<td>Folic acid</td>
</tr>
</tbody>
</table>

Microangiopathic Hemolytic Anemia (MAHA)

Definition
- hemolytic anemia due to intravascular fragmentation of RBCs

Etiology
- thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome (HUS), see H28
- disseminated intravascular coagulation (DIC), see H30
- eclampsia, HELLP syndrome, AFLP (see Obstetrics, OB17, OB19)
- malignant hypertension
- vasculitis
- malfunctioning heart valves
- metastatic carcinoma
- drugs (calcineurin inhibitors, quinine, simvastatin)
- infections (severe CMV or meningococcus)
- catastrophic antiphospholipid antibody syndrome

Investigations
- blood film: evidence of hemolysis, schistocytes
- hemolytic work-up
- urine: hemosiderinuria, hemoglobinuria

Hereditary Spherocytosis
- most common type of hereditary hemolytic anemia
- abnormality in RBC membrane proteins (e.g. spectrin)
  - spleen makes defective RBCs more spherocytic (and more fragile) by membrane removal; also acts as site of RBC destruction
  - autosomal dominant with variable penetrance

Investigations
- blood film shows spherocytes, increased osmotic fragility, molecular analysis for spectrin gene

Treatment
- in severe cases, splenectomy + vaccination against pneumococcus, meningococcus and H. influenzae b (avoid in early childhood)

Hereditary Elliptocytosis

Definition/Etiology
- abnormality in spectrin interaction with other membrane proteins
- autosomal dominant
- 25-75% elliptocytes
- hemolysis is usually mild
Treatment
• immunizations; splenectomy for severe hemolysis

G6PD Deficiency

Definition
• deficiency in glucose-6-phosphate dehydrogenase (G6PD) leads to RBC sensitivity to oxidative stress due to a lack of reduced glutathione (GSH) (Figure 11)

Pathophysiology
• X-linked recessive, prevalent in individuals of African, Asian and Mediterranean descent

Clinical Features
• frequently presents as episodic hemolysis precipitated by:
  ▪ oxidative stress
  ▪ drugs (e.g. sulfonamide, antimalarials, nitrofurantoin)
  ▪ infection
  ▪ food (fava beans)
• in neonates: can present as prolonged, pathologic neonatal jaundice

Investigations
• neonatal screening
• G6PD assay (may not be useful if result is normal)
  ▪ should not be done in acute crisis when reticulocyte count is high (reticulocytes have high G6PD levels)
• blood film
  ▪ Heinz bodies (granules in RBCs due to oxidized Hb); passage through spleen results in the generation of bite cells
  ▪ may have features of intravascular hemolysis (e.g. RBC fragments)

Treatment
• folic acid
• stop offending drugs and avoid triggers
• transfusion in severe cases

Macrocytic Anemia

• MCV >100 fL
• see Figure 3, Approach to Anemia, H5

| Table 15. Comparison Between Megaloblastic and Non-Megaloblastic Macrocytic Anemia |
|----------------------------------|----------------------------------|----------------------------------|
| **Megaloblastic** | **Non-Megaloblastic** |
| **Morphology** | Large, oval, nucleated RBC precursor | Large round RBC |
| | Hypersegmented neutrophils | Normal neutrophils |
| **Pathophysiology** | Failure of DNA synthesis resulting in asynchronous maturation of RBC nucleus and cytoplasm | Reflects membrane abnormality with abnormal cholesterol metabolism |

Vitamin B12 Deficiency

B12 (cobalamin) see Gastroenterology, G17 and Family Medicine – Nutrition, FM5
• binds to intrinsic factor (IF) secreted by gastric parietal cells
• absorbed in terminal ileum
• total body stores sufficient for 3-4 yr

Etiology

| Table 16. Etiology of Vitamin B12 Deficiency |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| **Diet** | **Gastric** | **Intestinal Absorption** | **Genetic** |
| Strict vegan | Mucosal atrophy | Malabsorption | Transcobalamin II deficiency |
| More likely to present in pediatric population | Gastritis, autoimmune | Crohn's, celiac sprue, pancreatic insufficiency |
| Vegetarian in pregnancy | Pernicious anemia (see H23) | Stagnant bowel | |
| Post-gastrectomy | | Blind loop, stricture |
| | | Fish tapeworm |
| | | Resection of ileum |
| | | Drugs |
| | | Neomycin, biguanides, PPI, N2O anesthesia |
Pathophysiology of Pernicious Anemia

- auto-antibodies produced against gastric parietal cells leading to achlorhydria and lack of intrinsic factor secretion
- intrinsic factor is required to stabilize B₁₂ as it passes through the bowel
- decreased intrinsic factor leads to decreased ileal absorption of B₁₂
- may be associated with other autoimmune disorders (polyglandular endocrine insufficiency)
- female:male = 1.6:1; often >60 yr old

Clinical Features

- neurological
  - cerebral (common, reversible with B₁₂ therapy)
  - confusion, delirium, dementia
  - cranial nerves (rare)
  - optic atrophy
  - cord (irreversible damage)
  - subacute combined degeneration
    - posterior columns: decreased vibration sense, proprioception and 2-point discrimination
    - pyramidal tracts: spastic weakness, hyperactive reflexes
  - peripheral neuropathy (variable reversibility)
  - usually symmetrical, affecting lower limbs more than upper limbs

Investigations

- CBC, reticulocyte count
- anemia often severe ± neutropenia ± thrombocytopenia
- MCV >110 fL
- low reticulocyte count relative to the degree of anemia (<2%)
- serum B₁₂ and RBC folate
  - caution: low serum B₁₂ leads to low RBC folate because of failure of folate polyglutamate synthesis in the absence of B₁₂
  - alternatively, can measure urine metabolites (methylnalenate, homocysteine)
- blood film
  - oval macrocytes, hypersegmented neutrophils
- bone marrow
  - hypercellularity
  - nuclear-cytoplasmic asynchrony in RBC precursors (less mature nuclei than expected from the development of the cytoplasm)
- bilirubin and LDH
  - elevated unconjugated bilirubin and LDH due to breakdown of cells in BM
- Schilling test (see sidebar) to distinguish pernicious anemia from other causes
  - anti-intrinsic factor antibody, anti-parietal cell antibody

Treatment

- vitamin B₁₂ 1000 µg IM monthly for life or 1000-1200 µg PO daily if intestinal absorption intact
- less frequent, higher doses may be as effective (e.g. 1000 µg IM q3mo)
- watch for hypokalemia and rebound thrombocytosis when treating severe megaloblastic anemia

Folate Deficiency

- uncommon in developed countries due to extensive dietary supplementation
- folate stores are depleted in 3-6 mo
- folate commonly found in green, leafy vegetables and fortified cereals

Etiology

<table>
<thead>
<tr>
<th>Diet/Deficiency</th>
<th>Malabsorption</th>
<th>Drugs</th>
<th>Increased Demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism</td>
<td>Celiac sprue</td>
<td>Anti-folates (methotrexate)</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>IBD</td>
<td>Anticonvulsants (phenytoin)</td>
<td>Hemolyisis</td>
</tr>
<tr>
<td>Elderly/Infants</td>
<td>Infiltrative bowel disease</td>
<td>Alcohol</td>
<td>Prematurity</td>
</tr>
<tr>
<td>Poor intake</td>
<td>Short bowel syndrome</td>
<td>Oral contraceptive</td>
<td>Exfoliative dermatitis/psoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hemodialysis</td>
</tr>
</tbody>
</table>

Clinical Features

- mild jaundice due to hemolysis of RBCs secondary to ineffective hemoglobin synthesis
- glossitis and angular stomatitis
- melanin pigmentation (rare)
- purpura secondary to thrombocytopenia (rare)
- unlike B₁₂ deficiency, folate deficiency has no neurologic manifestations
Investigations
- similar to $B_12$ deficiency (CBC, reticulocytes, blood film, RBC folate, serum $B_12$)
- if decreased RBC folate, rule out $B_12$ deficiency as cause

Management
- folic acid 1-5 mg PO OD x 1-4 mo; then 1 mg PO OD maintenance if cause is not reversible

Hemostasis

Three Phases of Hemostasis

1. Primary Hemostasis
- goal is rapid cessation of bleeding; main effect is on mucocutaneous bleeding
- vessel injury results in collagen/subendothelial matrix exposure and release of vasoconstrictors
- blood flow is impeded and platelets come into contact with damaged vessel wall (Figure 12a)
  - adhesion: platelets adhere to subendothelium via von Willebrand factor (vWF)
  - activation: platelets are activated resulting in change of shape and release of ADP and thromboxane $A_2$
  - aggregation: these factors further recruit and aggregate more platelets resulting in formation of localized hemostatic plug

2. Secondary Hemostasis
- platelet plug is reinforced by production of fibrin clot in secondary hemostasis (Figure 12b)
  - extrinsic pathway
    - initiation of coagulation in vivo
  - intrinsic pathway
    - amplification once coagulation has started

3. Fibrin Stabilization and Fibrinolysis (resolution)
- conversion from soluble to insoluble clot
- once healing initiated, clot dissolution (anticoagulant pathway)
### Table 18. Commonly Used Tests of Hemostasis

<table>
<thead>
<tr>
<th>Type of Hemostasis</th>
<th>Test</th>
<th>Reference Range</th>
<th>Purpose</th>
<th>Examples of Associated Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Platelet count</td>
<td>150-400 x 10⁹/L</td>
<td>To quantify platelet number</td>
<td>Low in ITP, HUS/TTP, DIC</td>
</tr>
<tr>
<td>Secondary</td>
<td>aPTT</td>
<td>22-35 s</td>
<td>Measures intrinsic pathway (factors VIII, IX, XI, XII) and common pathway</td>
<td>Prolonged in hemophilias A and B</td>
</tr>
<tr>
<td></td>
<td>PTT</td>
<td>11-24 s</td>
<td>Measures extrinsic pathway (factor VII in particular) and common pathway</td>
<td>Prolonged in factor VII deficiency</td>
</tr>
<tr>
<td></td>
<td>INR</td>
<td>0.9-1.2</td>
<td>Permits determination of extrinsic pathway status independent of laboratory performing measurement</td>
<td>Clotting factor(s) deficiency if test becomes normal</td>
</tr>
<tr>
<td></td>
<td>Mixing studies</td>
<td></td>
<td>Differentiate inhibitors of clotting factor(s) from a deficiency in clotting factor(s)</td>
<td>Inhibitors of clotting factor(s) if test still abnormal</td>
</tr>
<tr>
<td></td>
<td>Euglobulin lysis time</td>
<td>N &gt;90 min</td>
<td>Looks for accelerated fibrinolysis</td>
<td>May be accelerated in DIC or factor XIII deficiency</td>
</tr>
</tbody>
</table>

**Other**
- Fibrinogen
- Fibrinogen degradation products (FDPs), D-dimers
- Specific factor assays
- Tests of physiological inhibitors (antithrombin, protein S, protein C, hereditary resistance to activated protein C (APC))
- Tests of pathologic inhibitors (e.g. lupus anticoagulant)

### Table 19. Signs and Symptoms of Disorders of Hemostasis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Primary Platelet</th>
<th>Secondary Coagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface Cuts</td>
<td>Excessive, prolonged bleeding</td>
<td>Normal/slightly prolonged bleeding</td>
</tr>
<tr>
<td>Onset After Injury</td>
<td>Immediate</td>
<td>Delayed</td>
</tr>
<tr>
<td>Site of Bleeding</td>
<td>Superficial i.e. mucosal (nasal, gingival, GI tract, uterine), skin</td>
<td>Deep i.e. joints, muscles, GI tract, GU tract</td>
</tr>
<tr>
<td>Lesions</td>
<td>Petechiae, ecchymoses</td>
<td>Hemathroses, hematomas</td>
</tr>
</tbody>
</table>

### Table 20. Lab Values in Disorders of Hemostasis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>PT</th>
<th>PTT</th>
<th>Platelet Count</th>
<th>RBC Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A/B</td>
<td>N</td>
<td>↑</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>vWD</td>
<td>N</td>
<td>±</td>
<td>N↓</td>
<td>N</td>
</tr>
<tr>
<td>DIC</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>N↓</td>
</tr>
<tr>
<td>Liver Failure</td>
<td>↑</td>
<td>N↑</td>
<td>N↓</td>
<td>N</td>
</tr>
<tr>
<td>ITP</td>
<td>N</td>
<td>N</td>
<td>↓</td>
<td>N</td>
</tr>
<tr>
<td>TTP</td>
<td>N</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

vWD = von Willebrand disease; DIC = disseminated intravascular coagulation; ITP = idiopathic thrombocytopenic purpura; TTP = thrombotic thrombocytopenic purpura

### Disorders of Primary Hemostasis

**Definition**
- inability to form an adequate platelet plug due to:
  - disorders of blood vessels
  - disorders of platelets
    - abnormal function
    - abnormal numbers (thrombocytopenia)
  - disorders of vWF
Classification

1. Hemostasis Disorders

- Platelets
  - Low platelet count: Thrombocytopenia (see H6)
  - Normal platelet count: Platelet dysfunction
- vWD
- Acquired

Decreased production: Aplastic anemia
Increased destruction: ITP
Sequestration: Splenomegaly
Hereditary
- Bernard Soulier syndrome (GP1b deficiency)
- Glanzmann syndrome (GP IIb/IIIa deficiency)
Acquired
- Purpura simplex (easy bruising)
- Sickle purpura
- Dysproteinemias
- HSP
- Scurvy
- Cushing’s syndrome
- Infections, drugs

CRF = chronic renal failure; HSP = Henoch-Schönlein purpura

Figure 14. Approach to disorders of primary hemostasis

# Immune Thrombocytopenic Purpura (ITP)

**Table 21. Immune Thrombocytopenic Purpura**

<table>
<thead>
<tr>
<th>Features</th>
<th>Acute ITP</th>
<th>Chronic ITP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Age</td>
<td>2-6 yr</td>
<td>20-40 yr</td>
</tr>
<tr>
<td>Gender</td>
<td>None</td>
<td>F &gt; M (3:1)</td>
</tr>
<tr>
<td>History of Recent Infection</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Onset of Bleed</td>
<td>Abrupt</td>
<td>Insidious</td>
</tr>
<tr>
<td>Duration</td>
<td>Usually weeks</td>
<td>Months to years</td>
</tr>
<tr>
<td>Spontaneous Remissions</td>
<td>80% or more</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

**ACUTE (CHILD-TYPE) ITP**
- see Pediatrics, P49

**CHRONIC (ADULT-TYPE) ITP**
- most common cause of isolated thrombocytopenia
- diagnosis of exclusion [i.e. isolated thrombocytopenia (platelets <100 x 10^9/L) and the absence of any obvious initiating and/or underlying cause]

**Pathophysiology**
- an acquired immune-mediated disorder with:
  - anti-platelet antibodies bind to platelet surface → increased splenic destruction and clearance
  - impaired platelet production
  - helper T-cell and cytotoxic T-cell activation also implicated in platelet destruction

**Clinical Presentation**
- can present with no symptoms, minimal bruising to a serious bleed (including GI bleed, skin and mucosal hemorrhage or intracranial hemorrhage), lethargy, fatigue

**Investigations**
- CBC and reticulocyte count: thrombocytopenia (request retic count if not an isolated thrombocytopenia)
- PT and aPTT: normal
- peripheral blood film: decreased platelets, giant platelets (to rule out platelet clumping)
- HIV, HCV (if risk factors are present)
- bone marrow aspirate and biopsy: increased number of megakaryocytes
- recommended in patients >60 yr of age, pre-splenectomy or have failed multiple lines of ITP treatment, those with systemic symptoms, an abnormal blood film and/or abnormal signs to rule out other causes of thrombocytopenia (e.g. myelodyplasia)

**Mechanisms for HIV-associated Thrombocytopenia**
- Direct effect of HIV on marrow
- Immune-mediated platelet destruction
- Some antiretrovirals reduce platelet production

**Drugs Associated with Thrombocytopenia**

<table>
<thead>
<tr>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP-SMX</td>
</tr>
<tr>
<td>Heparin</td>
</tr>
<tr>
<td>NSAIDs</td>
</tr>
<tr>
<td>Vancomycin</td>
</tr>
<tr>
<td>Digoxin</td>
</tr>
<tr>
<td>Acamprosate</td>
</tr>
<tr>
<td>Rituximab</td>
</tr>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Ethanol</td>
</tr>
<tr>
<td>Ethambutol</td>
</tr>
<tr>
<td>Quinidine</td>
</tr>
<tr>
<td>Hy-arantivials</td>
</tr>
<tr>
<td>Amphotericin B</td>
</tr>
<tr>
<td>Quinine</td>
</tr>
</tbody>
</table>

**Should Rituximab be Used Before or After Splenectomy in Patients with Immune Thrombocytopenic Purpura (ITP)?**

**Curr Opin Hematol** 2007;14(4):42-46

**Purpose:** To determine whether the optimal timing for rituximab is before splenectomy, or after failure of splenectomy.

**Results:** Rituximab produces an initial response in approximately 60% of cases, with no significant difference between splenectomized and non-splenectomized patients. Long-term complete responses are observed in 15-20% of cases. Adverse events related to the drug were usually mild or moderate, with a low incidence of infections. Long-term safety data, however, are still lacking. Deaths have been reported for 2.9% of ITP cases treated with rituximab, but they could not be attributed to the study drug.

**Conclusion:** Both the response rate and the response duration appear lower following rituximab than following splenectomy. Although the side effects may be fewer, there is insufficient evidence to support the replacement of splenectomy with rituximab as a second-line treatment of chronic ITP outside a clinical trial. At the present time, the use of immunotherapy before splenectomy can be recommended only in patients at high risk for splenectomy and in those not willing to undergo surgery.
Heparin-Induced Thrombocytopenia (HIT) (Previously Known as HIT Type II)

**Pathophysiology**
- Immune mediated
  - Ab recognizes a complex of heparin and platelet factor 4 (PF4) leading to platelet activation via platelet Fc receptor and activation of coagulation system

**Diagnosis**
- 50% reduction in platelets while on heparin within 5-15 wk of initiation

**Onset of Decreased Platelets**
- 5-15 wk (if previously exposed to heparin, HIT can develop in hours)

**Risk of Thrombosis**
- ~30% (25% of events are arterial)

**Clinical Features**
- Bleeding complications uncommon
  - Venous thrombosis: DVT, PE, limb gangrene, cerebral sinus thrombosis
  - Arterial thrombosis: MI, stroke, acute limb ischemia, organ infarct (mesentery, kidney)
  - Heparin-induced skin necrosis (with LMWH)
  - Acute platelet activation syndromes: acute inflammatory reactions (e.g. fever/chills, flushing, etc.)
  - Transient global amnesia (rare)

**Specific Tests**
- 
  - $^{14}$C serotonin release assay (uses donor platelets with $^{14}$C serotonin and heparin with patient’s plasma)
  - ELISA for HIT-Ig (more sensitive, less specific than serotonin assay)
  - Ultrasound of lower limb veins for DVT

**Management**
- Clinical suspicion of HIT should prompt discontinuation of heparin (specific tests take several days)
  - Because of 90% cross-reactivity, LMWH should not be substituted
  - Alternative agents include: Argatroban (effective thrombin inhibitor, monitored with aPTT, use with caution in liver disease), fondaparinux (treatment dose, not prophylaxis)

**Prognosis**
- ~20% will not attain a hemostatic platelet count after first and second line therapy
- Fluctuating course
- Overall relatively benign, mortality 1-2%, (2X higher mortality than the unaffected population)
- Major concern is cerebral hemorrhage at Plt <5 x 10^9/L, although very rare

**Evaluation of Pretreatment Clinical Score (4 Ts) for the Diagnosis of Heparin-induced Thrombocytopenia in Two Clinical Settings**
*J Thromb Haemos 2006;4:759-1765*

Study: Prospective and retrospective clinical score application in two clinical settings (Hamilton General Hospital, HGH; and Greifswald in Germany, GW).

Population: 336 patients with suspected HIT.

Intervention: Risk stratification with a 4Ts clinical score compared with serology for HIT antibody.

Results: 1/64 (1.6%) in HGH and 0/55 (0%) in GW with low scores tested positive on HIT serology, 9/28 (32.1%) in HGH and 11/139 (7.9%) in GW with intermediate scores tested positive for HIT, 8/8 (100%) in HGH and 9/42 (21.4%) in GW with high scores tested positive for HIT.

Conclusion: A low pretreatment clinical score can help to rule out HIT in patients with thrombocytopenia.

Heparin-Induced Thrombocytopenia (HIT) is a rare and potentially serious complication of heparin therapy, characterized by the development of thrombocytopenia associated with the administration of heparin. It is divided into two subtypes based on its pathogenesis: immune-mediated HIT and non-immune-mediated HIT.

### Clinical Features
- **Bleeding complications:** Uncommon, but can include venous thrombosis (DVT, PE), limb gangrene, cerebral sinus thrombosis, arterial thrombosis (MI, stroke), acute limb ischemia, organ infarct (e.g., mesentery, kidney), and heparin-induced skin necrosis (with LMWH).
- **Acute platelet activation syndromes:** These can manifest as acute inflammatory reactions such as fever, chills, flushing, etc., and transient global amnesia.

### Specific Tests
- **$^{14}$C serotonin release assay:** Uses donor platelets with $^{14}$C serotonin and patient’s plasma.
- **ELISA for HIT-Ig:** More sensitive than the serotonin assay.
- **Ultrasound of lower limb veins for DVT:** To rule out other causes of thrombosis.

### Management
- **Clinical suspicion of HIT:** Prompt discontinuation of heparin (specific tests may take several days).
- **Alternative agents:** Argatroban (effective thrombin inhibitor, monitored with aPTT), fondaparinux (treatment dose, not prophylaxis).

### Prognosis
- Typically, HIT carries a relatively benign prognosis overall, with a mortality rate of 1-2% (2X higher than the unaffected population).
- However, a major concern is cerebral hemorrhage, especially in patients with platelet counts below 5 x 10^9/L.

### Preventive Measures
- **Avoidance of 4 Ts makes HIT unlikely:**
  - **Thrombocytopenia:** Timing of platelet count fall
  - **Thrombosis or other sequelae:** Other causes for thrombocytopenia

LMWH is also associated with HIT, but the risk is less than unfractionated heparin (2.8% in UFH vs. 0.2% in LMWH).

Heparin-associated thrombocytopenia (previously known as HIT type I)
- **Direct heparin-mediated platelet aggregation (non-immune):**
- **Platelets > 100 x 10^9/L:**
- **Self-limited (no thrombotic risk):**
- **May continue with heparin therapy:**
- **Onset 24-72 h**
**Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS)**

<table>
<thead>
<tr>
<th>Table 23. TTP and HUS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TTP</strong></td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Investigations (both TTP, HUS)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Management (both TTP, HUS)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Von Willebrand Disease (vWD)**

**Pathophysiology**
- heterogeneous group of defects
- usually autosomal dominant (type 3 is autosomal recessive)
- qualitative or quantitative abnormality of vWF
  - vWF needed for platelet adhesion and acts as carrier for Factor VIII; abnormality of vWF can affect both primary and secondary hemostasis
  - vWF exists as a series of multimers ranging in size
    - largest multimers are most active in mediation of platelet adhesion
    - both large and small multimers complex with Factor VIII
- usually mild in severity

**Classification**
- type 1: mild quantitative defect (decreased amount of vWF and proportional decrease in vWF activity) – 75% of cases
- type 2: qualitative defect (vWF activity disproportionally lower than quantity) – 20-25% of cases
- type 3: severe total quantitative defect (no vWF produced) – rare

**Clinical Features**
- mild
  - asymptomatic
  - mucosal and cutaneous bleeding, easy bruising, epistaxis, menorrhagia
- moderate to severe
  - as above but more severe, occasionally soft-tissue hematomas, petechiae (rare), GI bleeding, hemarthroses

**Investigations**

<table>
<thead>
<tr>
<th>Table 24. Investigations in vWD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
</tr>
<tr>
<td>PTT</td>
</tr>
<tr>
<td>Factor VII</td>
</tr>
<tr>
<td>Plt count</td>
</tr>
<tr>
<td>Ristocetin activity</td>
</tr>
</tbody>
</table>

**Notes:**
- Consider vWD in all women with menorrhagia.
Hematology Disorders of Primary Hemostasis/Disorders of Secondary Hemostasis Toronto Notes 2014

Treatment
• desmopressin (DDAVP+) is treatment of choice for type 1 vWD
  ▫ causes release of vWF and Factor VIII from endothelial cells
  ▫ variable efficacy depending on disease type; tachyphylaxis occurs
  ▫ need good response before using with further bleeding
  ▫ caution in children due to hyponatremia
• tranexamic acid (Cyklokapron®, antifibrinolytic) to stabilize clot formation
• high-purity Factor VIII concentrate containing vWF (Hemate P®) in select cases and type
  ▫ frozen plasma (FP) is not useful
  ▫ need to monitor vWF and factor VIII levels (very high factor VIII level can cause thrombosis)
• conjugated estrogens (increase vWF levels)

Prognosis
• may fluctuate, often improves during pregnancy, inflammation and with age

Disorders of Secondary Hemostasis

Definition
• inability to form an adequate fibrin clot
  ▫ disorders of clotting factors or co-factors
  ▫ disorders of proteins associated with fibrinolysis
  ▫ characterized by delayed bleeding, deep muscular bleeding, spontaneous joint bleeding

Table 25. Classification of Secondary Hemostasis Disorders

<table>
<thead>
<tr>
<th>Hereditary</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII: Hemophilia A, vWD</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Factor IX: Hemophilia B (Christmas Disease)</td>
<td>DIC</td>
</tr>
<tr>
<td>Factor XI</td>
<td>Vitamin K deficiency</td>
</tr>
<tr>
<td>Other factor deficiencies are rare</td>
<td>Acquired inhibitors</td>
</tr>
</tbody>
</table>

Hemophilia A (Factor VIII Deficiency)

Pathophysiology
• X-linked recessive, 1/5,000 males
• mild (>5% of normal factor level), moderate (1-5%), severe (<1%)

Clinical Features
• see Table 19 – Signs and Symptoms of Disorders of Hemostasis, H25
• older patients may also have HIV or HCV from contaminated blood products

Investigations
• prolonged aPTT, normal INR (PT)
• decreased Factor VIII (<40% of normal)
• vWF usually normal or increased

Treatment
• desmopressin (DDAVP+) in mild hemophilia A
• recombinant Factor VIII concentrate for
  ▫ prophylaxis (2-3 times a week at home)
  ▫ minor but not trivial bleeding (e.g. hemarthroses)
  ▫ major potentially life-threatening bleeding (e.g. multiple trauma)
• anti-fibrinolytic agents (e.g. tranexamic acid)

Hemophilia B (Factor IX Deficiency)

• aka Christmas disease
• X-linked recessive, 1/30,000 males
• clinical and laboratory features identical to hemophilia A (except decreased Factor IX)
• treatment: recombinant Factor IX concentrate, anti-fibrinolytic agents

Factor XI Deficiency

• aka Rosenthal syndrome
• autosomal recessive; more common in Ashkenazi Jews
• usually mild, often diagnosed in adulthood
• Factor XI level does not correlate with bleeding risk
• treatment: frozen plasma, Factor XI concentrate
Liver Disease

- see Gastroenterology, G28

Pathophysiology
- deficient synthesis of all factors except VIII (also made in endothelium and in acute phase response)
- aberrant synthesis of fibrinogen
- deficient clearance of hemostatic ‘debris’ and fibrinolytic activators
- accelerated destruction due to dysfibrinogenemias: increased fibrinolysis, DIC
- miscellaneous: inhibition of secondary hemostasis by FDPs

Investigations
- peripheral blood film: target cells
- primary hemostasis affected
  - thrombocytopenia due to hypersplenism, folate deficiency, alcohol intoxication, DIC, decreased production of thrombopoietin
  - platelet dysfunction (e.g. alcohol abuse)
- secondary hemostasis affected
  - elevated INR (PT), aPTT and TT, low fibrinogen in end-stage liver disease

Treatment
- supportive, treat liver disease, blood products if active bleeding (frozen plasma, platelets, cryoprecipitate)

Vitamin K Deficiency

Etiology
- drugs
  - oral anticoagulants which inhibit Factors II, VII, IX, X, proteins C and S
  - antibiotics eradicating gut flora, altering vitamin K uptake
- poor diet (especially in alcoholics)
- biliary obstruction
- chronic liver disease (decreased stores)
- malabsorption (e.g. celiac disease)
- hemorrhagic disease of newborn, see Pediatrics, P71

Investigations
- INR (PT) is elevated out of proportion to elevation of the aPTT
- decreased Factors II, VII, IX and X (vitamin K-dependent)

Treatment
- hold anticoagulant
- vitamin K 1 mg PO for INR between 4.5 and 10 and no active bleeding (excludes hemorrhagic disease of the newborn)
- if bleeding, give vitamin K 10 mg IV
- if life-threatening bleeding and vitamin K antagonist use, give frozen plasma or prothrombin complex concentrate (PCC)
  - PCCs are contraindicated if there is a previous history of HIT
  - use FFP if PCC is contraindicated or unavailable
- note: excessive vitamin K will delay therapeutic warfarin anticoagulation once re-started

Disseminated Intravascular Coagulation (DIC)

- see also Obstetrics, OB21

Definition
- uncontrolled release of plasmin and thrombin leading to intravascular coagulation and depletion of platelets, coagulation factors and fibrinogen
- risk of life-threatening hemorrhage

Etiology
- occurs as a complication of many other conditions
- widespread endothelial damage ± extensive inflammatory cytokine release

DIC is a spectrum which may include thrombosis, bleeding or both.
Clinical Features
• presence of both hemorrhage and clotting

Table 27. Clinical Features of DIC

<table>
<thead>
<tr>
<th>Signs of Microvascular Thrombosis</th>
<th>Signs of Hemorrhagic Diathesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological: multilocular infarcts, delirium, coma, seizures</td>
<td>Bleeding from any site in the body (2° to decreased platelets and clotting factors)</td>
</tr>
<tr>
<td>Renal: oliguria, azotemia, cortical necrosis</td>
<td>Neurologic: intracranial bleeding</td>
</tr>
<tr>
<td>Pulmonary: ARDS</td>
<td>Skin: petechiae, ecchymosis, oozing from puncture sites</td>
</tr>
<tr>
<td>GI: acute ulceration</td>
<td>Renal: hematuria</td>
</tr>
<tr>
<td>RBC: microangiopathic hemolysis</td>
<td>Muscosal: gingival oozing, epistaxis, massive bleeding</td>
</tr>
</tbody>
</table>

Investigations
• primary hemostasis: decreased platelets
• secondary hemostasis: prolonged INR (PT), aPTT, TT, decreased fibrinogen and other factors
• fibrinolysis: increased FDPs or D-dimers, short euglobulin lysis time (i.e. accelerated fibrinolysis)
• extent of fibrin deposition: urine output, urea, RBC fragmentation

Treatment
• recognize early
• treat underlying disorder
• individualized critical care support
• in hemorrhage: replacement of hemostatic elements with platelet transfusion, frozen plasma, cryoprecipitate
  ▪ maintain platelets >50 x10⁹ and hemoglobin >80 g/L
  ▪ 4-5 units of FFP if INR >1.5 or aPTT >38
  ▪ 10 units of cryoprecipitate if fibrinogen <1 g/L
• 1 adult dose of buffy-coat platelets if <10 x10⁹ (<20 if febrile, <50 before invasive procedure)
• in thrombotic phase: UFH or LMWH in critically ill, non-bleeding patients

Table 28. Screening Test Abnormalities in Coagulopathies

<table>
<thead>
<tr>
<th>Increased INR Only</th>
<th>Increased PTT Only</th>
<th>Both Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Hemophilia A and B</td>
<td>Prothrombin deficiency</td>
</tr>
<tr>
<td>Vitamin K deficiency</td>
<td>vWD</td>
<td>Fibrinogen deficiency</td>
</tr>
<tr>
<td>Factor VII deficiency</td>
<td>Heparin</td>
<td>Factor V and X deficiency</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Antiphospholipid Ab</td>
<td>Severe liver disease</td>
</tr>
<tr>
<td>Factor VIII inhibitors</td>
<td>Factor inhibitors</td>
<td>Factor V and X, prothrombin, and fibrinogen inhibitors</td>
</tr>
<tr>
<td>Factor XI and XII deficiency</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Venous Thromboembolism

Definition
• thrombus formation and subsequent inflammatory response in a superficial or deep vein
• superficial thrombophlebitis, deep vein thrombosis (DVT) and pulmonary embolism (PE)
• thrombi propagate in the direction of blood flow (commonly originating in calf veins)
• more common in lower extremity than upper extremity
• incidence ~1% if age >60 yr
• most important sequelae are pulmonary embolism (~50% chance with proximal DVT) and chronic venous insufficiency
Etiology (Virchow’s Triad)

- endothelial damage
  - exposes endothelium to prompt hemostasis
  - leads to decreased inhibition of coagulation and local fibrinolysis
- venous stasis
  - immobilization (post-MI, CHF, stroke, post-op) inhibits clearance and dilution of coagulation factors
- hypercoagulability
  - inherited (see Hypercoagulable Disorders, H34)
  - acquired
    - age (risk increases with age)
    - surgery (especially orthopedic, thoracic, GI and GU)
    - trauma (especially fractures of spine, pelvis, femur or tibia, spinal cord injury)
    - neoplasms (especially lung, pancreas, colon, rectum, kidney and prostate)
    - blood dyscrasias (myeloproliferative neoplasms, especially PV, ET), PNH, hyperviscosity
      (multiple myeloma, polycythemia, leukemia, sickle cell disease)
    - prolonged immobilization (CHF, stroke, MI, leg injury)
    - hormone related (pregnancy, OCP, HRT, SERMs)
    - APS
    - heart failure (risk of DVT greatest with right heart failure and peripheral edema)
- idiopathic (10-20% are later found to have cancer)

Clinical Features of DVT

- absence of physical findings does not rule out disease
- unilateral leg edema, erythema, warmth and tenderness
- palpable cord (thrombosed vein)
- phlebitis or varicose veins
- leg swelling in deep veins
- calf pain or swelling
- muscle strain or tear, lymphangitis or lymph obstruction, venous valvular insufficiency
- tenderness (knee, ankle, posterior tibial arch)
- sites of phlebitis (femoral, iliac, popliteal)
- Pitting edema greater in the calf than in the thigh
- calf tenderness on palpation
- calf swelling > 3 cm than other leg
- localized tenderness in deep vein system
- Swelling of entire leg
- Calf swelling > 3 cm than other leg
- recent major trauma
- brain metastases
- muscle damage (proximal, distal)
- muscle weakness
- increased muscle tone
- postural hypotension
- weight loss
- fever
- acute onset
- recent neurosurgery or ocular surgery within 10 d
- active cancer
- recent major surgery within past 4 wk
- localized tenderness in deep vein system
- recent stroke

Differential Diagnosis of DVT

- muscle strain or tear, lymphangitis or lymph obstruction, venous valvular insufficiency, ruptured popliteal cysts, cellulitis, arterial occlusive disease

Investigations for DVT

- D-dimer test only useful to rule out DVT if negative with low clinical suspicion of disease and no other acute medical issues/recent surgery
- doppler ultrasound is most useful diagnostic test for DVT
  - sensitivity and specificity for proximal DVT ~95%
  - sensitivity for calf DVT ~70%
- other non-invasive tests include MRI and impedance plethysmography
- venography is the gold standard, but is expensive, invasive and higher risk
- for Clinical Features and Treatment of PE, see Respirology, R17

Approach to Treatment of Venous Thromboembolism (VTE)

Purpose

- prevent further clot extension
- prevent acute pulmonary embolism (occurs in up to 50% of untreated patients)
- reduce the risk of recurrent thrombosis
- treatment of massive iliofemoral thrombosis with acute lower limb ischemia and/or venous gangrene (phlebitis cerulea dolens)
- limit development of late complications, e.g. postphlebitic syndrome, chronic venous insufficiency and chronic thromboembolic pulmonary HTN

Absolute Contraindications to Treatment

- active bleeding
- severe bleeding diathesis or platelet count <20 x 10^9/L (<20,000/mm^3)
- intracranial bleeding
- neurosurgery or ocular surgery within 10 d

Relative Contraindications to Treatment

- mild-moderate bleeding diathesis or thrombocytopenia
- brain metastases
- recent major trauma
- major abdominal surgery within the past 2 d
- GI or GU bleeding within 14 d
- endocarditis
- severe hypertension (sBP >200 or dBP >120)
- recent stroke
Initial Treatment
- low molecular weight heparin (LMWH)
  - administered SC, at least as effective as UFH with a lower bleeding risk
  - advantages: predictable dose response and fixed dosing schedule; lab monitoring not required; <1% HIT; safe and effective outpatient therapy
  - disadvantages: only partially reversible by protamine, long-term use associated with osteoporosis
  - renally cleared – must adjust dose in patients with renal dysfunction
- unfractionated heparin (UFH)
  - in patient with average risk of bleed; use hospital-based nomograms that use bleeding risk and patient weight to determine appropriate dose
  - advantages: rapidly reversible by protamine
  - disadvantages: must monitor aPTT with adjustment of dose to reach therapeutic level (~2x normal value); monitor platelet counts for development of HIT
- alternatives to LMWH and UFH
  - heparinoids (patients with HIT), direct thrombin inhibitors (hirudin, lepirudin, argatroban, dabigatran), Factor Xa inhibitors (fondaparinux, rivaroxaban)
  - thrombolytic drugs (e.g. streptokinase, tPA) reserved for acute limb/life-threatening thrombosis, and low bleeding risk

Long-term Treatment
- warfarin:
  - standard treatment; should be initiated with heparin overlap: dual therapy for at least 5 d, due to initial prothrombotic state, half life of vitamin K factors and risk of warfarin-induced skin necrosis
  - discontinue heparin after INR >2.0 for two consecutive days
  - warfarin should be dosed to maintain INR at 2-3 except in select cases
  - monitor INR twice weekly for 1-2 wk, then weekly until INR stable, then every 2-4 wk
  - LMWH more effective than warfarin at preventing recurrence of venous thrombosis in cancer patients (see sidebar, H32)
- duration of anticoagulant treatment (with warfarin unless otherwise noted):
  - first episode DVT with no identifiable risk factor (idiopathic) or single inherited risk factor (e.g. Factor V Leiden): 6-12 mo or indefinite therapy (controversial)
  - recurrent DVT (2 or more episodes): indefinite therapy
  - IVC filters:
    - temporary filter indicated only if distal acute DVT (<4 wk) with significant contraindications to anticoagulant therapy (i.e. active bleeding)
    - must remove once safe to do so as filter is pro-thrombotic in the longterm (anticoagulation if left in)
  - special considerations
    - pregnancy: treat with LMWH during pregnancy, then warfarin for 4-6 wk post-partum (minimum total anticoagulation time of 3-6 mo)
    - surgery: avoid elective surgery in the first month after a venous or arterial thromboembolic event
      - preoperatively: IV heparin may be used up to 6 h pre-operatively
      - perioperatively: surgery safe when INR <1.5; warfarin should be discontinued for at least 4 wk pre-operatively to allow INR to fall
      - postoperatively: IV heparin or LMWH can be used for anticoagulation (start 12 h after major surgery until therapeutic INR reached after restarting warfarin)
      - for patients at high risk for thromboembolism (VTE <12 wk, recurrent VTE, lupus anticoagulant, atrial fibrillation with prior stroke, mechanical heart valve), IV heparin or LMWH (bridging) should be given before and after the procedure while the INR is below 2.0

Prophylaxis
- see sidebar
- consider for those with a moderate to high risk of thrombosis without contraindications
- non-pharmacological measures include: early ambulation, elastic compression stockings (TEDs), intermittent pneumatic compression (IPC)
- UFH 5000 IU SC bid for moderate risk
- UFH 5000 IU SC tid or LMWH as per hospital protocol (i.e. enoxaparin 40 mg SC daily) or UFH 5000 IU SC tid for high risk

Contraindications and Adverse Reactions of Anticoagulant Therapy
- absolute: active bleeding, severe bleeding diathesis or platelets <20 x 10^9/L (<20,000/mm³), intracranial bleeding, neuro or ocular surgery within <10 d
- relative: mild-moderate neurologic diathesis or thrombocytopenia, brain metastases, recent major trauma, major abdominal surgery within page 2 d, GI/GU bleed within 14 d, endocarditis, severe HTN (SBP >200 or DBP >120), recent stroke

Treatment of Pulmonary Embolism (PE)
- see Respirology, R19

Duration of Treatment with Vitamin K Antagonists in Symptomatic Venous Thromboembolism
- Cochrane GB Spor Rev 2006;1:C0001367
- Study: Meta-analysis of 8 RCTs (2994 patients) comparing different durations of treatment with vitamin K antagonists in patients with symptomatic venous thromboembolism (VTE).
- Main Results: In patients treated with vitamin K antagonists for a prolonged period, the reduction in risk of recurrent VTE remained consistent regardless of the period of time since the index event (OR 0.89, CI 0.53-1.50). In addition, there was no observed excess of VTE recurrences following cessation of prolonged vitamin K, antagonist therapy (OR 1.24, CI 0.87-1.79). However, patients who received prolonged treatment had a persistent increase in their risk of major bleeding complications (OR 2.61, CI 1.48-4.61).
- Conclusion: Prolonged treatment with vitamin K antagonists leads to a consistent reduction in the risk of recurrent VTE that is maintained over time. The absolute risk of recurrent VTE (which remains constant over time) is of greater concern than the absolute risk of major bleeding complications (which declines over time). No specific recommendation was made regarding optimal duration of treatment.

Common Medications that Interact with Warfarin
- Acetaminophen (interference with vit K metabolism)
- Allopurinol
- NSAIDs (GI injury)
- Fluconazole
- Metronidazole
- Sulfamethoxazole
- Tamoxifen

Initiation of Warfarin Therapy Requires Overlap with Heparin Therapy for 4-5 Days
- 10 mg loading dose of warfarin causes a precipitous decline in protein C levels in first 36 h resulting in a transient hypercoagulable state.
- Warfarin decreases Factor VII levels in first 48 h INR is prolonged (most sensitive to Factor VII levels), however full antithrombotic effect is not achieved until Factor IX, X, and II are sufficiently reduced (occurs after approx. 4 d).

Low risk surgical patients:
- <40 yr, no risk factors for VTE, general anesthetic (GA) <30 min, minor elective, abdominal or thoracic surgery.
- Moderate risk surgical patients:
  - >40 yr, >1 risk factor for VTE, GA >30 min.
- High risk surgical patients:
  - >40 yr, surgery for malignancy or lower extremity orthopedic surgery lasting >30 min, inhibitor deficiency or other risk factor.
- High risk medical patients: heart failure, severe respiratory disease, ischemic stroke and lower limb paralysis, confined to bed and have >1 additional risk factor (e.g. active cancer, previous VTE, sepsis, acute neurologic disease, IBD).

Toronto Notes 2014
Hypercoagulability Workup – Venous Thrombosis
- workup for malignancy or hypercoagulable state indicated for idiopathic VTE in presence of the following: age <50, recurrent VTE, family history of VTE and age <50, unusual site of DVT (portal, hepatic, mesenteric vascular beds), heparin-resistant disease (AT deficiency), warfarin-induced skin necrosis or neonatal purpura fulminans (proteins C or S deficiency). Consider for women with VTE within 12 mo of exposure to OCP
- workup:
  - initial
    - CBC, blood smear, coagulation studies, liver/renal function, urinalysis, fasting homocysteine
    - malignancy work up (see sidebar)
    - anti-phospholipid antibodies (APLA): anticardiolipin antibodies (ACA) and lupus anticoagulant (LA)
    - activated protein C resistance (APCR)
    - DNA: FVL (Factor V Leiden), PT (prothrombin G20210A)
  - post initial insult (>72 h) as protein levels depleted/consumed by clot
    - antithrombin (not on heparin)
    - Factor VIII (increased levels predict recurrence)
  - post-treatment
    - proteins C, S (not on warfarin)
- Note: most of these tests do not change management, and a negative test does not rule out a hypercoagulable state. Thus more focus is on the reversible/treatable causes (APLA, cancer, etc.)

CAUSES OF HYPERCOAGULABILITY LEADING TO VENOUS THROMBOEMBOLISM

Activated Protein C Resistance (Factor V Leiden)
- most common cause of hereditary thrombophilia
- 5% of general population are heterozygotes
- point mutation in the Factor V gene (R506Q) results in resistance to inactivation of Factor Va by activated protein C

Prothrombin (PT) G20210A
- G to A transposition at nucleotide position 20210 of the prothrombin gene promoter region results in increased levels of prothrombin, thus increased thrombin generation

Protein C and Protein S Deficiency
- protein C inactivates Factor Va and VIIIa using protein S as a cofactor
- protein C deficiency
  - homozygous: neonatal purpura fulminans
  - heterozygous:
    - type I: decreased protein C levels
    - type II: decreased protein C activity
  - acquired: liver disease, sepsis, DIC, warfarin
  - 1/3 of patients with warfarin necrosis have underlying protein C deficiency
- protein S deficiency
  - type I: decreased free and total protein S levels
  - type II: decreased protein S activity
  - type III: decreased free protein S levels
  - acquired: liver disease, DIC, pregnancy, nephrotic syndrome, inflammatory conditions, warfarin

Antithrombin Deficiency
- antithrombin slowly inactivates thrombin in the presence of heparin, rapidly inactivates thrombin in the presence of heparin
- autosomal dominant inheritance or urinary losses in nephrotic syndrome
  - type I: decreased AT levels
  - type II: decreased AT activity
- diagnosis must be made outside window of acute thrombosis and anticoagulation treatment (acute thrombosis, heparin, systemic disease all decrease antithrombin levels)
- deficiency may result in resistance to unfractionated heparin (LMWH must be used)

Elevated Factor VIII Levels
- an independent marker of increased thrombotic risk
- genetic basis for increased levels poorly understood

Disorders of Fibrinolysis
- include congenital plasminogen deficiency, tissue plasminogen activator deficiency

Antiphospholipid Antibody Syndrome (APS)
- definition: ≥1 clinical and ≥1 laboratory criteria
  - clinical: thrombosis, spontaneous abortions, fetal loss, premature birth before 34 wk
  - laboratory: anticardiolipin or lupus anticoagulant antibodies
- mechanism: not well understood, antibodies interact with platelet membrane phospholipid causing increased adhesion and aggregation; can also interfere with action of proteins C and S
- see Rheumatology, RH12
Acute Myeloid Leukemia (AML)

Definition
- rapidly progressive malignancy characterized by failure of myeloid cells to differentiate beyond blast stage

Epidemiology
- incidence increases with age; median age of onset is 65 yr old
- accounts for 10-15% of childhood leukemias

Risk Factors
- myelodysplastic syndromes (MDS), benzene, radiation, alkylating agents as treatment for previous malignancy

Pathophysiology
- etiology subdivided into:
  - primary: de novo
  - secondary: hematologic malignancies (e.g. myeloproliferative disorders and MDS) or previous chemotherapeutic agents (e.g. alkylating agents)
- uncontrolled growth of blasts in marrow leads to:
  - suppression of normal hematopoietic cells
  - appearance of blasts in peripheral blood
  - accumulation of blasts in other sites (e.g. skin, gums)
  - metabolic consequences; tumour lysis syndrome

Clinical Features
- anemia, thrombocytopenia (associated with DIC in PML), neutropenia (even with normal WBC), leads to infections, fever
- thrombocytopenia (associated with DIC in promyelocytic leukemia)
- accumulation of blast cells in marrow
  - skeletal pain, bony tenderness (especially sternum)
- organ infiltration
  - gingival hypertrophy (particularly myelomonocytic leukemia) – may present to dentist first
  - hepatosplenomegaly (in ALL)
  - lymphadenopathy (not marked)
  - skin: leukemia cutis
  - gonads (in ALL)
  - eyes: Roth spots, cotton wool spots, vision changes (uncommon)
- leukostasis/hyperleukosisis syndrome (medical emergency)
  - large numbers of blasts interfere with circulation and lead to hypoxia and hemorrhage – can cause diffuse pulmonary infiltrates, CNS bleeding, respiratory distress, altered mental status, priapism

Typical Age of Presentation of Leukemias
- ALL: Children and older adults
- CML: 40-60 yr
- AML, CLL: >60 yr

Leukemia: malignant cells arise in bone marrow and may spread elsewhere (including blood, lymph nodes and lymphoid tissue).

Lymphoma: malignant cells arise in lymph nodes and lymphoid tissues and may spread elsewhere (including blood and bone marrow).

BUT the location where the malignant cells are found does not solely define the type of hematologic malignancy – classified based on the characteristics of the cell (histology, histochemistry, immunophenotyping, cytogenetics, molecular changes).
• metabolic effects; aggravated by treatment (rare)
  - increased uric acid → nephropathy, gout
  - release of phosphate → decreased Ca\(^{2+}\), decreased Mg\(^{2+}\)
  - release of procoagulants → DIC (higher risk in acute promyelocytic leukemia)
  - decreased or normal K\(^{+}\) before treatment, increased K\(^{+}\) after treatment

Investigations

- bloodwork:
  - CBC: anemia, thrombocytopenia, variable WBC
  - INR, aPTT, fibrin degradation products (FDP), fibrinogen (in case of DIC)
  - increased LDH, increased uric acid, increased PO\(_4^{3-}\) (released by leukemic blasts), decreased Ca\(^{2+}\)
  - baseline renal and liver function tests
- peripheral blood film – circulating blasts with Auer rods (azurophilic granules) are pathognomonic for AML
- bone marrow aspirate:
  - blast count: AML >20% (normal is <5%)
  - morphologic, cytochemical and/or immunotypic features are used to establish lineage and maturation (see sidebar for WHO classification of AML, H35)
- CXR to r/o pneumonia, ECG, MUGA scan prior to chemotherapy (cardiotoxic)

Treatment

- mainstay of treatment is chemotherapy (rapidly fatal without treatment)
  - all AML subtypes treated similarly except promyelocytic variant with t(15:17) translocation
    - all-trans-retinoic acid (ATRA) added to induce differentiation
- treatment strategy:
  1. Induction: chemotherapy to induce complete remission of AML (see sidebar)
    - several possible regimens [e.g. cytarabine with anthracycline (daunorubicin)]
    - patients with poor response to initial induction therapy – worse prognosis
    - must ensure reversal of DIC, platelet transfusions if <10
  2. Consolidation: to prevent recurrence
    - intensive consolidation chemotherapy
    - stem cell transplantation – autologous or allogeneic (younger patients with better performance status)
- consider acceleration with hematopoietic growth factors (e.g. G-CSF) if severe infection develops
- supportive care
  - screening for infection via regular C&S of urine, stool, sputum, oropharynx, catheter sites, perianal area
  - fever: C&S of all orifices, CXR, start antibiotics
  - platelet and RBC transfusions (irradiated to prevent transfusion-related GVHD) ± EPO
  - prevention and treatment of metabolic abnormalities
    - allopurinol for prevention of hyperuricemia

Prognosis

- achievement of first remission
  - 70-80% if ≤60 yr old, 50% if >60 yr old
  - median survival 12-24 mo
  - 5 yr survival 40%
- prognosis related to cytogenetics (favourable, intermediate or adverse)

Myelodysplastic Syndromes (MDS)

Definition

- heterogeneous group of malignant stem cell disorders characterized by dysplastic and ineffective blood cell production resulting in peripheral cytopenias
- syndromes defined according to World Health Organization (WHO) classifications (see sidebar)

Pathophysiology

- disordered maturation: ineffective hematopoiesis despite presence of adequate numbers of progenitor cells in bone marrow (usually hypercellular)
- intramedullary apoptosis: programmed cell death within bone marrow
  - both processes lead to reduced mature cells in periphery
- <30% develop AML

Risk Factors

- elderly, post-chemotherapy, benzene or radiation exposure
- occurs in 60/100,000 in patients >60 yr old

Clinical Features

- insidious onset: associated with those of pancytopenia
- infections and bleeding out of proportion with peripheral blood counts

2008 WHO MDS Classification

- Refractory cytopenia with unilineage dysplasia
- Refractory anemia
- Refractory neutropenia
- Refractory thrombocytopenia
- Refractory anemia with ringed sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)
- Refractory anemia with excess blasts (RAEB)
- Myelodysplastic syndrome with isolated del (5q)
- Myelodysplasia unclassified (seen in cases of megakaryocyte dysplasia with fibrosis and others)
- Childhood myelodysplastic syndrome

MDS is a cause of macrocytic anemia.

Myelodysplastic Syndromes: ineffective maturation

Myeloproliferative Neoplasms: overproduction of mature cells
Investigations
- diagnosed by:
  - anemia ± thrombocytopenia ± neutropenia
  - CBC and peripheral blood film
  - RBC: usually macrocytic with oval shaped red cells (macro-ovalocytes), decreased reticulocyte count
  - WBC: decreased granulocytes and abnormal morphology (e.g. bilobed or unsegmented nuclei = Pelger abnormality)
  - platelets: thrombocytopenia, abnormalities of size and cytoplasm (e.g. giant hypogranular platelets)
- bone marrow aspirate and biopsy with cytogenetic analysis required for definitive diagnosis
  - bone marrow: dysplastic and often normocellular/hypercellular
  - cytogenetics: partial or total loss of chromosomes 5, 7, Y, or trisomy 8

Prognosis
- Revised International Prognostic Scoring System (IPSS-R) uses 5 factors to estimate mean survival:
  - cytology, % bone marrow blasts, hemoglobin, platelets, absolute neutrophil count
  - based on the calculated score, a patient's MDS prognostic risk is "Very Low", "Low", "Intermediate", "High" or "Very High" with a mean survival of 8.7, 5.3, 3.0, 1.6 and 0.8 yr, respectively

Treatment
- low risk of transformation to acute leukemia (IPSS-R Very Low or Low)
  - erythropoietin stimulating agents weekly is first line in reducing transfusion requirements
  - 5q(-) cytogenetic: Revlimid® PO
  - supportive care: RBC and platelet transfusion (consider iron chelation if frequent RBC transfusions)
- high risk of transformation to acute leukemia (IPSS-R Intermediate, High or Very High)
  - supportive care
  - stem cell transplantation if age <65 yr
  - epigenetic therapy: DNA methyltransferase inhibitors (e.g. 5-Azacytidine), histone deacetylase inhibitors

Myeloproliferative Neoplasms (MPNs)

Definition
- clonal myeloid stem cell abnormalities leading to overproduction of one or more cell lines (leading to abnormalities in erythrocytes, platelets and other cells of myeloid lineage)

Epidemiology
- mainly middle-aged and older patients (peak 60-80 yr)

Prognosis
- may develop marrow fibrosis with time
- all disorders may progress to AML

Table 29. Chronic Myeloproliferative Disorders

<table>
<thead>
<tr>
<th></th>
<th>CML</th>
<th>PV</th>
<th>IMF</th>
<th>ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct</td>
<td>↓/N</td>
<td>↑↑</td>
<td>↓</td>
<td>N</td>
</tr>
<tr>
<td>WBC</td>
<td>↑↑</td>
<td>↑</td>
<td>↑/↓</td>
<td>N</td>
</tr>
<tr>
<td>Plt</td>
<td>↑/↓</td>
<td>↑</td>
<td>↑/↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Marrow fibrosis</td>
<td>±</td>
<td>±</td>
<td>+++</td>
<td>±</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Genetic Association</td>
<td>bcr-abl mut. (90 %)</td>
<td>JAK2 mut. (95%)</td>
<td>JAK2 mut. (~50%)</td>
<td>JAK2 mut. (~50%)</td>
</tr>
</tbody>
</table>

PV = polycythemia vera; CML = chronic myeloid leukemia; IMF = idiopathic myelofibrosis; ET = essential thrombocythemia

Basophilia is uncommon in other medical conditions.
Chronic Myeloid Leukemia (CML)

Definition
- myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate

Epidemiology
- occurs in any age group (mostly middle age to elderly) with a median age of 65 yr

Pathophysiology
- Philadelphia chromosome (Ph)
  - translocation between chromosomes 9 and 22
  - the c-abl proto-oncogene is translocated from chromosome 9 to "breakpoint cluster region" (bcr) of chromosome 22 to produce bcr-abl fusion gene, an active tyrosine kinase

Clinical Features
- 3 clinical phases
  - chronic phase: 85% diagnosed here
    - few blasts (<10%) in peripheral film
    - ± slightly elevated eosinophils and basophils
    - no significant symptoms
  - accelerated phase: impaired neutrophil differentiation
    - circulating blasts (10-19%) with increasing peripheral basophils (pruritus)
    - CBC: thrombocytopenia <100 x 10^9/L
    - cytogenetic evidence of clonal evolution
    - worsening constitutional symptoms and splenomegaly (extramedullary hematopoiesis)
  - blast crisis: more aggressive course, blasts fail to differentiate
    - blasts (>20%) in peripheral blood or bone marrow; reflective of acute leukemia (1/3 ALL, 2/3 AML)
- clinical presentation
  - 20-50% of patients are asymptomatic when diagnosed (incidental lab finding)
  - nonspecific symptoms
    - fatigue, weight loss, malaise, excessive sweating, fever
  - secondary to splenic involvement
    - early satiety, LUQ pain/fullness, shoulder tip pain (referred)
    - splenomegaly (most common physical finding)
  - anemia
  - bleeding: secondary to platelet dysfunction
    - pruritus, PUD: secondary to increased blood histamine
  - leukostasis, priapism, encephalopathy (rare): secondary to very elevated WBC (rare)

Investigations
- high increase in WBC, decreased/normal RBC, increased/decreased platelets, increased basophils
- WBC differential shows a bimodal distribution, with predominance of myelocytes and neutrophils
- peripheral blood film
  - leukoerythroid picture (immature red cells and granulocytes present, e.g. myelocytes and normoblasts)
  - presence of different mid-stage progenitor cells differentiates it from AML
- bone marrow
  - myeloid hyperplasia with left shift, increased megakaryocytes, mild fibrosis
- molecular and cytogenetic studies of bone marrow or peripheral blood for Philadelphia chromosome
- abdominal imaging for spleen size

Treatment
- symptomatic:
  - allopurinol and antihistamines
- chronic phase:
  - imatinib mesylate (Gleevec®): inhibits proliferation and induces apoptosis by inhibiting tyrosine kinase activity in cells positive for bcr-abl
  - if loss of response or intolerance (~25%), trial of 2nd (dasatinib) or 3rd (nilotinib) generation inhibitors
  - interferon-β: may improve response to tyrosine kinase inhibitors
  - hydroxyurea in palliative setting
  - bone marrow transplantation if progression to accelerated or blast phases: CML (curative)
- accelerated phase or blast phase:
  - refer for clinical trial or 2nd/3rd generation TKI and prepare for allogenic stem cell transplant patients, in blast phase typically get standard AML induction
  - stem cell transplantation may be curative: to be considered in young patients who do not meet therapeutic milestones

Chronic Myeloproliferative Neoplasias: Six-year follow-up of patients receiving imatinib for the first-line treatment of CML

Leukemia 2009;23:1054-1061

The Randomized Study of Interferon vs. STI571 (IRIS) trial enrolled patients with chronic phase chronic myeloid leukemia (CML-CP) to either imatinib (n=533) or interferon-α (IFN) plus cytarabine (n=553). Assessing the imatinib arm specifically at the sixth year point, there were no reports of disease progression to accelerated phase (AP) or blast crisis (BC), toxicity profile was unchanged, and cytogenetic response rate was 82%. Estimated event-free survival was 83% and rate of freedom from progression to AP and BC was 93%. This 6-year update of IRIS demonstrates the efficacy and safety of imatinib as first-line therapy for CML patients.

Detection of the bcr-abl fusion gene is a diagnostic test for CML (present in over 90% of patients).
• treatment success is monitored based on therapeutic milestones:
  ▪ hematologic: improved WBC and platelet counts, reduced basophils
  ▪ cytogenetic: undetectable Philadelphia-chromosome in the bone marrow
  ▪ molecular: reduction/absence of bcr-abl transcripts in periphery and marrow

**Prognosis**

- survival dependent on response
  ▪ those achieving complete cytogenetic response (CCR) on imatinib by 18 mo of therapy: 6 yr overall survival >90%
  ▪ those who do NOT achieve CCR on imatinib: 6 yr overall survival of 66%
- acute phase (blast crisis – usually within 3-5 yr)
  ▪ 2/3 develop a picture similar to AML
  ▪ unresponsive to remission induction
  ▪ 1/3 develop a picture similar to ALL
  ▪ remission induction (return to chronic phase) achievable

**Polycythemia Vera (PV)**

**Definition**

- stem cell disorder characterized by elevated RBC mass (erythrocytosis) ± increased white cell and platelet production

**Clinical Features**

- symptoms are secondary to high red cell mass and hyperviscosity (see *Erythrocytosis, H6*)
  ▪ bleeding complications: epistaxis, gingival bleeding, ecchymoses and GI bleeding
  ▪ due to platelet abnormalities
  ▪ thrombotic complications: DVT, PE, thrombophlebitis, increased incidence of stroke, MI
  ▪ due to increased blood viscosity, increased platelet number and/or activity
  ▪ erythromelalgia (burning pain in hands and feet and erythema of the skin)
  ▪ due to increased blood viscosity
  ▪ pruritus, especially after warm bath or shower (40%)
  ▪ due to cutaneous mast cell degranulation and histamine release
  ▪ epigastric distress, PUD
  ▪ due to increased histamine from tissue basophils, alterations in gastric mucosal blood flow
  ▪ due to increased blood viscosity
  ▪ gout (hyperuricemia)
  ▪ due to increased cell turnover
  ▪ characteristic physical findings
    ▪ plethora (ruddy complexion) of face (70%), palms
    ▪ splenomegaly (70%), hepatomegaly (40%)

**Investigations**

- see *Erythrocytosis, H6*
- must rule out secondary polycythemia
diagnosis (WHO 2008) requires either both major criteria plus one minor criteria OR the first major criterion plus 2 minor criteria:
  ▪ Major Criteria:  
    1. hemoglobin >18.5 g/dL in men, 16.5 g/dL in women or other evidence of increase red cell volume
    2. presence of JAK2 V617F or other functionally similar mutation such as JAK2 exon 12 mutation
  ▪ Minor Criteria:  
    1. bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic and megakaryocytic proliferation
    2. serum erythropoietin level below the reference range for normal
    3. endogenous erythroid colony formation in vitro

**Treatment**

- phlebotomy to keep hematocrit <45%
- hydroxyurea (prior thrombosis or symptoms, severe coronary artery disease, refractory to phlebotomy)
- low-dose Aspirin® (for antithrombotic prophylaxis, will also treat erythromelalgia)
- alloprimol: as needed
- antihistamines: as needed

**Prognosis**

- 10-20 yr survival with treatment
- complicated by thrombosis, hemorrhage, leukemic transformation (AML)
**Idiopathic Myelofibrosis (IMF)**

**Definition**
- excessive bone marrow fibrosis leading to marrow failure
- characterized by anemia, extramedullary hematopoiesis, leukoerythroblastosis, teardrop red cells in peripheral blood and hepatosplenomegaly

**Epidemiology**
- rare, median age at presentation is 65 yr

**Pathophysiology**
- abnormal myeloid precursor postulated to produce dysplastic megakaryocytes that secrete fibroblast growth factors
  - stimulates fibroblasts and stroma to deposit collagen in marrow
- increasing fibrosis causes early release of hematopoietic precursors leading to:
  - leukoerythroblastic blood film (primitive RBCs and WBCs present in blood)
  - migration of precursors to other sites: extramedullary hematopoiesis (leading to hepatosplenomegaly)

**Clinical Features**
- anemia (severe fatigue is most common presenting complaint, pallor on exam in >60%)
- weight loss, fever, night sweats → secondary to hypermetabolic state
- splenomegaly (90%) → secondary to extramedullary hematopoiesis; may cause early satiety
- hepatomegaly (70%) → may get portal hypertension
- bone and joint pain → secondary to osteosclerosis, gout
- signs of extramedullary hematopoiesis (depends on organ involved)

**Investigations**
- CBC: anemia, variable platelets, variable WBC
- biochemistry: increased ALP (liver involvement, bone disease), increased LDH (2° to ineffective hematopoiesis), increased uric acid (increased cell turnover), increased B12 (2° to increased neutrophil mass)
- blood film: leukoerythroblastosis with teardrop RBCs, nucleated RBCs, variable polychromasia, large platelets and megakaryocyte fragments
- JAK2 PCR
- bone marrow aspirate: “dry tap” in as many as 50% of patients (no blood cells aspirated)
- bone marrow biopsy (essential for diagnosis): fibrosis, atypical megakaryocytic hyperplasia, thickening and distortion of the bony trabeculae (osteosclerosis)

**Treatment**
- allogeneic stem cell transplant is potentially curative
- symptomatic treatment:
  - transfusion for anemia
  - erythropoietin: 30-50% of patients respond
  - androgens (e.g. danazol has shown transient response with response rates of <30%)
  - hydroxyurea for splenomegaly, thrombocytosis, leukocytosis, systemic symptoms
  - α-interferon (as second line therapy)
  - splenectomy (as third line therapy; associated with high mortality and morbidity)
  - radiation therapy for symptomatic extramedullary hematopoiesis, symptomatic splenomegaly
  - thalidomide, JAK2 inhibitors, and etanercept may improve quality of life and spleen size, but not survival

**Prognosis**
- International Prognostic Scoring System (IPSS) for IMF uses 5 factors to determine mean survival:
  - presence of constitutional symptoms: age >65; hemoglobin <100 g/L; leukocyte count >25,000/mm³; circulating blast cells ≥1%
  - based on the calculated score, a patient’s IMF is categorized as “low”, “intermediate 1”, “intermediate 2”, or “high” with a mean survival of 135, 95, 48 and 27 mo respectively
  - risk of transformation to AML (8-10%)

**Essential Thrombocythemia (ET)**

**Definition**
- overproduction of platelets in the absence of recognizable stimulus
- must rule out secondary thrombocythemia
Epidemiology
- Increases with age; F:M = 2:1, but F=M at older age

Diagnosis (2008 WHO Criteria) requires meeting all four criteria:
1. Sustained platelet count >450 x 10^9/L
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased number of enlarged, mature megakaryocytes. No significant increase or left shift of neutrophil granulopoiesis or erythropoiesis
3. Not meeting WHO criteria for PV, primary myelofibrosis, BCR-ABL CML or myelodysplastic syndrome or other myeloid neoplasms
4. Demonstration of JAK2 V617F (or in its absence another clonal marker), no evidence for reactive thrombocytosis

Clinical Features
- Often asymptomatic
  - Vasomotor symptoms (40%)
    - Headache (common), dizziness, syncope
    - Erythromelalgia (burning pain of hands and feet, dusky colour, usually worse with heat, caused by platelet activation → microvascular thrombosis)
  - Thrombosis (arterial and venous)
  - Bleeding (often GI, associated with platelets >1000 x 10^9/L)
  - Constitutional symptoms, splenomegaly
  - Pregnancy complications; increased risk of spontaneous abortion
  - Risk of transformation to AML (0.6-5%), myelofibrosis

Investigations
- CBC: increased platelets; may have abnormal platelet aggregation studies
- JAK2 PCR assay
- Bone marrow hypercellularity, megakaryocytic hyperplasia, giant megakaryocytes
- Increased K+, increased PO43- (2o to release of platelet cytoplasmic contents)
- Diagnosis: exclude other myeloproliferative disorders and reactive thrombocytosis

Treatment
- Low dose ASA if previous history of thrombotic event, ≥1 cardiovascular risk factors, older or symptomatic
- Cytoreductive therapy if thrombosis or thrombotic symptoms: hydroxyurea (HU) (1st line therapy), anagrelide, interferon-α, or 32P (age >80 or lifespan <10 yr)
- Splenectomy not recommended (increased risk of bleeding episodes, thrombosis)

Lymphoid Malignancies

Acute Lymphoblastic Leukemia (ALL)

Definition
- Malignant disease of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow
- WHO subdivides ALL into two types depending on cell of origin
  1. B-cell: precursor B lymphoblastic leukemia
  2. T-cell: precursor T lymphoblastic leukemia
- The French-American-British (FAB) classification (L1, L2, L3) is no longer encouraged, as morphology is not prognostic

Clinical Features
- See Acute Myeloid Leukemia, H35 for full list of symptoms
- Distinguish ALL from AML based on Table 30
- Clinical symptoms usually secondary to:
  - Bone marrow failure: anemia, neutropenia (50% present with fever; also infections of oropharynx, lungs, perianal region), thrombocytopenia
  - Organ infiltration: tender bones, lymphadenopathy, hepatosplenomegaly, meningeal signs (headache, N/V, visual symptoms; especially in ALL relapse)

Investigations
- CBC: increased leukocytes >10 x 10^9/L (occurs in 50% of patients); neutropenia, anemia or thrombocytopenia
- May have increased uric acid, K+, PO43-, Ca2+, LDH
- PT, aPTT, fibrinogen, D-dimers for DIC
- Leukemic lymphoblasts lack specific morphological (no granules) or cytochemical features, therefore diagnosis depends on immunophenotyping
- Cytogenetics: Philadelphia (Ph) chromosome in ~25% of adult ALL cases
• CXR: patients with ALL may have a mediastinal mass
• LP prior to systemic chemotherapy to assess for CNS involvement (ensure adequate platelet count and PT/PTT)

**Treatment**

• eliminate abnormal cloned cells:
  1. **Induction:** to induce complete remission (undetectable leukemic blasts, restore normal hematopoiesis)
  2. **Consolidation and/or intensification chemotherapy**
     - consolidation: same chemotherapy to eliminate subclinical leukemic cells
     - intensification: high doses of different (non-cross-reactive) chemotherapy drugs to eliminate cells with resistance to primary treatment
  3. **Maintenance chemotherapy:** low dose intermittent chemotherapy over prolonged period (2-3 yr) to prevent relapse
  4. **Prophylaxis:** CNS radiation therapy or methotrexate (intrathecal or systemic)
• hematopoietic stem cell transplantation: potentially curative (due to pre-implant myeloablative chemoradiation and post-implant graft-versus-leukemia effect) but relapse rates and non-relapse mortality high

**Prognosis**

• depends on response to initial induction or if remission is achieved following relapse
• good prognostic factors: young, WBC <30 x 10^9/L, T-cell phenotype, absence of Ph chromosome, early attainment of complete remission
• achievement of first remission: 60-90% 
• childhood ALL: 80% long term remission (>5 yr)
  - higher cure rates in children because of better chemotherapy tolerance, lower prevalence of bcr-abl fusion gene (associated with chemotherapeutic resistance)
• adult ALL: 30-40% 5-yr survival

**Table 30. Differentiating AML From ALL**

<table>
<thead>
<tr>
<th>AML</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Big people (adults)</td>
<td>Small people (kids)</td>
</tr>
<tr>
<td>Big blasts</td>
<td>Small blasts</td>
</tr>
<tr>
<td>Big mortality rate</td>
<td>Small mortality rate (kids)</td>
</tr>
<tr>
<td>Lots of cytoplasm</td>
<td>Less cytoplasm</td>
</tr>
<tr>
<td>Lots of nucleoli (3-5)</td>
<td>Few nucleoli (1-3)</td>
</tr>
<tr>
<td>Lots of granules and Auer rods</td>
<td>No granules</td>
</tr>
<tr>
<td>Myeloperoxidase, Sudan black stain</td>
<td>PAS (periodic acid-Schiff)</td>
</tr>
<tr>
<td>Maturation defect beyond myeloblast or promyelocyte</td>
<td>Maturation defect beyond lymphoblast</td>
</tr>
</tbody>
</table>

**Lymphomas**

**Definition**

• collection of lymphoid malignancies in which malignant lymphocytes accumulate at lymph nodes and lymphoid tissues
  - leading to lymphadenopathy, extranodal disease and constitutional symptoms

**Table 31. Ann Arbor System for Staging Lymphomas**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region or extralymphatic organ or site</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of two or more lymph node regions or an extralymphatic site and one or more lymph node regions on same side of diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm; may or may not be accompanied by single extra lymphatic site or splenic involvement</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse involvement of one or more extralymphatic organs including bone marrow</td>
</tr>
</tbody>
</table>

• subtypes:
  - A = absence of B-symptoms (see Approach to Lymphadenopathy, H11)
  - B = presence of B-symptoms

**Treatment of ALL vs. AML**

• No proven benefit of maintenance chemotherapy in AML
• No routine CNS prophylaxis in AML

**To Differentiate AML From ALL:** Remember Big and Small ALL

• Ann Arbor staging can be used for both Hodgkin and non-Hodgkin lymphoma, but grade/histology is more important for non-Hodgkin lymphoma because the outcome differs significantly depending on type of lymphoma.
• Prognostic scores are different for indolent versus aggressive lymphomas.
• Highly aggressive lymphomas act like acute leukemias.

**Hodgkin is distinguished from non-Hodgkin lymphoma by the presence of Reed-Sternberg cells.**
Table 32. Chromosome Translocations

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Gene Activation</th>
<th>Associated Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(8;14)</td>
<td>c-myc activation</td>
<td>Burkitt’s lymphoma</td>
</tr>
<tr>
<td>t(14;18)</td>
<td>bcl-2 activation</td>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td>t(9;22)</td>
<td>Philadelphia chromosome (bcr-abl hybrid)</td>
<td>CML, ALL in adults (25% of the time)</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>Overexpression of cyclin D1 protein</td>
<td>Mantle cell lymphoma</td>
</tr>
</tbody>
</table>

Hodgkin Lymphoma

Definition
• malignant proliferation of lymphoid cells with Reed-Sternberg cells (thought to arise from germinal centre B-cells)

Epidemiology
• bimodal distribution with peaks at 20 yr and >50 yr
• association with Epstein-Barr virus in up to 50% of cases, causal role not determined

Clinical Features
• asymptomatic lymphadenopathy (70%)
  ▪ non-tender, rubbery consistency
  ▪ cervical/supraclavicular (60-80%), axillary (10-20%), inguinal (6-12%)
• splenomegaly (50%) ± hepatomegaly
• mediastinal mass
  ▪ found on routine CXR, may be symptomatic (cough)
  ▪ rarely may present with SVC syndrome, pleural effusion
• systemic symptoms
  ▪ B symptoms (especially in widespread disease; fever in 30%), pruritus
• non-specific/paraneoplastic
  ▪ alcohol-induced pain in nodes, nephrotic syndrome
• starts at a single site in lymphatic system (node), spreads first to adjacent nodes
  ▪ disease progresses in contiguity with lymphatic system

Investigations
• CBC
  ▪ anemia (chronic disease, rarely hemolytic), eosinophilia, leukocytosis, platelets normal or increased early, decreased in advanced disease
• biochemistry
  ▪ HIV serology
  ▪ LFTs (liver involvement)
  ▪ RFTs (prior to initiating chemotherapy)
  ▪ ALP, Ca++ (bone involvement)
  ▪ ESR, LDH (monitor disease progression)
• imaging
  ▪ CXR, CT chest (lymph nodes, mediastinal mass), CT abdomen/pelvis (liver or spleen involvement), gallium scan (assess treatment response)
  ▪ cardiac function assessment (MUGA or echocardiography): for patients at high risk of pre-treatment cardiac disease (age >60, history of HTN, CHF, PUD, CAD, MI, CVA), treatment can be cardiotoxic
  ▪ PFTs: if history of lung disease (COPD, smoking, previous radiation to lung)
• excisional lymph node biopsy confirms diagnosis
• bone marrow biopsy to assess marrow infiltration (only necessary if B-symptoms, stage III or IV, bulky disease or cytopenia)

Treatment
• stage I-II: chemotherapy (ABVD) followed by involved field radiotherapy (XRT)
• stage III-IV: chemotherapy (ABVD) with XRT for bulky disease
• relapse, resistant to therapy: high dose chemotherapy, bone marrow transplant
  ▪ new imaging modalities increasingly used including PET scans used to follow response to treatment

Complications of Treatment
• cardiac disease: secondary to XRT, adriamycin is also cardiotoxic
• pulmonary disease: secondary to bleomycin (interstitial pneumonitis)
• infertility: recommend sperm banking
• secondary malignancy in irradiated field
  ▪ <2% risk of MDS, AML (secondary to treatment, usually within 8 yr)
  ▪ solid tumours of lung, breast; >8 yr after treatment
• non-Hodgkin lymphoma
• hypothyroidism: post XRT

Common Chemotherapeutic Regimens

CHOP: cyclophosphamide, hydroxydoxorubicin (Adriamycin), vincristine (Oncovin), prednisone
VAD: vincristine, adriamycin, dexamethasone
ABVD: adriamycin, bleomycin, vinblastine, dacarbazine
BEACOPP: bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone
**Prognosis**

- Hasenclever adverse prognostic factors:
  1. serum albumin <40 g/L (4 g/dL)
  2. hemoglobin <105 g/L (10.5 g/dL)
  3. male
  4. stage IV disease
  5. age ≥45 yr
  6. leukocytosis (WBC >1.5 x 10^9/L)
  7. lymphocytopenia (lymphocytes <0.06 x 10^9/L or <8% of WBC count or both)

- prognostic score
  - each additional adverse prognostic factor decreases freedom from progression at 5 yr (FFP)

**Non-Hodgkin Lymphoma (NHL)**

**Definition**

- malignant proliferation of lymphoid cells of progenitor or mature B- or T-cells

**Classification**

- multiple classification systems exist at present and may be used at different centres
- can originate from both B- (85%) and T- or NK- (15%) cells
  - B-cell NHL: e.g. diffuse large B-cell lymphoma, follicular lymphoma, Burkitt’s lymphoma, mantle cell lymphoma
  - T-cell NHL: e.g. mycosis fungoides, anaplastic large cell lymphoma
- WHO/REAL classification system: 3 categories of NHLs based on natural history
  - indolent (35-40% of NHL): e.g. follicular lymphoma, small lymphocytic lymphoma/CLL, mantle cell lymphoma
  - aggressive (~50% of NHL): e.g. diffuse large B-cell lymphoma
  - highly aggressive (~5% of NHL): e.g. Burkitt’s lymphoma

**Clinical Features**

- painless superficial lymphadenopathy, usually >1 lymph node region
- usually presents as widespread disease (exception is aggressive lymphoma)
- constitutional symptoms not as common as in Hodgkin lymphoma
- cytopenia: anemia ± neutropenia ± thrombocytopenia can occur when bone marrow is involved
- abdominal signs
  - hepatosplenomegaly
  - retroperitoneal and mesenteric involvement (2nd most common site of involvement)
- oropharyngeal involvement in 5-10% with sore throat and obstructive apnea
- extranodal involvement: most commonly GI tract; also testes, bone, kidney
- CNS involvement in 1% (often with HIV)

**Investigations**

- CBC:
  - normocytic normochromic anemia
  - autoimmune hemolytic anemia
  - advanced disease: thrombocytopenia, neutropenia and leukoerythroblastic anemia
- peripheral blood film may show lymphoma cells
- flow cytometry of peripheral blood is valuable for low-grade NHL
- biochemistry:
  - increase in uric acid
  - abnormal LFTs in liver metastases
  - increased LDH (rapidly progressing disease, poor prognostic factor)
- CXR, CT neck, abdomen, pelvis for staging
- PET is useful for monitoring response to treatment and evaluation of residual tumour following therapy in aggressive histological disease
- diagnosed by:
  - lymph node biopsy: excisional biopsy preferred, FNA unreliable
  - bone marrow biopsy: not optimal for diagnosis as BM may not be involved

**Treatment**

- localized disease (e.g. GI, brain, bone, head and neck)
- radiotherapy to primary site and adjacent nodal areas
- adjuvant chemotherapy
- surgery: splenic marginal zone lymphoma
- **indolent lymphoma**: goal of treatment is symptom management
  - watchful waiting
  - radiation therapy for localized disease
  - CHOP + rituximab, an anti-CD20 antibody (CHOP-R) for advanced stage disease

---

**Prognostic Factors Project 1998**

<table>
<thead>
<tr>
<th>Prognostic Factors</th>
<th>FFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84%</td>
</tr>
<tr>
<td>1</td>
<td>77%</td>
</tr>
<tr>
<td>2</td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td>60%</td>
</tr>
<tr>
<td>4</td>
<td>51%</td>
</tr>
<tr>
<td>5-7</td>
<td>42%</td>
</tr>
</tbody>
</table>

FFP = freedom from progression at 5 yr.

**International Prognostic Factors**

- **Project 1998**
- **Prognostic Factors**
- **FFP**
- 0: 84%
- 1: 77%
- 2: 67%
- 3: 60%
- 4: 51%
- 5-7: 42%

**FFP = freedom from progression at 5 yr.**

**Non-Hodgkin Lymphoma (NHL): Associated Conditions**

- Immunodeficiency (e.g. HIV)
- Autoimmune diseases (e.g. SLE)
- Infections (e.g. EBV)

**NHL: Associated Conditions**

- Infections (e.g. EBV)
- Autoimmune diseases (e.g. SLE)
- Immunodeficiency (e.g. HIV)

**CHOP-like Chemotherapy with or without Rituximab in Young Patients with Good-Prognosis Diffuse Large B-Cell Lymphoma (MInT)**

- **Lancet Oncol** 2011;12:1013-1022
- **Study**: International RCT with a median follow-up of 72 mo.
- **Participants**: 824 patients with good-prognosis diffuse large B-cell lymphoma who had ≤1 risk factor, stage I/IV disease or stage I disease with bulk (age: 18 to 60 yr).
- **Intervention**: Patients received either 6 cycles of CHOP-like chemotherapy and rituximab (CCR; n=413) or 6 cycles of CHOP-like chemotherapy alone (CLC; n=411). Bulky and extranodal sites received additional radiotherapy.
- **Primary Outcome**: Event-free survival.
- **Results**: Patients receiving CCR had an increased 6-yr event-free survival compared with the CLC group (74.3% vs. 55.8%; p<0.0001). Event-free survival was affected by treatment group, presence of bulky disease, and age-adjusted International Prognostic Index (IPI). Overall survival was affected by treatment group and presence of bulky disease. Within the CCR group, a favourable subgroup (IPI=0, no bulk) and less favourable subgroup (IPI=1 or bulk, or both) could be defined; event-free survival was 84.3% vs. 71.0%.
- **Conclusion**: Rituximab added to six cycles of CHOP is an effective treatment for young patients with good-prognosis diffuse large B-cell lymphoma. The definition of two prognostic subgroups allows a more refined therapeutic approach to these patients than does assessment by IPI alone.
• **aggressive lymphoma**: goal of treatment is curative
  - combination chemotherapy: CHOP is mainstay, plus rituximab if B-cell lymphoma
  - radiation for localized/bulky disease
  - CNS prophylaxis with high-dose methotrexate if certain sites involved (testicular, nasopharyngeal)
  - relapse, resistant to therapy: high dose chemotherapy, BMT

• **highly aggressive lymphoma**
  - Burkitt Lymphoma: short bursts of intensive chemotherapy
  - "CODOX-M" chemotherapy regimen also often used ± IVAC
  - CNS prophylaxis and tumour lysis syndrome prophylaxis

**Complications**
- hypersplenism
- infection
- autoimmune hemolytic anemia and thrombocytopenia
- vascular obstruction (from enlarged nodes)
- tumour lysis syndrome (particularly in very aggressive lymphoma) – see H50

**Prognosis**
- follicular lymphoma: Follicular Lymphoma International Prognostic Index is used (5 adverse prognostic factors): age >60; number of nodal areas >4; elevated LDH; Ann Arbor stage III-IV; hemoglobin <120 g/L
  - based on calculated risk, mean 5 yr survival ranges from 53-91%
  - rarely curative, typically relapsing course with risk of transformation to aggressive lymphoma such as diffuse large B-cell lymphoma
- diffuse large B-cell lymphoma: The International Prognostic Factor Index is used (5 adverse prognostic factors): age >60; Ann Arbor stage (III-IV); performance status (ECOG/Zubrand 2-4); elevated LDH; >1 extranodal site
  - based on calculated risk, mean 5 yr survival ranges from 26-73%
  - has ~40% rate of cure

### Table 33. Characteristics of Select Non-Hodgkin Lymphomas

<table>
<thead>
<tr>
<th></th>
<th>Follicular Lymphoma</th>
<th>Diffuse Large B-Cell Lymphoma (DLBCL)</th>
<th>Burkitt Lymphoma</th>
<th>Mantle Cell Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of NHLs</td>
<td>22-30%</td>
<td>33%</td>
<td>&lt;1% adult NHLs 30% childhood NHLs</td>
<td>6%</td>
</tr>
<tr>
<td>Genetic Mutation</td>
<td>Bcl-2 activation</td>
<td>Bcl-2, Bcl-6, MYC rearrangements</td>
<td>c-myc activation</td>
<td>Overexpression of cyclin D1 (Bcl-1 activation)</td>
</tr>
<tr>
<td>Classification</td>
<td>Indolent</td>
<td>Aggressive (high-grade)</td>
<td>Very aggressive</td>
<td>Indolent</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Widespread painless LAD* ± bone marrow involvement</td>
<td>Rapidly progressive LAD and extranodal infiltration 50% present at stage VII, 50% widely disseminated</td>
<td>Endemic form: massive jaw LAD &quot;Starry-sky&quot; histology High risk of tumour lysis syndrome upon treatment</td>
<td>Often presents Stage IV with palpable LAD Involvement of GI tract (lymphomatosis polyposis), Waldeyer’s Ring Extremely aggressive, 5-yr survival 25%</td>
</tr>
</tbody>
</table>

*LAD = lymphadenopathy*
Malignant Clonal Proliferations of Mature B-Cells

Table 34. Characteristics of B-Cell Malignant Proliferation

<table>
<thead>
<tr>
<th></th>
<th>CLL</th>
<th>Macroglobulinemia</th>
<th>Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell Type</strong></td>
<td>Lymphocyte</td>
<td>Plasmacytoid</td>
<td>Plasma cell</td>
</tr>
<tr>
<td><strong>Protein</strong></td>
<td>IgM if present</td>
<td>IgM</td>
<td>IgG, A, light chain (rarely M, D or E)</td>
</tr>
<tr>
<td><strong>Lymph Nodes</strong></td>
<td>Very common</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Hepatosplenomegaly</strong></td>
<td>Common</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Bone Lesions</strong></td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Hypercalcemia</strong></td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Renal Failure</strong></td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Immunoglobulin Complications</strong></td>
<td>Common</td>
<td>Rare</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Chronic Lymphocytic Leukemia (CLL)

**Definition**

- indolent disease characterized by clonal malignancy of mature B-cells

**Epidemiology**

- most common leukemia in Western world
- mainly older patients; median age 65 yr
- M>F

**Pathophysiology**

- accumulation of neoplastic lymphocytes in blood, bone marrow, lymph nodes and spleen

**Clinical Features**

- 25% asymptomatic (incidental finding)
- 5-10% present with B-symptoms (≥1 of: unintentional weight loss ≥10% of body weight within previous 6 mo, temperature >38°C or night sweats for ≥2 wk without evidence of infection, extreme fatigue)
- lymphadenopathy (50-90%), splenomegaly (25-55%), hepatomegaly (15-25%)
- immune dysregulation: autoimmune hemolytic anemia (Coombs positive), ITP, hypogammaglobulinemia ± neutropenia
- bone marrow failure: late, secondary to marrow involvement by CLL cells

**Investigations**

- CBC: absolute lymphocytes >5 x 10^9/L with a CLL phenotype
- peripheral blood film
  - lymphocytes are small and mature
  - smudge cells
- flow cytometry (CD5, CD20, CD23, etc.)
- cytogenetics: FISH (dictates response to therapy and prognosis)
- bone marrow aspirate
  - lymphocytes >30% of all nucleated cells
  - infiltration of marrow by lymphocytes in 4 patterns: nodular (10%), interstitial (30%), diffuse (35%, worse prognosis) or mixed (25%)

**Natural History and Treatment**

- natural history: indolent but incurable, with slow progression; thus select gentlest treatment that will control symptoms
  - observation if early, stable, asymptomatic
  - intermittent chlorambucil or fludarabine chemotherapy combined with rituximab, chlorambucil in the elderly
  - corticosteroids, IVIG: especially for autoimmune phenomena
  - radiotherapy
- small minority present with aggressive disease; usually associated with chromosomal abnormalities (e.g. p53 deletion)
- 9 yr median survival, but varies greatly

Rouleaux formation on peripheral blood smear, if not artifact, denotes hyperglobulinemia (but not necessarily monoclonality).

Smudge cells are artifacts of damaged lymphocytes from slide preparation.
• prognosis predicted by Rai staging
  ▪ low risk: lymphocytosis in blood and bone marrow only
  ▪ intermediate risk: lymphocytosis with enlarged nodes in any site or splenomegaly, hepatomegaly
  ▪ high risk: lymphocytosis with disease-related anemia (<110 g/L) or thrombocytopenia (<100 x 10^9/L)

Complications
• bone marrow failure
• immune complications: AIHA, ITP, immune deficiency (hypogammaglobulinemia, impaired T-cell function)
• polyclonal or monoclonal gammopathy (often IgM)
• hyperuricemia with treatment
• 5% undergo Richter’s transformation: aggressive transformation to diffuse large B-cell lymphoma (see Table 33)

Multiple Myeloma (MM)

Definition
• neoplastic clonal proliferation of plasma cells producing a monoclonal immunoglobulin resulting in end organ dysfunction
• usually single clone of plasma cells, although biclonal myeloma also occurs. Rarely non-secretory

Epidemiology
• incidence 3 per 100,000, most common plasma cell malignancy
• increased frequency with age; median age of diagnosis is 68 yr; M>F

Pathophysiology
• malignant plasma cells secrete monoclonal antibody
  ▪ 95% produce M protein (monoclonal Ig = identical heavy chain + identical light chain, or light chains only)
    ▪ IgG 50%, IgA 20%, IgD 2%, IgM 0.5%
    ▪ 15-20% produce free light chains or light chains alone found in either:
      – serum as an increase in the quantity of either kappa or lambda light chain (with an abnormal kappa:lambda ratio)
      – urine has Bence-Jones protein
  ▪ <5% are non-secretors

Clinical Features and Complications
• bone disease: pain (usually back), bony tenderness, pathologic fractures
  ▪ lytic lesions are classical (skull, spine, proximal long bones, ribs)
  ▪ increased bone resorption secondary to osteoclast activating factors such as PTHrP
• anemia: weakness, fatigue, pallor
  ▪ secondary to bone marrow suppression
• weight loss
• infections
  ▪ usually S. pneumoniae and Gram-negatives
  ▪ secondary to suppression of normal plasma cell function
• hypercalcemia: N/V, confusion, constipation, polyuria, polydipsia
  ▪ secondary to increased bone turnover
• renal disease/renal failure
  ▪ most frequently causes cast nephropathy (see Nephrology, NP30)
• bleeding
  ▪ secondary to thrombocytopenia, may see petechiae, purpura
  ▪ can also be caused by acquired von Willebrand disease
• extramedullary plasmacytoma
  ▪ soft tissue mass composed of monoclonal plasma cells, purplish colour
• hyperviscosity: may manifest as headaches, stroke, angina, MI
  ▪ secondary to increased viscosity caused by M protein
• amyloidosis
  ▪ accumulation of insoluble fibrillar protein (Ig light chain) in tissues; can cause infiltration of any organ system: cardiac infiltration – diastolic dysfunction, cardiac arrhythmias, syncope, sudden death; GI involvement – malabsorption, beefy large or laterally scalloped tongue; neurologic involvement – orthostatic hypotension, carpal tunnel syndrome
  ▪ may cause Factor X deficiency if fibrils bind Factor X → bleeding (raccoon eyes)
• neurologic disease: muscle weakness, pain, paresthesias
  ▪ radiculopathy caused by vertebral fracture, extramedullary plasmacytoma
  ▪ spinal cord compression (10-20% of patients) is a medical emergency

Routine urinalysis will not detect light chains as dipstick detects albumin. Need sulfosalicylic acid or 24 h urine protein for immunofixation or electrophoresis.

Amyloid
The general term for a variety of proteinaceous materials that have a similar structural organization and are abnormally deposited in tissues. Found in a variety of clinical disorders and can cause systemic (e.g. MM [light chains]) or localized amyloidosis (e.g. Alzheimer disease [AB amyloid]).
Investigations
- CBC:
  - normocytic anemia, thrombocytopenia, leukopenia
  - rouleaux formation on peripheral film
- biochemistry:
  - increased Ca\(^2+\), increased ESR, decreased anion gap, increased Cr, albumin, \(\beta_2\)-microglobulin
    (as part of staging), proteinuria (24 h urine collection)
- monoclonal proteins:
  - serum protein electrophoresis (SPEP): demonstrates monoclonal protein spike in serum in 80% (i.e. M protein)
  - urine protein electrophoresis (UPEP): demonstrates light chains in urine = Bence-Jones protein (15% only secrete light chains)
  - immunofixation: demonstrates M protein and identifies Ig type; also identifies light chains
  - serum free light chain quantification: kappa and lambda light chains, calculated ratio
- bone marrow aspirate and biopsy
  - often focal abnormality, greater than 10% plasma cells, abnormal morphology, clonal plasma cells; send for FISH or cytogenetics (prognostic implications)
- skeletal series (x-rays), MRI if symptoms of cord compression
  - presence of lytic lesions and areas at risk of pathologic fracture
  - bone scans are not useful since they detect osteoblast activity
- \(\beta_2\)-microglobulin, LDH and CRP are poor prognosticators

Diagnosis
- International Myeloma working group criteria
  1. serum or urinary monoclonal protein
  2. presence of clonal plasma cells in bone marrow or a plasmacytoma
  3. presence of end-organ damage related to plasma cell dyscrasia, such as:
     - increased serum Ca\(^2+\)
     - lytic bone lesions
     - anemia
     - renal failure

Treatment
- treatment is non-curative
- treatment goals:
  - improvement in quality of life (improve anemia, reverse renal failure, bony pain)
  - prevention of progression and complications
  - increase overall survival
- autologous stem cell transplant if <65 yr old
  - usually preceded by 4-6 mo of cytoreductive therapy: steroid based with novel agents
    (i.e. ImIDs or proteosome inhibitors)
- chemotherapy if >65 yr old or transplant-ineligible
  - melphalan, prednisone and novel agent (i.e. bortezomib)
- dexamethasone and bortezomib if ARF; bortezomib ± dexamethasone in light chain amyloidosis
- supportive management:
  - bisphosphonates for those with osteopenia or lytic bone lesions (requires renal dosing)
  - local XRT for bone pain, spinal cord compression
  - kyphoplasty for vertebral fractures to improve pain relief and regain height
  - treat complications: hydration for hypercalcemia and renal failure, bisphosphonates for severe hypercalcemia, prophylactic antibiotics, erythropoietin for anemia, DVT prophylaxis
- all patients will relapse; choice of retreatment regimen depends on duration of remission, organ involvement, patient’s comorbidities and preferences

Prognosis
- International Staging System (\(\beta_2\)-microglobulin and albumin) used to stage and estimate prognosis
  - cytogenetic profile (i.e. p53 mutation associated with poor survival and resistance to chemotherapy)
- median survival based on stage, usually 16-70 mo

Light Chain Disease
15% of MM produce only light chains. Renal failure is a major problem. Kappa > lambda light chain has better prognosis.
Monoclonal Gammopathy of Unknown Significance (MGUS)

Definition
- presence of M protein in serum in absence of any clinical or laboratory evidence of a plasma cell dyscrasia or lymphoproliferative disorders
  - incidence: 0.15% in general population, 5% of people >70 yr of age
  - asymptomatic

Diagnosis
- presence of a serum monoclonal protein (M-protein) at a concentration <30 g/L
- <10% plasma cells in bone marrow
- absence of hyperCalcemia, Renal insufficiency, Anemia, Bony disease related to the plasma cell proliferative process (absence of "CRAB")
- 0.3-1% of patients develop a hematologic malignancy each year
  - patients with M protein peak ≥15 g/L or patients with IgA or IgM MGUS are at higher risk of malignant transformation
  - patients with serum free light chains are at increased risk of malignant transformation
  - monitor with annual history, physical, CBC, Cr, calcium, albumin, serum protein electrophoresis (considered pre-malignant)

Lymphoplasmacytic Lymphoma (Waldenstrom’s Macroglobulinemia)

Definition
- proliferation of lymphoplasmacytoid cells
  - presence of monoclonal IgM paraprotein

Clinical Features
- chronic disorder of elderly patients; median age 64 yr
- symptoms: weakness, fatigue, bleeding (oronasal), weight loss, recurrent infections, dyspnea, CHF (triad of anemia, hyperviscosity, plasma volume expansion), neurological symptoms, peripheral neuropathy, cerebral dysfunction
- signs: pallor, splenomegaly, hepatomegaly, lymphadenopathy, retinal lesions
- key complication to avoid: hyperviscosity syndrome (see below)
  - because IgM (unlike IgG) confined largely to intravascular space

Investigations and Diagnosis
- bone marrow shows plasmacytoid lymphocytes
- bone lesions usually not present
- bloodwork rarely see hypercalcemia
- cold hemagglutinin disease possible: Raynaud's phenomenon, hemolytic anemia precipitated by cold weather
- normocytic anemia, rouleaux, high ESR if hyperviscosity not present

Management
- R-CVP, alkylating agents (chlorambucil), nucleoside analogues (fludarabine), thalidomide, rituximab, or combination therapy
- corticosteroids
- plasmapheresis for hyperviscosity: acute reduction in serum IgM

Complications of Hematologic Malignancies

Hyperviscosity Syndrome

Definition
- refers to clinical sequelae of increased blood viscosity (when relative serum viscosity >5-6 units), resulting from increased circulating serum lgs or from increased cellular blood components in hyperproliferative disorders (e.g. multiple myeloma, leukemia, PV)
- Waldenstrom's macroglobulinemia accounts for 85% of all cases of hyperviscosity syndrome.
**Clinical Features**
- hypervolemia causing: CHF, headache, lethargy, dilutional anemia
- CNS symptoms due to decreased cerebral blood flow: headache, vertigo, ataxia, stroke
- retina shows venous engorgement and hemorrhages
- bleeding diathesis
  - due to impaired platelet function, absorption of soluble coagulation factors (e.g. nasal bleeding, oozing gums)
- ESR usually very low

**Treatment**
- plasmapheresis, chemotherapy

---

**Tumour Lysis Syndrome**

**Definition**
- group of metabolic complications that result from spontaneous or treatment-related breakdown of cancer cells
- more common in diseases with large tumour burden and high proliferative rate (high grade lymphoma, leukemia)

**Clinical Features**
- metabolic abnormalities
  - cells lyse, releasing K⁺, uric acid, PO₄³⁻ (increased levels)
  - PO₄³⁻ binds Ca²⁺ (decreased Ca²⁺)
- complications
  - lethal cardiac arrhythmia (increased K⁺)
  - acute renal failure (urate nephropathy, see Nephrology, NP30)

**Treatment**
- prevention
  - aggressive IV hydration
  - alkalinization of the urine
  - allopurinol or rasburicase
  - correction of pre-existing metabolic abnormalities
- dialysis

---

**Blood Products and Transfusions**

**Blood Products**
- RBCs, platelets and coagulation factors (frozen plasma [FP], cryoprecipitate, factor concentrates) are available for transfusion
- donated blood (1 U = 450-500 mL) is fractionated into these various components
  - centrifugation separates whole blood into RBCs and platelet-rich plasma
  - platelet-rich plasma is further fractionated into platelets and plasma
  - need to pool together multiple units to obtain therapeutic amounts
  - FP (previously known as FFP) is plasma frozen within 24 h of collection
  - cryoprecipitate is the high MW precipitate generated when FP is thawed at low temperatures

**Specialized Products**
- irradiated blood products
  - prevent proliferation of donor T-cells in potential or actual BMT recipients
  - used for immunocompromised patients or for patients on purine analogue chemotherapy, first-degree relatives, HLA-matched products and intrauterine transfusions
- CMV-negative blood products
  - potential transplant recipients
  - neonates
  - AIDS patients
  - seronegative pregnant women

**Blood Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Antigen (on RBC)</th>
<th>Antibody (in serum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>H</td>
<td>Anti-A, anti-B</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>Anti-B</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>Anti-A</td>
</tr>
<tr>
<td>AB</td>
<td>A and B</td>
<td>Nil</td>
</tr>
</tbody>
</table>

In Canada, blood products are leukodepleted via filtration immediately after donation. Therefore it is considered:
- Low in lymphokines, resulting in a lower incidence of febrile nonhemolytic transfusion reactions
- CMV negative (because CMV is found in leukocytes)
Red Blood Cells

Packed Red Blood Cells
- stored at 4°C
- transfuse within 42 d of collection, otherwise cell lysis may result in hyperkalemia
- infuse each unit over 2 h, max of 4 h

Indications for packed RBC Transfusion
- Hb <70 g/L (7 g/dL); this may change as per patient’s tolerance or symptoms
  - maintain Hb between 70 and 100 g/L during active bleeds (7 g/dL to 10 g/dL)
- consider maintaining a higher Hb for patients with:
  - CAD/unstable coronary syndromes
  - uncontrolled, unpredictable bleeding
  - impaired pulmonary function
  - increased O₂ consumption

Selection of Red Cells for Transfusion
- when a need for RBC transfusion is anticipated, the following should be ordered:
  - group and screen
    - determines the blood group and Rh status of the recipient as well as the presence of autoantibodies vs. major/minor blood group antigens in the patient’s serum
  - crossmatch
    - involves mixing the recipient’s blood with potential donor blood and looking for agglutination
    - takes 30-45 min
- when blood is required, several options are available
  - 1st line: fully crossmatched blood (not always available in emergency situations)
  - 2nd line: donor blood of the same group and Rh status as the recipient
  - 3rd line: O- blood for females of reproductive age; O+ blood for all others

Platelets

Table 35. Platelet Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random donor (pooled)</td>
<td>Thrombocytopenia with bleeding</td>
</tr>
<tr>
<td>Single donor platelets</td>
<td>Potential BMT recipients</td>
</tr>
<tr>
<td>HLA matched platelets</td>
<td>Refractory to pooled or single donor platelets, presence of HLA antibodies</td>
</tr>
</tbody>
</table>

- stored at 20–24°C
- random donor platelets are transfused from a pool of 4 units; this should increase the platelet count by ≥15 x 10⁹/L
- single donor platelets (transfused as single units) should increase the platelet count by 40–60 x 10⁹/L
- if an increase in the platelet count is not seen post-transfusion: autoantibodies (i.e. ITP), alloantibodies, consumption (bleeding, sepsis) or hypersplenism may be present

Table 36. Indications for Platelet Transfusion

<table>
<thead>
<tr>
<th>Plt (x 10⁹/L)</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>Non-immune thrombocytopenia</td>
</tr>
<tr>
<td>&lt;20</td>
<td>Procedures not associated with significant blood loss</td>
</tr>
<tr>
<td>&lt;50</td>
<td>Procedures associated with blood loss or major surgery (&gt;500 mL EBL)</td>
</tr>
<tr>
<td>&lt;100</td>
<td>Pre-neurosurgery or head trauma</td>
</tr>
<tr>
<td>Any</td>
<td>Platelet dysfunction (or antiplatelet agents) and marked bleeding</td>
</tr>
</tbody>
</table>

Relative Contra-indications of Platelet Transfusion
- TTP, HIT, post-transfusion purpura, HELLP
Coagulation Factors

Table 37. Coagulation Factor Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frozen plasma (FP)</td>
<td>Depletion of multiple coagulation factors (e.g. sepsis, DIC, dilution, TTP/HUS, liver disease), emergency reversal of life-threatening bleeding secondary to warfarin overdose</td>
</tr>
<tr>
<td>Cryoprecipitate (enriched fibrinogen, vWF, VIII, XIII)</td>
<td>Factor VIII deficiency, von Willebrand's disease, Hypofibrinogenemia</td>
</tr>
<tr>
<td>Hemate P</td>
<td>von Willebrand's disease</td>
</tr>
<tr>
<td>Factor VIII concentrate</td>
<td>Factor VIII deficiency (Hemophilia A)</td>
</tr>
<tr>
<td>Factor IX concentrate</td>
<td>Factor IX deficiency (Hemophilia B)</td>
</tr>
<tr>
<td>Recombinant VIIa</td>
<td>Factor VII deficiency with bleeding, Hemophilia A or B with inhibitors</td>
</tr>
<tr>
<td>Prothrombin Complex (Octaplex®)</td>
<td>Reversal of warfarin therapy or vitamin K deficiency in bleeding patient or in patient requiring urgent (&lt;6 h) surgical procedure</td>
</tr>
</tbody>
</table>

Acute Blood Transfusion Reactions

IMMUNE

Acute Hemolytic Transfusion Reactions (AHTR)
- ABO incompatibility resulting in intravascular hemolysis secondary to complement activation
- Most commonly due to incorrect patient identification
- Occurs immediately after transfusion
- Risk per unit of blood is <1 in 40,000
- Presents with fever, chills, hypotension, back or flank pain, dyspnea, hemoglobinuria
- Acute renal failure (<24 h) and DIC
- Treatment:
  - Stop transfusion
  - Notify blood bank and check for clerical error
  - Maintain BP with vigorous IV fluids ± inotropes
  - Maintain urine output with diuretics, crystalloids, dopamine

Febrile Nonhemolytic Transfusion Reactions (FNHTR)
- Due to alloantibodies to WBC, platelets or other donor plasma antigens and release of cytokines from blood product cells
- Occurs within 0-6 h of transfusion
- Risk per unit of blood is 1 in 100 (minor), 1 in 10,000 to 40,000 (severe)
- Presents with fever ± rigors, facial flushing, headache, myalgia, hypotension
- Treatment:
  - Rule out hemolytic reaction or infection
  - If temperature <38°C, continue with transfusion but decrease rate and give antipyretics
  - If temperature >38°C, stop transfusion, give antipyretics and anti-histamine

Allergic Nonhemolytic Transfusion Reactions
- Alloantibodies (IgE) to proteins in donor plasma result in mast cell activation and release of histamine
- Occurs mainly in those with history of multiple transfusions or multiparous women
- Risk per unit of blood is 1 in 100
- Presents mainly as urticaria and occasionally with fever
- Can present as anaphylactoid reaction with bronchospasm, laryngeal edema and hypotension, but this occurs mainly in IgA deficient patients that have anti-IgA antibodies
- Treatment:
  - Mild: slow transfusion rate and give diphenhydramine
  - Moderate to severe: stop transfusion, give IV diphenhydramine, steroids, epinephrine, IV fluids and bronchodilators

Transfusion-Related Acute Lung Injury (TRALI)
- New-onset acute lung injury that occurs during transfusion or within 6 h of transfusion completion
  - Insidious, acute onset of pulmonary insufficiency
  - Profound hypoxemia (PaO₂/FiO₂ <300 mmHg)
  - Bilateral pulmonary edema on CXR
  - Pulmonary artery wedge pressure <18 mmHg
  - No clinical evidence of left atrial hypertension
- Pathogenesis uncertain; perhaps due to binding of donor antibodies to WBC of recipient and release of mediators that increase capillary permeability in the lungs
- Typically occurs 2-4 h post transfusion and resolves in 24-72 h
- Risk per unit of blood is 1:10,000
- Is currently the leading cause of transfusion-related morbidity and mortality
- Treatment: supportive therapy (oxygen)
- Inform blood bank; patient and donor testing will be arranged

DDx of Post-Transfusion Fever:
- Acute hemolytic transfusion reaction
- Febrile non-hemolytic transfusion reaction
- Bacterial contamination
- Allergy

DDx of Post-Transfusion Dyspnea:
- Circulatory overload (TACO)
- Transfusion-related acute lung injury (TRALI)
- Allergy (bronchospasm/anaphylaxis)
NONIMMUNE

Bacterial Infection
• Gram positive: S. aureus, S. epidermidis, Bacillus cereus
• Gram negative: Klebsiella, Serratia, Pseudomonas, Yersinia
• overall risk is 1 in 100,000 for RBC and 1 in 10,000 for platelets
• never store blood >4 h after bag has left blood bank
• treatment: stop transfusion, blood cultures, IV antibiotics, fluids

Transfusion Associated Circulatory Overload (TACO)
• due to impaired cardiac function and/or excessive rapid transfusion
• presents as dyspnea, orthopnea, hypotension, tachycardia, crackles at base of lung and increased venous pressure
• incidence is 1 in 700
• treatment: transfuse at lower rate, give diuretics and oxygen

Hyperkalemia
• due to K+ release from stored RBC
• risk increases with storage time and if blood is irradiated
• decreased risk if given fresh blood
• occurs in 5% of massively transfused patients
• treatment: see Nephrology, NP13

Citrate Toxicity
• occurs with massive transfusion in patients with liver disease – patients are unable to clear citrate from blood
• citrate binds to Ca2+ and causes signs and symptoms of hypocalcemia
• treatment: IV calcium gluconate (10 mL of 10%) for every 2 units of blood

Dilutional Coagulopathy
• occurs with massive transfusion (>10 units)
• pRBC contains no clotting factors, fibrinogen, cryoprecipitate or platelets
• treatment: FP, platelets and cryoprecipitate

Delayed Blood Transfusion Reactions

IMMUNE

Delayed Hemolytic
• due to alloantibodies to minor antigens such as Rh, Kell, Duffy, and Kidd
• level of antibody at time of transfusion is too low to cause hemolysis; later the level of antibody increases due to secondary stimulus and causes extravascular hemolysis
• occurs 5-7 d after transfusion
• presents as anemia and mild jaundice
• treatment: no specific treatment required; important to note for future transfusion

Transfusion-Associated Graft Versus Host Disease (GVHD)
• transfused T-lymphocytes recognize and react against “host” (recipient)
• occurs 4-30 d following transfusion
• most patients already have severely impaired immune systems (e.g. Hodgkin lymphoma or leukemia)
• presents as fever, diarrhea, liver function abnormalities and pancytopenia
• can be prevented by giving irradiated blood products

NONIMMUNE

Iron Overload
• due to repeated transfusions over long period of time (e.g. β-thalassemia major)
• can cause secondary hemochromatosis
• treatment: iron chelators or phlebotomy if not longer requiring blood transfusion and not anemic

Viral Infection Risk
• HBV <1 in 153,000
• Human T-lymphotropic virus (HTLV) <1 in 4,300,000
• HCV <1 in 2,300,000
• HIV <1 in 7,000,000
• other infections include EBV, CMV, WNV (West Nile virus)
Antiplatelet Therapy

• see Figure 12a, Platelet Activation Cascade, H24

Table 38. Antiplatelet Therapy

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Dose/Route of Administration</th>
<th>Onset/Peak/Duration</th>
<th>Specific Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin® (ASA)</td>
<td>Irreversibly acetylates COX, inhibiting TXA2 synthesis, thus inhibiting platelet aggregation</td>
<td>Single loading 200-300 mg PO, followed by dose of 75-100 mg PO daily</td>
<td>Onset: 5-30 min Peak: 0.25-3 h Duration: 3-6 h</td>
<td>GI ulcer/bleeding Tinnitus Bronchospasm Angioedema Reye's syndrome in pediatric patients</td>
</tr>
<tr>
<td>Aggrenox® (ASA + dipyridamole)</td>
<td>1 capsule PO bid Peak: 75 min</td>
<td></td>
<td>Headache Dyspepsia Nausea/vomiting Abdominal pain Cardiac failure Hemorrhoids</td>
<td>More effective than ASA in secondary prevention of stroke Dipyridamole potentiates antiplatelet action of ASA</td>
</tr>
<tr>
<td>Clopidogrel (Plavix®)</td>
<td>Inhibit ADP binding to platelets, thus decreased platelet aggregation 75-300 mg PO daily</td>
<td>Onset: 2 h Peak: 1 h</td>
<td>URI Chest pain Headache Flu-like syndrome Depression URTI GI hemorrhage Pancytopenia May cause TTP</td>
<td>Prevention of cardiovascular events in high-risk patients CYP2C19 poor metabolizers have diminished response to clopidogrel Caution with hepatic/renal impairment</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitors [Reopro® (abciximab), Integrelin® (epti)]</td>
<td>Blocking GP IIb/IIIa receptor inhibits fibrinogen and vWF binding, leading to decreased platelet aggregation</td>
<td>Variable IV</td>
<td>Variable</td>
<td>Hypotension Back pain Nausea/vomiting Chest pain Abdo pain Thrombocytopenia</td>
</tr>
</tbody>
</table>
Anticoagulant Therapy

Table 39. Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Dose/Route of Administration</th>
<th>Onset/Peak/Duration</th>
<th>Reversing Agent</th>
<th>Monitoring</th>
<th>Specific Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>Accelerates activity of antithrombin</td>
<td>As per hospital nomogram</td>
<td>Onset: 20-60 min Peak: 2-4 h</td>
<td>Protamine sulphate</td>
<td>aPTT (intrinsic pathway), UFH (anti-Xa) levels</td>
<td>Hemorrhage HIT Increased liver enzymes</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Vitamin K antagonist: inhibits production of II, VII, IX, X, proteins C and S</td>
<td>Individualized dosing by monitoring PT/INR PO</td>
<td>Onset: 36-48 h Peak: 1.5-3 d</td>
<td>IV vitamin K PCC FFP</td>
<td>PT/INR maintain 2-3 (2.5-3.5 for mechanical values)</td>
<td>Hemorrhage Fever Cholesterol embolism syndrome Intracranial hemorrhage</td>
</tr>
<tr>
<td>LMWH (enoxaparin, dalteparin, tinzaparin)</td>
<td>Inhibits FXa</td>
<td>Variable SC/IV</td>
<td>Onset: 3-5 h Peak: 3-5 h Duration: 12 h</td>
<td>Partial reversibility with protamine sulphate</td>
<td>FXa in pediatrics, pregnancy and weight &gt;150 kg</td>
<td>Hemorrhage Fever Increased liver enzymes &lt;1% HIT</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Selective inhibitor of FXa</td>
<td>Variable SC daily</td>
<td>Onset: 2 h Peak: 2-3 h</td>
<td>Not reversible</td>
<td>None</td>
<td>Anemia Fever Nausea Rash</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Anti-FXa</td>
<td>PO</td>
<td>Peak: 2-4 h</td>
<td>Not reversible</td>
<td>None</td>
<td>Syncope GI hemorrhage</td>
</tr>
<tr>
<td>Argatroban</td>
<td>Direct thrombin inhibitor</td>
<td>Variable IV</td>
<td>Onset: 5-10 min Duration: 20-40 min</td>
<td>Not reversible</td>
<td>aPTT</td>
<td>Dyspnea Hypotension Fever</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibitor</td>
<td>150 mg PO bid</td>
<td>Peak: 1 h</td>
<td>Not reversible</td>
<td>None (prolonged aPTT can suggest residual drug on board)</td>
<td>GI upset Dyspepsia</td>
</tr>
</tbody>
</table>

Adverse Reactions of Heparin

- Hemorrhage: depends on dose, age, and concomitant use of antiplatelet agents or thrombolytics
- Heparin-induced thrombocytopenia: associated with venous or arterial thrombosis (see Table 22, H27)
- Osteoporosis: with long term use

Low Molecular Weight Heparin (enoxaparin, dalteparin, tinzaparin)

- Increased bioavailability compared to normal heparin
- Increased duration of action
- SC route of administration
- Do not need to monitor aPTT
- Adverse reactions less common than UFH
- Patients with renal failure (CrCl <30) can accumulate LMWH, therefore must adjust dose
- Only partially reversible with protamine sulphate

Table 40. Recommended Therapeutic INR Ranges of Common Indications for Oral Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>INR Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis of venous thrombosis (high-risk surgery)</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Treatment of venous thrombosis</td>
<td></td>
</tr>
<tr>
<td>Most cases of thrombosis with antiphospholipid antibody syndrome</td>
<td></td>
</tr>
<tr>
<td>Treatment of pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>Prevention of systemic embolism</td>
<td></td>
</tr>
<tr>
<td>Tissue heart valves</td>
<td></td>
</tr>
<tr>
<td>AMI (to prevent systemic embolism)</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Bileaflet mechanical valve in aortic position</td>
<td></td>
</tr>
<tr>
<td>Mechanical prosthetic mitral valves (high risk)</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>Prophylaxis of recurrent myocardial infarction</td>
<td></td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction
### Table 41. Recommended Management of a Supratherapeutic INR

<table>
<thead>
<tr>
<th>INR</th>
<th>Bleeding Present</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;Therapeutic to 4.5</td>
<td>No</td>
<td>Lower warfarin dose, OR&lt;br&gt;Omit a dose and resume warfarin at a lower dose when INR is in therapeutic range, OR&lt;br&gt;No dose reduction needed if INR is minimally prolonged</td>
</tr>
<tr>
<td>&gt;4.5 to 10.0</td>
<td>No</td>
<td>Omit the next 1 to 2 doses of warfarin, monitor INR more frequently and resume treatment at a lower dose when INR is in therapeutic range, OR&lt;br&gt;Omit a dose and administer 1 to 2.5 mg oral vit K in patients with increased risk of bleeding</td>
</tr>
<tr>
<td>&gt;10.0</td>
<td>No</td>
<td>Hold warfarin and administer 5 to 10 mg oral vit K. Monitor INR more frequently and administer more vit K as needed. Resume warfarin at a lower dose when INR is in therapeutic range</td>
</tr>
<tr>
<td>Any</td>
<td>Serious or life threatening</td>
<td>Hold warfarin and administer 10 mg vit K by slow IV infusion; supplement with four-factor prothrombin complex concentrate. Monitor and repeat as needed</td>
</tr>
</tbody>
</table>


### Chemotherapeutic and Biologic Agents Used in Oncology

#### Table 42. Selected Chemotherapeutic and Biologic Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Mechanism of Action or Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating Agent</td>
<td>chlorambucil, cyclophosphamide, melphalan (nitrogen mustards), carboplatin, cisplatin, dacarbazine, procarbazine, busulfan</td>
<td>Damage DNA via alkylation of base pairs&lt;br&gt;Leads to cross-linking of bases, abnormal base-pairing, DNA breakage</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>methotrexate (folic acid antagonist), 6-mercaptopurine, fludarabine (purine antagonist), 5-fluorouracil (5-FU) (pyrimidine antagonist), hydroxyurea, cytarabine</td>
<td>Inhibit DNA synthesis</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>adriamycin (anthracycline), bleomycin, mitomycin C, daunorubicin</td>
<td>Interfere with DNA and RNA synthesis</td>
</tr>
<tr>
<td>Taxanes</td>
<td>paclitaxel, docetaxel</td>
<td>Stabilize microtubules against breakdown once cell division complete</td>
</tr>
<tr>
<td>Vinca-alkaloids</td>
<td>vinblastine, vincristine, vinorelbine</td>
<td>Inhibit microtubule assembly (mitotic spindles), blocking cell division</td>
</tr>
<tr>
<td>Topoisomerase Inhibitors</td>
<td>irinotecan, topotecan (topo I), etoposide (topo II)</td>
<td>Interfere with DNA unwinding necessary for normal replication and transcription</td>
</tr>
<tr>
<td>Steroids</td>
<td>prednisone, dexamethasone</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Monoclonal Antibodies</td>
<td>trastuzumab (Herceptin&lt;sup&gt;®&lt;/sup&gt;), bevacizumab (Avastin&lt;sup&gt;®&lt;/sup&gt;), rituximab (Rituxan&lt;sup&gt;®&lt;/sup&gt;), cetuximab (Erbitux&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>HER2&lt;br&gt;VEGF&lt;br&gt;CD20&lt;br&gt;EGFR</td>
</tr>
<tr>
<td>Small Molecule Inhibitors</td>
<td>imatinib mesylate (Gleevec&lt;sup&gt;®&lt;/sup&gt;), dasatinib, nilotinib, erlotinib (Tarceva&lt;sup&gt;®&lt;/sup&gt;), gefitinib (Iressa&lt;sup&gt;®&lt;/sup&gt;), bortezomib (Velcade&lt;sup&gt;®&lt;/sup&gt;), sunitinib (Sutent&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Bcr-Abl&lt;br&gt;Bcr-Abl&lt;br&gt;Bcr-Abl&lt;br&gt;EGFR&lt;br&gt;EGFR&lt;br&gt;26S proteasome&lt;br&gt;VEGFR, PDGFR</td>
</tr>
<tr>
<td>Trial</td>
<td>Reference</td>
<td>Results</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>AZA-001</td>
<td><em>Lancet Oncol</em> 2009; 10:223-32</td>
<td>Azacitidine increases overall survival in higher-risk myelodysplastic syndrome than conventional care</td>
</tr>
<tr>
<td>CHOP</td>
<td><em>NEJM</em> 1993; 328:1002-6</td>
<td>In NHL, CHOP has lowest incidence of fatal toxic reactions and shows no significant difference from 3 other regimens in response or disease-free/overall survival. CHOP is the standard for advanced NHL</td>
</tr>
<tr>
<td>CLL8</td>
<td><em>Lancet</em> 2010; 378:1164-74</td>
<td>Rituximab plus fludarabine and cyclophosphamide (FCR) improves progression-free survival and overall survival compared with fludarabine and cyclophosphamide alone (FC) in the treatment of CLL</td>
</tr>
<tr>
<td>CLOT</td>
<td><em>NEJM</em> 2003; 349:146-53</td>
<td>In patients with cancer and acute venous thromboembolism, LWMH was more effective than warfarin in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding</td>
</tr>
<tr>
<td>CML: Imatinib vs. IFN + Cytarabine</td>
<td><em>NEJM</em> 2003; 349:994-1004</td>
<td>In patients with chronic-phase CML, imatinib was more effective than IFNα + cytarabine in inducing cytogenetic response and freedom from progression to accelerated phase/blast crisis</td>
</tr>
<tr>
<td>Dabigatran versus warfarin in VTE</td>
<td><em>NEJM</em> 2009; 361:2342-52</td>
<td>In the treatment of venous thromboembolism, dabigatran is as effective as warfarin and also has a similar safety profile. Note: many problems in the trial, making it less pivotal in having drug approval</td>
</tr>
<tr>
<td>Dose of platelet transfusion</td>
<td><em>NEJM</em> 2010; 362:600-13</td>
<td>Low dose prophylactic platelet transfusion decreases total number of platelets transfused but increases number of transfusions but not incidence of bleeding in patients with hypoproliferative thrombocytopenia</td>
</tr>
<tr>
<td>ESPIRIT</td>
<td><em>Lancet</em> 2006; 367:1665-73</td>
<td>ASA plus dipyridamole is recommended over ASA alone as antithrombotic therapy after cerebral ischemia of arterial origin</td>
</tr>
<tr>
<td>Hodgkin Lymphoma: ABVD vs. MOPOP</td>
<td><em>NEJM</em> 1992; 327:1478-84</td>
<td>In Hodgkin lymphoma, ABVD regimen has equal failure-free and overall survival to MOPOP + ABVD, but less myelotoxicity. ABVD is standard chemotherapy for Hodgkin lymphoma</td>
</tr>
<tr>
<td>ITP: Dexamethasone</td>
<td><em>NEJM</em> 2003; 349:831-6</td>
<td>A four-day course of high-dose dexamethasone is effective initial therapy for adults with immune thrombocytopenic purpura</td>
</tr>
<tr>
<td>MInT Group</td>
<td><em>Lancet Oncol</em> 2011; 12:1013-1022</td>
<td>Rituximab added to CHOP-like chemotherapy improved long-term outcomes for young patients with good-prognosis DLBCL</td>
</tr>
<tr>
<td>MSH</td>
<td><em>NEJM</em> 1995; 332:1317-22</td>
<td>Hydroxyurea is effective in reduction of complications and clinical manifestations of sickle cell disease</td>
</tr>
<tr>
<td>Platelet transfusion threshold</td>
<td><em>NEJM</em> 1997; 337:1870-5</td>
<td>The risk of major bleeding in patients with AML undergoing induction chemotherapy was similar whether the platelet-transfusion threshold was set at 20 or 10. Use of the lower threshold reduced platelet usage by 21.5 percent</td>
</tr>
<tr>
<td>PT1</td>
<td><em>NEJM</em> 2005; 353:85-6</td>
<td>Hydroxyurea plus low-dose ASA is superior to anagrelide plus low-dose ASA for patients with essential thrombocythema at high risk for vascular events</td>
</tr>
<tr>
<td>R-CHOP</td>
<td><em>NEJM</em> 2002; 346:235-42</td>
<td>Addition of rituximab to CHOP increases complete response rate and prolongs event-free survival and overall survival in elderly with DLBCL</td>
</tr>
<tr>
<td>Therapeutic platelet transfusion</td>
<td><em>Lancet</em> 2012; 380:1309-16</td>
<td>Therapeutic platelet transfusions (when bleeding occurs) may be used if severe bleeding can be identified early in autologous stem-cell transplant patients. Prophylactic transfusion (when platelets &lt;10) should remain standard of care in AML patients</td>
</tr>
<tr>
<td>TRICC</td>
<td><em>NEJM</em> 1999; 340:409-17</td>
<td>A restrictive strategy of red-cell transfusion (when Hb &lt;70) is at least as effective as and possibly superior to a liberal transfusion strategy (when Hb &lt;100) in ICU patients; one possible exception is patients with an acute MI or unstable angina</td>
</tr>
<tr>
<td>VISTA</td>
<td><em>JCO</em> 2010; 28:2259-66</td>
<td>Bortezomib plus melphalan and prednisone (MPV) is superior to melphalan and prednisone (MP) in overall survival of non-transplant-eligible multiple myeloma patients</td>
</tr>
</tbody>
</table>
### Acronyms

- Candida albicans
- Aspergillus spp.
- Parasitic Infections
  - Protozoa – Intestinal/Genitourinary Infections
    - Entamoeba histolytica (Amoebas)
    - Giardia lamblia
    - Trichomonas vaginalis
    - Cryptosporidium spp.
- Blood and Tissue Infections
  - Plasmodium spp. (malaria)
  - Trypanosoma cruzi
  - Toxoplasma gondii
- Helminths
  - Roundworms – Nematodes
  - Flatworms
  - Cestodes/Trematodes
  - Trematodes/Flukes
  - Schistosoma spp.
  - Ectoparasites
- Travel Medicine
  - Fever in the Returned Traveller
- Fever of Unknown Origin (FUO)
- Infections in the Immunocompromised Host
  - Febrile Neutropenia (FN)
  - Infections in Solid Organ Transplant Recipients
  - Immune Reconstitution Syndrome (IRS)
- HIV and AIDS
  - Epidemiology
  - Definition and Pathophysiology
  - Modes of Transmission
  - Natural History
  - Laboratory Diagnosis
  - Management of the HIV-Positive Patient
  - Highly Active Antiretroviral Treatment (HAART)
  - Prevention of HIV Infection
  - Types of Testing
  - HIV Pre- and Post-test Counselling
- A Simplified Look at Antibiotics
- Antimicrobials
- Antibiotics
- Antivirals
- Antifungals
- Antiparasitics
- Quick Reference: Common Infections and their Antibiotic Management
- References

### Principles of Microbiology

- Bacteriology
- Virology
- Mycology
- Parasitology
- Transmission of Infectious Diseases
- Prevention of Infectious Diseases

### Nosocomial Infections

- Respiratory Infections
  - Pneumonia
  - Influenza
- Skin and Soft Tissue Infections
  - Cellulitis
  - Necrotizing Fasciitis
- Gastrointestinal Infections
  - Acute Diarrhea
  - Traveller’s Diarrhea
  - Chronic Diarrhea
  - Peptic Ulcer Disease (H. pylori)
- Bone and Joint Infections
  - Septic Arthritis
  - Diabetic Foot Infections
  - Osteomyelitis
- Cardiac Infections
  - Infective Endocarditis (IE)
- Neurological Infections
  - Meningitis
  - Encephalitis
  - Generalized Tetanus
  - Rabies
- Systemic Infections
  - Sepsis and Septic Shock
  - Tuberculosis (TB)
  - Leprosy (Hansen’s Disease)
  - Syphilis
  - Lyme Disease
  - Toxic Shock Syndrome (TSS)
  - Cat Scratch Disease
  - Rocky Mountain Spotted Fever
  - West Nile Virus
- Fungal Infections
  - Skin and Subcutaneous Infections
  - Superficial Fungal Infections
  - Dermatophytes
  - Subcutaneous Fungal Infection
  - Endemic Mycoses
  - Opportunistic Fungi
  - Pneumocystis jiroveci (formerly P. carinii)
  - Cryptococcus spp.
**Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFB</td>
<td>acid-fast bacilli</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>ANC</td>
<td>absolute neutrophil count</td>
</tr>
<tr>
<td>AOM</td>
<td>acute otitis media</td>
</tr>
<tr>
<td>APN</td>
<td>anti-penicillin</td>
</tr>
<tr>
<td>BAL</td>
<td>bronchoalveolar lavage</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacillus Calmette-Guérin</td>
</tr>
<tr>
<td>CMG</td>
<td>culture and sensitivity</td>
</tr>
<tr>
<td>CFU</td>
<td>colony forming units</td>
</tr>
<tr>
<td>CNV</td>
<td>cytomegalovirus</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CXR</td>
<td>chest X-ray</td>
</tr>
<tr>
<td>EET</td>
<td>Ehrlichia tick-borne encephalitis</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>ECT</td>
<td>electron transport chain</td>
</tr>
<tr>
<td>DVT</td>
<td>deep vein thrombosis</td>
</tr>
<tr>
<td>EGB</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>EIE</td>
<td>enteroinvasive E. coli</td>
</tr>
<tr>
<td>EHEC</td>
<td>enterohemorrhagic E. coli</td>
</tr>
<tr>
<td>EHE</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>EIG</td>
<td>enterotoxigenic E. coli</td>
</tr>
<tr>
<td>EIE</td>
<td>enteroinvasive E. coli</td>
</tr>
<tr>
<td>EHEC</td>
<td>enterohemorrhagic E. coli</td>
</tr>
<tr>
<td>EHE</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>EIG</td>
<td>enterotoxigenic E. coli</td>
</tr>
<tr>
<td>EIE</td>
<td>enteroinvasive E. coli</td>
</tr>
<tr>
<td>EHEC</td>
<td>enterohemorrhagic E. coli</td>
</tr>
<tr>
<td>EHE</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>EIG</td>
<td>enterotoxigenic E. coli</td>
</tr>
<tr>
<td>EIE</td>
<td>enteroinvasive E. coli</td>
</tr>
<tr>
<td>EHEC</td>
<td>enterohemorrhagic E. coli</td>
</tr>
<tr>
<td>EHE</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>EIG</td>
<td>enterotoxigenic E. coli</td>
</tr>
<tr>
<td>EIE</td>
<td>enteroinvasive E. coli</td>
</tr>
<tr>
<td>EHEC</td>
<td>enterohemorrhagic E. coli</td>
</tr>
<tr>
<td>EHE</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>EIG</td>
<td>enterotoxigenic E. coli</td>
</tr>
<tr>
<td>EIE</td>
<td>enteroinvasive E. coli</td>
</tr>
<tr>
<td>EHEC</td>
<td>enterohemorrhagic E. coli</td>
</tr>
</tbody>
</table>

**Principles of Microbiology**

**Bacteriology**

- **Bacteria Basics**
  - Bacteria are prokaryotic cells that divide asexually by binary fission
  - Chromosomal or plasmid DNA may be shared between bacteria through **conjugation** or **transduction**
  - Gram stain divides most bacteria into two groups based on cell wall
    - **Gram positive** (GP): thick, rigid layer of peptidoglycan
    - **Gram negative** (GN): thin peptidoglycan layer + thicker outer membrane composed of lipopolysaccharides
  - Clinical significance: GN thick outer membrane makes it resistant to penicillin's attack
  - Acid-fast bacilli: "acid-fast" due to high mycolic acid content in cell wall, e.g. *Mycobacteria, Nocardia*
  - "Atypical" bacteria: not seen on Gram stain and difficult to culture
    - Obligate intracellular bacteria: e.g. *Chlamydia*
    - Bacteria lacking cell wall: e.g. *Mycoplasma*
    - Spirochetes: e.g. *Treponema pallidum*
  - O2 can be either vital or detrimental to growth
    - Obligate aerobes: require O2
    - Obligate anaerobes: require environment without O2
    - Facultative anaerobes: can survive in environments with or without O2

**Mechanisms of Bacterial Disease**

1. Adherence to and colonization of skin or mucous membranes
   - E.g. fimbriae (pili): microfilaments extending through the cell wall – like burrs sticking to your clothes, they attach to epithelial cells e.g. *E. coli* in the urinary tract
2. Invasion or crossing normal epithelial barriers
3. Evasion of host defense system through inhibition of:
   - Phagocytic uptake: polysaccharide capsule (*S. pneumoniae, N. meningitidis, H. influenzae*) or surface proteins (*Staphylococcus, Streptococcus*)
4. Toxin production
   - Exotoxins are secreted by living pathogenic bacteria and cause disease even if the bacteria is not present (e.g. *Clostridium*)
   - Endotoxins are structural components of GN bacterial cell wall, and may be shed by live cells or released during cell lysis
5. Intracellular growth
   - Obligate intracellular: *Rickettsia* and *Chlamydia*
   - Facultative intracellular: *Salmonella, Neisseria, Brucella, Mycobacteria, Listeria, Legionella*
6. Biofilm
   - An extracellular polysaccharide network forming mesh around the bacteria (e.g. *S. epidermidis*) which can coat prosthetic devices like IV catheters

**Figure 1. Bacteria morphology**

Gram positive bacteria have thick peptidoglycan layers.
### Table 1. Common Bacteria

<table>
<thead>
<tr>
<th>Gram-positive Bacteria</th>
<th>Gram-negative Bacteria</th>
<th>Not Seen on Gram Stain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>Bacillus</td>
<td>Neisseria</td>
</tr>
<tr>
<td>S. aureus</td>
<td>B. anthracis</td>
<td>N. meningitidis</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>Listeria</td>
<td>N. gonorrhoaeae</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>N. mutans (modified acid fast positive)</td>
<td>Moraxella</td>
</tr>
<tr>
<td>S. pyogenes (GAS)</td>
<td></td>
<td>M. catarrhalis</td>
</tr>
<tr>
<td>S. agalactiae (GBS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. faecalis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anaerobes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptostreptococcus</td>
<td>Clostridium</td>
<td>Bacteroides</td>
</tr>
<tr>
<td>C. difficile, C tetani, C. botulinum, C perforingens</td>
<td></td>
<td>B. fragilis</td>
</tr>
<tr>
<td><strong>Acid Fast</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>M. tuberculosis</td>
<td></td>
</tr>
<tr>
<td>M. leprae</td>
<td>M. avium complex</td>
<td></td>
</tr>
<tr>
<td>M. bovis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obligate intracellular</td>
<td>Rickettsia</td>
<td></td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Chlamydia trachomatis</td>
<td></td>
</tr>
<tr>
<td>Coxiella burnetii</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Commensal Flora

<table>
<thead>
<tr>
<th>Site</th>
<th>Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Coagulase-negative staphylococci, Corynebacteria, Propionibacterium acnes, Bacillus, S. aureus</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>Viridans group streptococci, Haemophilus, Neisseria, anaerobes (Peptostreptococcus, Bacteroides, Veillonella, Fusobacterium, Actinomyces, Prevotella)</td>
</tr>
<tr>
<td>Small bowel</td>
<td>E. coli, anaerobes (low numbers)</td>
</tr>
<tr>
<td>Colon</td>
<td>E. coli, Klebsiella, Enterobacter, Enterococcus, anaerobes (Bacteroides, Peptostreptococcus, Clostridium)</td>
</tr>
<tr>
<td>Vagina</td>
<td>Lactobacillus acidophilus, Viridans group streptococci, coagulase-negative staphylococci, facultative GN bacilli, anaerobes</td>
</tr>
</tbody>
</table>

### Figure 2. Laboratory identification of bacterial species
Virology

Viral Basics
- Viruses are infectious particles consisting of RNA or DNA covered by a protein coat
  - Infect cells and use host metabolic machinery to replicate
  - Nucleic acid can be double stranded (ds) or single stranded (ss)
  - Can be enveloped or naked
- Virions are mature virus particles that can be released into the extracellular environment
- Host susceptibility is governed by the host cell and virus surface proteins (viral tropism) and cellular immunity

Viral Disease Patterns
1. Acute infections (e.g. adenovirus)
   - Host cells are lysed in the process of virion release
   - Some produce acute infections with late sequelae (e.g. measles virus → subacute sclerosing panencephalitis)
2. Chronic infections (>6 mo): (e.g. HBV, HIV)
   - Host cell machinery is used to produce and chronically release virions
3. Latent infections
   - Viral genome remains latent in host cell nucleus
   - Can reactivate (e.g. HSV, VZV)

Table 3. Common Viruses

<table>
<thead>
<tr>
<th>Nucleic Acid</th>
<th>Enveloped</th>
<th>Virus Family</th>
<th>Major Viruses</th>
<th>Medical Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>dsDNA</td>
<td>N</td>
<td>Adenoviridae</td>
<td>Adenovirus URTI</td>
<td>Conjunctivitis, Gastroenteritis</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Papillomaviridae</td>
<td>HPV1,4 Plantar warts, HPV6,11 Genital warts, HPV16,18, etc. Cervical/anal dysplasia and cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Herpesviridae</td>
<td>HHV1=HSV1 Oral, ocular and genital herpes; encephalitis, HHV2=HSV2 Genital, oral and ocular herpes; encephalitis, HHV3=VZV Chicken pox, shingles, HHV4=EBV Mononucleosis, viral hepatitis, HHV5=CMV Retinitis, pneumonitis, hepatitis, encephalitis, HHV6* Roseola, HHV8=KSHV Kaposi’s sarcoma, multicentric Castleman’s disease, body cavity lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Polyomaviridae</td>
<td>JC virus</td>
<td>Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Hepadnaviridae</td>
<td>Hepatitis B</td>
<td>Hepatitis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Poxviridae</td>
<td>Variola</td>
<td>Smallpox</td>
</tr>
<tr>
<td>ssDNA</td>
<td>N</td>
<td>Paroviridae</td>
<td>Parovirus B19</td>
<td>Erythema infectiosum (Fifth disease)</td>
</tr>
<tr>
<td>(+)ssRNA</td>
<td>N</td>
<td>Caliciviridae</td>
<td>Norwalk</td>
<td>Gastroenteritis</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Picornaviridae</td>
<td>Poliovirus</td>
<td>Poliomyelitis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Coronaviridae</td>
<td>Coronavirus</td>
<td>URTIs, SARS</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Flaviviridae</td>
<td>Yellow Fever</td>
<td>Yellow fever</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Togaviridae</td>
<td>Rubella</td>
<td>Rubella (German measles)</td>
</tr>
<tr>
<td>(+)ssRNA-RT</td>
<td>Y</td>
<td>Retroviridae</td>
<td>HIV</td>
<td>AIDS</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Arenaviridae</td>
<td>Lassa Fever</td>
<td>Lassa fever</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Filoviridae</td>
<td>Ebola, Marburg</td>
<td>Hemorrhagic fever</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Orthomyxoviridae</td>
<td>Influenza A, B, C</td>
<td>Influenza</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Paramyxoviridae</td>
<td>Measles</td>
<td>Measles</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Paramyxoviridae</td>
<td>Mumps</td>
<td>Mumps</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Paramyxoviridae</td>
<td>Parainfluenza</td>
<td>RSV</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Rhabdoviridae</td>
<td>Rabies</td>
<td>Rabies</td>
</tr>
<tr>
<td>dsRNA</td>
<td>N</td>
<td>Reoviridae</td>
<td>Rotavirus</td>
<td>Gastroenteritis</td>
</tr>
</tbody>
</table>

Note: __viridae = family, __virus = genus, # = species (e.g. Retroviridae-HIV-2)
*Rosalovirus, Herpes lymphotropic virus
Mycology

Fungal Basics
- fungi are eukaryotic organisms
  1. yeast (unicellular)
  2. molds (also known as filamentous fungi) (multicellular with hyphae)
  3. dimorphic fungi (found as mold at room temperature but grow as yeast-like forms at body temperature)

<table>
<thead>
<tr>
<th>Table 4.</th>
<th>Membrane Sterol</th>
<th>Cell wall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>–</td>
<td>Peptidoglycan</td>
</tr>
<tr>
<td>Human Cell</td>
<td>Cholesterol</td>
<td>–</td>
</tr>
<tr>
<td>Fungi</td>
<td>Ergosterol</td>
<td>Chitin (complex glycopoly saccharide)</td>
</tr>
</tbody>
</table>

Mechanisms of Fungal Disease
- primary fungal infection by:
  - overgrowth of normal flora (e.g. Candida species)
  - inhalation of fungal spores
  - traumatic inoculation into skin
- toxins produced by fungi (e.g. ingestion aflatoxins)
- allergic reaction to fungi (e.g. bronchopulmonary aspergillosis)

Parasitology

Parasite Basics
- parasite: an organism that lives in or on another organism (host) and damages the host in the process
- parasites with complex life cycle requires more than one host to reproduce
  - reservoir host: maintains a parasite and may be the source for human infection
  - intermediate host: maintains the asexual stage of a parasite or allows development of the parasite to proceed to the larval stage
  - definitive host: allows the parasite to develop to the adult stage where reproduction occurs
- 2 major groups of parasites: protozoa and helminths
- see Tables 21 and 22 for examples of clinically important parasites

<table>
<thead>
<tr>
<th>Table 5. Differences Between Protozoa and Helminths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protozoa</td>
</tr>
<tr>
<td>Unicellular</td>
</tr>
<tr>
<td>Motile trophozoite \ inactive cyst</td>
</tr>
<tr>
<td>Multiplication</td>
</tr>
<tr>
<td>± Eosinophilia</td>
</tr>
<tr>
<td>Indefinite life span</td>
</tr>
</tbody>
</table>

*Adult ascaris (roundworm) does not cause eosinophilia

Characteristics of Parasitic Disease
- spectrum of disease ranging from asymptomatic to severe illness
- symptoms are usually proportional to parasite burden
- tissue damage is due to the parasite and host immune response
- chronic infections may occur with or without overt disease
- immunocompromised hosts are more susceptible to manifestations of infection, reactivation of latent infections, and more severe disease
- eosinophilia may suggest a parasitic infection

Mechanisms of Parasitic Disease
1. mechanical obstruction (e.g. ascariasis, clonorchiasis)
2. competition with host for resources (e.g. anemia in hookworm disease, vitamin B₁₂ deficiency in diphyllolothriasis)
3. cytotoxicity leading to abscesses and ulcers (e.g. amoebiasis, leishmaniasis)
4. inflammatory
   - acute hypersensitivity (e.g. pneumonitis in Loeffler’s syndrome)
   - delayed hypersensitivity (e.g. egg granulomas in schistosomiasis)
   - cytokine-mediated (systemic illness of malaria, disseminated strongyloidiasis)
5. immune-mediated injury
   - autoimmune (e.g. myocarditis of Chagas disease, tissue destruction of mucocutaneous leishmaniasis)
   - immune complex (e.g. nephritis of malaria, schistosomiasis)
Transmission of Infectious Diseases

Table 6. Mechanism of Transmission

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Mode of Transmission</th>
<th>Examples</th>
<th>Preventative Measure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact</td>
<td>Direct physical contact, or indirect contact with a fomite.</td>
<td>Person-to-person (MRSA) Sexual (N. gonorrhoeae, C. trachomatis, HSV, HIV) Blood-borne (HIV, HBV, HCV)</td>
<td>For patients in health care facilities: Contact precautions (see Prevention of Infectious Diseases below) Barren precautions Safe needlestick/sharp practices</td>
</tr>
<tr>
<td>Droplet/Contact</td>
<td>Respiratory droplets (&gt;5 µm) can be projected short distances (&lt;2 m) and deposit on mucosal surfaces of the recipient (e.g. by coughing, sneezing, or talking); transmission can also occur by direct physical contact of respiratory fluids or indirect contact with a fomite contaminated with respiratory fluids</td>
<td>Influenza, mumps N. meningitidis, Bordetella pertussis</td>
<td>For patients in health care facilities: Contact/droplet precautions (see Prevention of Infectious Diseases below)</td>
</tr>
<tr>
<td>Airborne</td>
<td>Airborne droplet nuclei (&lt;5 µm) remain infectious over time and distance.</td>
<td>M. tuberculosis, VZV, measles</td>
<td>For patients in health care facilities: Airborne precautions (see Prevention of Infectious Diseases below)</td>
</tr>
<tr>
<td>Food/</td>
<td>Ingestion of contaminated food or water</td>
<td>V. cholerae, Salmonella, HAV, HEV</td>
<td>Prophylactic vaccinations where available Ensure clean food/water supply For patients in health care facilities: Contact precautions used for admitted patients with fecal incontinence when stool is unable to be contained in diapers</td>
</tr>
<tr>
<td>Waterborne</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoonotic</td>
<td>Disease transmission from animals to humans either directly or via an insect vector</td>
<td>Animals (rabies, Q fever) Arthropods (malaria, Lyme disease)</td>
<td>Prophylactic medications, vaccinations Protective clothing, insect repellent, mosquito nets, tick inspection</td>
</tr>
<tr>
<td>Vertical</td>
<td>Spread of disease from parent to offspring</td>
<td>Congenital syndromes (TORCH infections) Penitential (HIV, HBV, GBS)</td>
<td>Prenatal screening Prophylactic treatment</td>
</tr>
</tbody>
</table>

*see Prevention of Infectious Diseases for further detail

Overview

- efforts to control the spread of infectious disease involves infection control and prevention measures in health care settings and public health measures outside of health care settings

Infection Control and Prevention Measures

1. surveillance for important nosocomial infections or problem organisms (e.g. surgical site infections, vascular access-related infections, C. difficile infections, colonization or infections due to antimicrobial resistant organisms (e.g. methicillin-resistant S. aureus) (see Population and Community Health, PH19 for a definition of active vs. passive surveillance)

2. routine practices (also known as standard precautions) used for all patients

- perform hand hygiene before and after seeing patient or patient environment contact, before aseptic procedures, and after body fluid exposure
- use gloves for any encounter with body fluids
- wear eye protection, mask, and gown for any procedures likely to generate splashes of body fluids
- do not recap sharps by hand and dispose of sharps in puncture-resistant container near point-of-use
- use mouthpieces for resuscitator bags instead of using mouth-to-mouth resuscitation
- discard soiled waste properly

3. additional precautions used for various syndromes or known infectious diseases

- contact precautions (private room, gown, gloves to be used routinely) (e.g. used for patients with C. difficile)
- droplet/contact precautions (private room, gown, gloves, eye protection, fluid-resistant mask) (e.g. used for influenza, meningitis due to Neisseria meningitidis)
- airborne precautions (negative-pressure private room with door closed, fit-tested N95 respirator) (e.g. used for TB, measles, VZV)
4. decolonization [e.g. topical and oral antimicrobials be used in an attempt to decolonize methicillin-resistant S. aureus (MRSA)]
5. outbreak investigations (see Population and Community Health, PH18)

Public Health Measures
1. vaccination
2. post-exposure prophylaxis (e.g. use of immunoglobulin or vaccination post-exposure to infectious disease agents in an attempt to reduce the likelihood or severity of disease)
3. reportable diseases (e.g. list of reportable communicable diseases that physicians are legally required to report to local public health officials) (see Population and Community Health, PH25)
4. contact tracing (tracking of individuals who have been exposed to a person with a communicable disease during its period of communicability)
5. quarantine (restriction of the activities or well persons who have been exposed to a person with a communicable disease during its period of communicability to prevent disease transmission during the incubation period if infection should occur)
6. outbreak investigation (see Population and Community Health, PH18)

Nosocomial Infections

- definition: infections acquired >48 h after admission to a health care facility or within 30 d from discharge
- risk factors: prolonged hospital stay, antibiotic use, surgery, hemodialysis, intensive care, colonization with a resistant organism, immunodeficiency
- patients with nosocomial infections have higher mortality, longer hospital stays, and higher health-care costs
- hand hygiene is an essential precaution

Table 7. Common Nosocomial Infectious Agents

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Characteristics</th>
<th>Manifestation</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em> (MRSA)</td>
<td>Gram-positive cocci</td>
<td>Skin and soft tissue infection Bacteremia Pneumonia Endocarditis Osteomyelitis</td>
<td>Admission screening culture from nares and peri-anal region identifies colonization Culture of infection site CXR</td>
<td>Contact precautions For infection: vancomycin or daptomycin To decolonize: 2% chlorhexidine wash OD (+ rifampin + doxycycline + mupirocin cream bid to nares) x 7 d</td>
</tr>
<tr>
<td>Vancomycin-resistant <em>Enterococcus</em> (VRE)</td>
<td>Majority are E. faecium Resistant if minimum inhibitory concentration of vancomycin is ≥2 μg/mL</td>
<td>Rarely causes disease in healthy people UTI Bacteremia Endocarditis Meningitis</td>
<td>Rectal or perirectal swab OR stool culture for colonization Culture of infected site</td>
<td>Contact precautions Ampicillin if susceptible Otherwise, linezolid, tigecycline, or daptomycin depending on site of infection No effective decolonization methods identified</td>
</tr>
<tr>
<td><em>Clostridium difficile</em> (C. difficile)</td>
<td>Releases exotoxins A and B Hypervirulent strain has been responsible for increase in incidence and severity Fever, nausea, abdo pain Watery diarrhea ± occult blood Pseudomembranous colitis Severe: toxic megacolon Risk of bowel perforation Associated with antibiotic use Leukocytosis</td>
<td>Stool PCR Stool immunoassay for toxins A and B AXR (may see colonic dilatation) Endoscopy (if suspect fulminant colitis)</td>
<td>Contact precautions Stop culprit antibiotic therapy Supportive therapy (IV fluids) Mild-moderate disease: metronidazole PO/IV x 10-14 d Severe disease: vancomycin PO x 10-14 d Toxic megacolon: metronidazole IV + vancomycin PO (as above) and general surgery consult</td>
<td></td>
</tr>
<tr>
<td>Extended spectrum β-lactamases (ESBL e.g. <em>Escherichia coli</em>, <em>Klebsiella pneumoniae</em>)</td>
<td>Resistant to most β-lactam producing antibiotics e.g. penicillins, aztreonam and cephalosporins UTI Pulmonary infection Bacteremia Liver abscess in susceptible patients Meningitis</td>
<td>Blood, sputum, urine, or aspirated body fluid culture Imaging at infection site (CXR, CT, U/S)</td>
<td>Contact precautions depending on site of infection and institutional policies Depending on culture and sensitivity results, carbapenems can be used for empiric therapy</td>
<td></td>
</tr>
</tbody>
</table>
Respiratory Infections

Pneumonia

- see *Pediatrics*, P93
- see *Family Medicine*, FM18

Definition
- infection of the lung parenchyma

Etiology and Risk Factors
- impaired lung defenses
  - poor cough/gag reflex (e.g. illness, drug-induced)
  - impaired mucociliary transport (e.g. smoking, cystic fibrosis)
  - immunosuppression (e.g. steroids, chemotherapy, AIDS/HIV, DM, transplant, cancer)
- increased risk of aspiration
  - impaired swallowing mechanism (e.g. impaired consciousness, neurologic illness causing dysphagia, mechanical obstruction)
- no organism identified in 75% of hospitalized cases, and >90% of ambulatory cases

<table>
<thead>
<tr>
<th>Table 8. Common Organisms in Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Community Acquired</strong></td>
</tr>
<tr>
<td>Typical Bacteria</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>GAS</td>
</tr>
<tr>
<td>Atypical Bacteria</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
</tr>
<tr>
<td>Legionella pneumophila</td>
</tr>
<tr>
<td>Viral</td>
</tr>
<tr>
<td>Influenza virus</td>
</tr>
<tr>
<td>Adenoviruses</td>
</tr>
</tbody>
</table>

*See *Pediatrics* P93, Table 45 for Common Causes and Treatment of Pneumonia at Different Ages

Clinical Features
- cough (± sputum), fever, pleuritic chest pain, dyspnea, tachypnea, tachycardia
- elderly often present atypically; altered LOC is sometimes the only sign
- evidence of consolidation (dullness to percussion, bronchial breath sounds, crackles, increased fremitus, whisper pectoriloquy)
- features of parapneumonic effusion (decreased air entry, dullness to percussion, decreased fremitus) (see *Respirology*, R21)
- complications: ARDS, lung abscess, parapneumonic effusion/empyema, pleuritis ± hemorrhage

Investigations
- pulse oximetry to assess severity of respiratory distress
- CBC and differential, electrolytes, urea, Cr, ABG (if respiratory distress), troponin/CK, LFTs, urinalysis
- sputum Gram stain/C&S, blood C&S, ± serology/viral detection, ± pleural fluid C&S (if effusion >5 cm or respiratory distress)
- CXR±CT chest shows distribution (lobar consolidation or interstitial pattern), extent of infiltrate ± cavitation
- bronchoscopy ± washings for
  - (1) severely ill patients refractory to treatment or (2) immunocompromised patients

Treatment
- ABC, O₂, IV fluids, consider salbutamol (nebulized or MDI)
- determine prognosis and need for hospitalization and antibiotics

When Klebsiella causes pneumonia; see red currant jelly.

3 As of Klebsiella
- Aspiration pneumonia
- Alcoholics and diabetics
- Abscess in lungs

Aspiration pneumonias more commonly manifest as infiltrates in the right middle or lower lobes due to the larger caliber and more vertical orientation of the right bronchus.
Criteria for Hospitalization

Table 9. CURB 65 Score – Pneumonia Clinical Prediction Tool

<table>
<thead>
<tr>
<th>Component</th>
<th>Measurement(s)</th>
<th>Points</th>
<th>Total Score</th>
<th>Mortality</th>
<th>Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>Altered mental status</td>
<td>1</td>
<td>0-1</td>
<td>&lt;5%</td>
<td>Can treat as outpatient</td>
</tr>
<tr>
<td>Urea/BUN</td>
<td>Urea &gt; 7 mmol or BUN &gt;19</td>
<td>1</td>
<td>2-3</td>
<td>5-15%</td>
<td>Consider hospitalization</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>&gt;30 breaths/min</td>
<td>1</td>
<td>4-5</td>
<td>15-30%</td>
<td>Consider ICU</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Systolic &lt;90 or diastolic &lt;60 mmHg</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65 or older</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 10. IDSA/ATS Community Acquired Pneumonia Treatment Guidelines 2007

Table 11. IDSA/ATS Hospital/Ventilator/Healthcare-Associated Pneumonia Treatment Guidelines 2005

Table 11. IDSA/ATS Hospital/Ventilator/Healthcare-Associated Pneumonia Treatment Guidelines 2005

Table 12. IDSA/ATS Hospital/Ventilator/Healthcare-Associated Pneumonia Treatment Guidelines 2005

Table 12. IDSA/ATS Hospital/Ventilator/Healthcare-Associated Pneumonia Treatment Guidelines 2005

Table 12. IDSA/ATS Hospital/Ventilator/Healthcare-Associated Pneumonia Treatment Guidelines 2005

Table 12. IDSA/ATS Hospital/Ventilator/Healthcare-Associated Pneumonia Treatment Guidelines 2005

Prevention

- Public Health Agency of Canada recommends the following:
  - vaccine for influenza A and B recommended annually for all ages
  - pneumococcal polysaccharide vaccine (Pneumovax®) recommended for all adults >65 yr and in younger patients 24 mo of age and older at high risk for invasive pneumococcal disease (e.g. functional or anatomic asplenia; congenital or acquired immunodeficiency)
  - pneumococcal conjugate vaccine (Prevnar-13®) is recommended for all children <5 yr, and for children and adolescents at high risk for invasive pneumococcal disease who are 5-17 yr who have not previously received Prevnar-13® (CDC recommends giving Prevnar-13® to all adults at high risk for invasive pneumococcal disease)
Influenza

Definitions and Etiology
- influenza virus A and B
- influenza A further divided into subtypes based on envelope glycoproteins:
  - hemagglutinin (H) and neuraminidase (N)
- seasonal (epidemic) influenza
  - main circulating influenza viruses: human-origin A (H1N1) and B (H3N2) subtypes
  - associated with antigenic drift (gradual, minor changes due to random point mutations)
  - may create a new viral subtype resulting in a seasonal epidemic (disease prevalence is greater than expected)
  - outbreaks occur mainly during winter months (late December to early March)
- pandemic influenza
  - associated with antigenic shift (abrupt, major changes due to mixing of two different viral strains from different hosts)
  - may create a new viral strain resulting in a pandemic outbreak (worldwide)
  - antigenic shift occurs only in type A
- transmission: droplet, possibly airborne

Table 12. Difference between Influenza Strains

<table>
<thead>
<tr>
<th></th>
<th>Influenza A</th>
<th>Influenza B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Host(s)</td>
<td>Humans, Birds, Mammals</td>
<td>Humans only</td>
</tr>
<tr>
<td>Antigenic drift</td>
<td>Yes, new strains</td>
<td>Yes, new strains</td>
</tr>
<tr>
<td>Antigenic shift</td>
<td>Yes, new subtypes</td>
<td>No</td>
</tr>
<tr>
<td>Epidemics</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pandemics</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Clinical Features
- incubation period 1-4 d
- acute onset of systemic (fever, chills, myalgias, arthralgias, headache, fatigue) and respiratory symptoms (cough, dyspnea, pharyngitis)
- complications: respiratory (viral pneumonia, secondary bacterial pneumonia, otitis media, sinusitis), muscular (rhabdomyolysis, myositis), neurologic (encephalitis, meningitis, transverse myelitis, Guillain-Barré syndrome)

Investigations
- diagnosis is primarily clinical based on symptoms during the influenza season
- nasopharyngeal swabs for rapid antigen detection, DFA (Direct Fluorescent Antigen detection), RT-PCR (gold standard)
- serology: rarely used for clinical management

Treatment and Prevention
- primarily supportive unless severe infection or high-risk of complications (e.g. elderly, pulmonary or cardiac disease)
- neuraminidase inhibitors: zanamivir (Relenza®) and oseltamivir (Tamiflu®) for treatment and prophylaxis against type A and B
  - decreases duration (by 1-2 d) and severity of symptoms if given within <48 h of onset
  - treatment beyond 48 h time window may be warranted in immunosuppressed and critically ill patients
- M2-inhibitors: amantidine/rimantidine for treatment and prophylaxis against type A only when no longer recommended due to increased resistance
- vaccine for influenza A and B viruses is recommended annually for all ages
  - vaccine is reformulated each year to reflect circulating influenza A and B strains

Skin and Soft Tissue Infections

Cellulitis

Definition
- acute infection of the skin principally involving the dermis and subcutaneous tissue

Etiology
- common causative agents: S. aureus, β-hemolytic streptococci
- immunocompromised patients: may also include GN rods and fungi
- risk factors:
  - trauma with direct inoculation, recent surgery
  - peripheral vascular disease, lymphedema diabetes, cracked skin in feet/toes (tinea pedis)
Clinical Features
- pain, tenderness, edema, erythema with indistinct borders ± regional lymphadenopathy, systemic symptoms (fevers, chills, malaise)
- can lead to ascending lymphangitis (visible red streaking in skin along lymphatics proximal to area of cellulitis)

Investigations
- CBC and differential, blood C&S if febrile
- skin swab ONLY if open wound with pus

Treatment
- antibiotics: cephalexin
- if extensive erythema or systemic symptoms, consider cefazolin IV
- limb rest and elevation may help reduce swelling

Necrotizing Fasciitis

Definition
- life- and limb-threatening infection of the deep fascia characterized by rapid spread

Etiology
- Two main forms:
  - Type I: polymicrobial infection – aerobes and anaerobes (e.g. *S. aureus*, *Bacteroides*, *Enterobacteriaceae*)
  - Type II: monomicrobial infection with GAS

Clinical Features
- pain out of proportion to clinical findings and beyond border of erythema
- edema, ± crepitus (subcutaneous gas from anaerobes), ± fever
- infection spreads rapidly
- patients may rapidly become very sick (tachycardia, hypotension, lightheadedness)
- late findings:
  - skin turns dusky blue and black (secondary to thrombosis and necrosis)
  - induration, formation of hemorrhagic bullae

Investigations
- a clinical/surgical diagnosis – do NOT wait for results of investigations before beginning treatment
- blood and tissue C&S
- serum CK (elevated CK usually means myonecrosis – a late sign)
- plain film x-ray (soft tissue gas may be visualized)
- surgical exploration for debridement of infected tissue

Treatment
- resuscitation with IV fluids
- emergency surgical debridements to confirm diagnosis and remove necrotic tissue
- IV antibiotics
  - unknown organism: meropenem or piperacillin/tazobactam + clindamycin IV ± vancomycin
    - if MRSA is considered
  - Type I (polymicrobial): piperacillin/tazobactam + clindamycin IV
  - Type II (monomicrobial): penicillin G + clindamycin IV
  - with Type II, evaluate for streptococcal toxic shock syndrome and the need for IVIG

Gastrointestinal Infections

Acute Diarrhea
- see *Gastroenterology*, G15
- see *Pediatrics*, P35
- see *Family Medicine*, FM26

Epidemiology
- one of five leading causes of death worldwide, according to World Health Organization
- significant morbidity in developed countries (over 900,000 hospitalizations in United States each year)
Definition
• passage of ≥3 loose or liquid stools/d or >200 g stool/d for >2 d but ≤14 d

Approach to Acute Diarrhea
• rationale:
  ▪ the vast majority of acute diarrhea is caused by infection
  ▪ in most cases, acute diarrheal illness is viral and/or self-limited, and lasts <3 d
  ▪ investigations are costly and necessary only in certain circumstances
• therefore, the evaluation of acute diarrhea involves:
  ▪ identifying characteristics of the illness or patient that warrant further investigation
  ▪ assessing volume status to determine appropriate method of rehydration
• see Figure 7

Physical Exam
• volume status: appearance, level of alertness, pulse, BP, orthostatic vitals, JVP, mucous membranes, skin turgor, capillary refill
• abdominal exam: pain, guarding, peritoneal signs

Treatment
• rehydration is mainstay of treatment
  ▪ oral rehydration therapy
  ▪ IV rehydration if oral intake insufficient to replace fluid loss
• antidiarrheal agents reduce duration of diarrhea: loperamide, bismuth salicylate
  ▪ delays excretion of causative pathogens
  ▪ contraindications: diarrhea with fever, bloody stool or diarrhea caused by *Clostridium difficile*
• antibiotic therapy is rarely indicated because:
  ▪ most acute diarrheal illness is of viral etiology and is self-limited
  ▪ antibiotics can eradicate normal gut flora, predisposing to *C. difficile* infection
  ▪ antibiotics prolong the shedding of Salmonella and other causes of bacterial diarrhea
  ▪ in EHEC infection, antibiotics may increase the risk of HUS
  ▪ indications for antibiotic therapy are shown in Figure 7

Figure 7. Approach to acute diarrhea
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Source or Mode of Transmission</th>
<th>Incubation</th>
<th>Clinical Features</th>
<th>Duration</th>
<th>Antimicrobial Therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fever</strong></td>
<td><strong>Bloody Stool</strong></td>
<td><strong>Abdo Pain</strong></td>
<td><strong>N/V</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. cereus – Type A (emetic)</td>
<td>Rice dishes</td>
<td>1-6 h</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>B. cereus – Type B (diarrheal)</td>
<td>Meats, vegetables, dried beans, cereals</td>
<td>8-16 h</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>Uncooked meat, especially poultry</td>
<td>2-10 d</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Can be normally present in colon in small numbers (primary risk factor for disease is exposure to antimicrobials)</td>
<td>Unclear</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>–</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>Contaminated food, especially meet and poultry</td>
<td>8-12 h</td>
<td>±</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Enteroinvasive E. coli (IEC)</td>
<td>Contaminated food/water</td>
<td>1-3 d</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Enterotoxigenic E. coli (ETEC)</td>
<td>Contaminated food/water</td>
<td>1-3 d</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Enterohemorrhagic E. coli (EHEC) i.e. O157:H7</td>
<td>Contamination of hamburger, raw milk, drinking and recreational water</td>
<td>3-8 d</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Salmonella typhi</td>
<td>Fecal-oral</td>
<td>10-14 d</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Salmonella paratyphi</td>
<td>Fecal-oral</td>
<td>10-14 d</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Enterohemorrhagic S. typhimurium, S. enteritidis</td>
<td>Contaminated animal food products, especially eggs, poultry, meat, milk</td>
<td>12-72 h</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Shigella dysenteriae</td>
<td>Fecal-oral</td>
<td>1-4 d</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Unrefrigerated meat and dairy products (custard, pudding, potato salad, mayo)</td>
<td>2-4 h</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td>Contaminated food/water, especially shellfish</td>
<td>1-3 d</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Yersinia</td>
<td>Contaminated food</td>
<td>Unpasteurized milk</td>
<td>5 d</td>
<td>+</td>
<td>±</td>
<td>+</td>
</tr>
</tbody>
</table>
Traveller’s Diarrhea

• see Acute Diarrhea, ID11

Epidemiology
• the most common illness to affect travellers
• up to 50% of travellers to developing countries affected in first 2 wk and 10-20% after returning home

Etiology
• bacterial (80-90%): E. coli most common (ETEC), Campylobacter, Shigella, Salmonella, Vibrio (non-cholera); wide regional variation (e.g. Campylobacter more common in Southeast Asia)
• viral: norovirus, rotavirus, and astrovirus account for 5-8%
• protozoal (rarely): Giardia, Entamoeba histolytica, Cryptosporidium, Cyclospora for ~10% in long-term travellers
• pathogen-negative traveller’s diarrhea common despite exhaustive microbiological work-up

Treatment
• rehydration is mainstay of therapy
  ▪ rehydrate with sealed beverages
  ▪ in severe fluid loss use oral rehydration solutions (1 package in 1L boiled or treated water)
• treat symptoms: antidiarrheal agents (e.g. bismuth salicylate, loperamide)
• empiric antibiotics in moderate or severe illness: ciprofloxacin or azithromycin or rifaximin
  ▪ note: there is increasing fluoroquinolone resistance in causative agents, especially in Southeast Asia

Prevention
• proper hygiene practices
  ▪ avoid consumption of: foods or beverages from establishments with unhygienic conditions (e.g. street vendors), raw fruits or vegetables without a peel, raw or undercooked meat and seafood
  ▪ avoid untreated water
• bismuth salicylate (Pepto-Bismol®): 60% effective (2 tablets qid according to CDC website)
• CDC Guidelines: antibiotic prophylaxis not recommended
  ▪ increased risk of infection with resistant organisms
  ▪ high risk groups (e.g. immunocompromised) likely to be infected with pathogen not covered by standard antimicrobial agents

---

### Table 14. Parasites in Infectious Diarrhea

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Source or Mode of Transmission</th>
<th>Incubation</th>
<th>Clinical Features</th>
<th>Duration</th>
<th>Antimicrobial Therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptosporidium</td>
<td>Fecal-oral</td>
<td>7 d</td>
<td>Fever – Bloody Stool – Abdo Pain + N/V</td>
<td>1-20 d</td>
<td>Paramomycin + nitazoxanide</td>
<td></td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td>Worldwide endemic areas</td>
<td>2-4 wk</td>
<td>Fever – Bloody Stool – Abdo Pain + N/V</td>
<td>Variable</td>
<td>Metronidazole + iodoquinol if symptomatic infection Only iodoquinol for asymptomatic cyst passage If untreated, potential for liver abscess Sigmoidoscopy shows flat ulcers with yellow exudates</td>
<td></td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>Fecal-oral</td>
<td>1-4 wk</td>
<td>Fever – Bloody Stool – Abdo Pain + N/V</td>
<td>Variable</td>
<td>Metronidazole or nitazoxanide Treatment of asymptomatic carriers not recommended Higher risk in: day care children, intake of untreated water (“beaver fever”), MSM, immunodeficiency (decreased IgA) May need duodenal biopsy</td>
<td></td>
</tr>
</tbody>
</table>

### Table 15. Viruses in Infectious Diarrhea

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Source or Mode of Transmission</th>
<th>Incubation</th>
<th>Clinical Features</th>
<th>Duration</th>
<th>Antimicrobial Therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norovirus</td>
<td>Fecal-oral</td>
<td>24 h</td>
<td>Fever – Bloody Stool – Abdo Pain + N/V</td>
<td>24 h</td>
<td>None</td>
<td>Noroviruses includes Norwalk virus</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Fecal-oral</td>
<td>2-4 d</td>
<td>Fever – Bloody Stool – Abdo Pain + N/V</td>
<td>3-8 d</td>
<td>None</td>
<td>Can cause severe dehydration Virtually all children are infected by 3 yr of age Oral vaccine given at 2 and 4 mo of age</td>
</tr>
</tbody>
</table>

Bismuth salicylate (Pepto-Bismol®) can cause patients to have black stools, which may be mistaken for melena.
Dukoral®: oral vaccine that offers protection against *V. cholera* (efficacy ~80%) and ETEC (efficacy ~50-67%). Not recommended for routine use in travellers, but PHAC recommends that it may be considered in short-term travellers >2 yr who are high-risk (e.g. chronic illness) for whom there is an increased risk of serious consequences for traveller’s diarrhea (e.g. chronic renal failure, congestive heart failure, type 1 diabetes mellitus, inflammatory bowel disease), immunosuppressed, history of repeat traveller’s diarrhea, increased risk of acquiring traveller’s diarrhea (gastric hypochlorhydria or young children >2 yr).

### Chronic Diarrhea

- see *Gastroenterology*, G16

### Peptic Ulcer Disease (*H. pylori*)

- see *Gastroenterology*, G12

### Bone and Joint Infections

#### Septic Arthritis

**Routes of Infection**
- hematogenous (adults)
- contiguous osteomyelitis (children)
- direct inoculation via skin/trauma
- iatrogenic (surgery, arthroscopy, arthrocentesis)

**Etiology**
- gonococcal
  - *N. gonorrhoeae*: previously accounted for 75% of septic arthritis in young sexually active adults
- non-gonococcal
  - *S. aureus*: affects all ages, rapidly destructive, accounts for most non-gonococcal cases of septic arthritis in adults (especially in those with rheumatoid arthritis)
  - *Streptococcus* species (Group A and B)
  - Gram-negatives: affects neonates, elderly, IV drug users, immunocompromised
  - *S. pneumoniae*: affects children
  - *Kingella kingae*: affects children aged <2 yr since Hib immunization
  - *Salmonella* spp.: characteristic of sickle cell disease
  - coagulase-negative *Staphylococcus* species: prosthetic joints
- if culture negative: *Borrelia* spp. (Lyme disease) or *Tropheryma whippellii* (Whipple's disease)

**Risk Factors**
- gonococcal
  - age (<40 yr old), recent menses, pregnancy, MSM
- non-gonococcal
  - bacteremia (extra-articular infection with hematogenous seeding, endocarditis)
  - prosthetic joints/recent joint surgery
  - underlying joint disease (rheumatoid arthritis, osteoarthritis)
  - immunocompromise (diabetes, chronic kidney disease, alcoholism, cirrhosis)
  - loss of skin integrity (cutaneous ulcer, skin infection)
  - age >80 yr

**Clinical Features of Gonococcal Arthritis**

- two forms (although overlap often):
  - bacteremic form:
    - systemic symptoms: fever, malaise, chills
    - gonococcal triad: migratory polyarthralgias, tenosynovitis, dermatitis (pustular skin lesions)
  - septic arthritis form:
    - local symptoms in involved joint: swelling, warmth, pain, inability to bear weight, marked decreased in range of motion

**Clinical Features of Non-gonococcal Arthritis**

- acute onset of pain, swelling, warmth, decreased range of motion ± fever, chills
- most often in large weight bearing joints (knee, hip, ankle) and wrists
- usually monoarticular (polyarticular risk factors: rheumatoid arthritis, endocarditis, GBS)
Investigations

- consider rheumatologic causes for monoarthritis (see Rheumatology, RH3)
- gonococcal: blood C&S, as well as endocervical, urethral, rectal and oropharyngeal testing
- non-gonococcal: blood C&S
- arthrocentesis (synovial fluid analysis) is mandatory: CBC and differential, Gram stain, C&S, examine for crystals
  - infectious = opaque, increased WBC count (>15 000/mm³; likelihood of infection increases with increasing WBC count), PMNs >90%, culture positive
  - growth of N. gonorrheae from synovial fluid is successful in <50% of cases
- ± plain x-ray: assess for osteomyelitis, provides baseline to monitor treatment

Treatment

- medical
  - empiric IV antibiotics (vancomycin + ceftriaxone) – delay may result in joint destruction
  - Gram stain guides subsequent treatment
  - gonococcal: ceftriaxone + azithromycin, for concurrent treatment of C. trachomatis
  - non-gonococcal: antibiotics against Streptococcus spp. (2 wk), S. aureus (4 wk IV minimum), or GN rods (4 wk)
- surgical drainage if: (see Orthopedics, OR10)
  - persistent positive joint cultures on repeat arthrocentesis
  - hip joint involvement
  - prosthetic joint
- daily joint aspirations until culture sterile; no need to give intra-articular antibiotics
- physiotherapy

Prognosis

- gonococcal: responds well after 24-48 h of initiating antibiotics (usually complete recovery)
- non-gonococcal: up to 50% morbidity (decreased joint function/mobility)

Diabetic Foot Infections

Etiology

- neuropathy, peripheral vascular disease and hyperglycemia contribute to foot ulcers that heal poorly and are predisposed to infection
- organisms in mild infection: S. aureus, Streptococcus spp.
- organisms in moderate/severe infection: polymicrobial with aerobes (S. aureus, Streptococcus, Enterococcus, GN bacilli) and anaerobes (Peptostreptococcus, Bacteroides, Clostridium)

Clinical Features

- not all ulcers are infected
- diagnosis of infected ulcer: ≥2 of the cardinal signs of inflammation (redness, warmth, swelling, pain) or the presence of pus
- ± crepitus, osteomyelitis, systemic toxicity
- visible bone or probe to bone = osteomyelitis
- infection severity:
  - mild = superficial (no bone/joint involvement)
  - moderate = deep (beneath superficial fascia, involving bone/joint)
  - severe = infection in a patient with systemic toxicity (fevers, chills, tachycardia, hypotension)

Investigations

- curettage specimen from ulcer base, aspirate from an abscess or bone biopsy (results from superficial swabs do not represent organisms responsible for deeper infection)
- blood C&S if febrile
- assess for osteomyelitis by x-ray (although not sensitive in early stages)
  - if initial x-ray normal, repeat 2-4 wk after initiating treatment to increase test sensitivity
  - if initial x-ray equivocal, do MRI or bone biopsy (most reliable test)

Treatment

- evaluate for early surgical debridement ± revascularization or amputation
- eliminate/reduce pressure and provide regular local wound care
- mild: cephalexin or clindamycin
- moderate or severe: clindamycin + ciprofloxacin PO or pip/tazo IV ± vancomycin if MRSA known or suspected
- encourage glycemic control

Osteomyelitis

- see Orthopedics, OR10

Intra-articular steroids are contraindicated until septic arthritis has been excluded.
Cardiac Infections

Infective Endocarditis (IE)

Definition
- infection of cardiac endothelium, most commonly the valves
- classifications: acute vs. subacute, native valve vs. prosthetic valve, right sided vs. left sided
- leaflet vegetation = platelet-fibrin thrombi, WBCs and bacteria

Risk Factors and Etiology
- predisposing conditions:
  - high risk: prosthetic cardiac valve, previous IE, congenital heart disease (unrepaired, repaired within 6 mo, repaired with defects), cardiac transplant with valve disease (surgically constructed systemic-to-pulmonary shunts or conduits)
  - moderate risk: other congenital cardiac defects, acquired valvular dysfunction, hypertrophic cardiomyopathy
  - low/no risk: secundum ASD or surgically repaired ASD < VSD, PDA, MV prolapse, IHD, previous CABG
  - opportunity for bacteremia: intravenous drug use (IVDU), indwelling venous catheter, hemodialysis, poor dentition, diabetes, HIV
- frequency of valve involvement MV >> AV > TV > PV
  - but in 50% of IVDU-related IE the tricuspid valve is involved

Table 16. Microbial Etiology of Infective Endocarditis Based on Risk Factors

<table>
<thead>
<tr>
<th>Native Valve</th>
<th>IVDU</th>
<th>Prosthetic Valve (recent surgery &lt;2 months)</th>
<th>Prosthetic Valve (remote surgery &gt;2 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus (36%)</td>
<td>S. aureus (68%)</td>
<td>Streptococcus (13%)</td>
<td>S. aureus (36%)</td>
</tr>
<tr>
<td>S. epidermidis (28%)</td>
<td>Enterococcus</td>
<td>S. epidermidis (17%)</td>
<td>Other</td>
</tr>
<tr>
<td>GNB</td>
<td>Candida</td>
<td>Enterococcus</td>
<td>GNB</td>
</tr>
<tr>
<td>Other</td>
<td>Other</td>
<td>Other</td>
<td>Other</td>
</tr>
</tbody>
</table>

Organisms in bold are the most common isolates.
1. Streptococcus includes mainly Viridans group streptococci
2. Other includes less common organisms such as:
   - Streptococcus bovis (usually associated with underlying GI malignancy, cirrhosis)
   - Culture-negative organisms including nutritionally-deficient streptococci, HACEK, Bartonella, Chlamydia, Legionella, Brucella
3. IVDU endocarditis pathogens depend on substance used to dilute the drugs (i.e. tap water = Pseudomonas, saliva = oral flora, toilet water = GI flora)

Clinical Features
- systemic
  - fever (80-90%), chills, weakness, rigors, night sweats, weight loss, anorexia
- cardiac
  - dyspnea, chest pain, clubbing (subacute)
  - regurgitant murmur (new onset or increased intensity)
  - signs of CHF (secondary to acute MR, AR)
- embolic/vascular
  - petechiae over legs, splinter hemorrhages (linear, reddish-brown lesion within nail bed)
  - Janeway lesions (painless, 5 mm, erythematous, hemorrhagic pustular lesions on soles/palms)
  - focal neurological signs (CNS emboli), headache (mycotic aneurysm)
  - splenomegaly (subacute)
  - microscopic hematuria, flank pain (renal emboli) ± active sediment
- immune complex
  - Osler’s nodes (painful, raised, red/brown, 3-15 mm on digits)
  - glomerulonephritis
  - arthritis
  - Roth’s spots (retinal hemorrhage with pale centre)

Diagnosis
- Modified Duke Criteria, see Table 17
  - definitive diagnosis if: 2 major, or 1 major + 3 minor, or 5 minor
  - possible diagnosis if: 1 major + 1 minor, or 3 minor
Table 17. Modified Duke Criteria

Major Criteria (2)

1. Positive blood cultures for IE
   - Typical microorganisms for IE from 2 separate blood cultures (Streptococcus viridans, HACEK group [see ID17], Streptococcus bovis, Staphylococcus aureus, community-acquired enterococci) OR
   - Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from blood drawn >12 h apart or all of 3 or a majority of 4 or more separate blood cultures, with first and last drawn >1 h apart OR
   - Single positive blood culture for Coxiella burnetii or antiphase I IgG antibody titer >1:800

2. Evidence of endocardial involvement
   - Positive echocardiogram for IE (oscillating intracardiac mass on valve or supporting structures, or in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation OR abscess OR new partial dehiscence of prosthetic valve)
   - OR New valvar regurgitation (insufficient if increase or change in preexisting murmur)

Minor Criteria (5)

1. Predisposing condition (abnormal heart valve, IVDU)
2. Fever (38.0°C/100.4°F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, ICH, conjunctival hemorrhages, Janeway lesions
4. Immunologic phenomena: glomerulonephritis, rheumatoid factor, Osler’s nodes, Roth’s spots
5. Positive blood culture but not meeting major criteria OR serologic evidence of active infection with organism consistent with IE

Investigations

- serial blood cultures: 3 sets (each containing one aerobic and one anaerobic sample) collected from different sites >1 h apart
  - persistent bacteremia is the hallmark of endovascular infection (such as IE)
- repeat blood cultures (at least 2 sets) after 48 to 72 h of appropriate antibiotics to confirm clearance
- blood work: CBC and differential (normochromic, normocytic anemia), ESR (increased), RF (+), BUN/Cr
- urinalysis (proteinuria, hematuria, red cell casts) and urine C&S
- ECG: prolonged PR interval may indicate perivalvular abscess
- ECHO findings: vegetations, regurgitation, abscess
  - TTE (poor sensitivity) inadequate in 20% (obesity, COPD, chest wall deformities)
  - TEE indicated if TTE is non-diagnostic in patients with at least possible endocarditis or if suspect prosthetic valve endocarditis or complicated endocarditis (e.g. paravalvular abscess/perforation) (~90% sensitivity)

Treatment

- medical
  - usually non-urgent and can wait for confirmation of etiology before initiating treatment
  - empiric antibiotic therapy if patient is unstable
    - first-line: vancomycin + gentamicin or ceftriaxone
  - targeted antibiotic therapy: antibiotic and duration (usually 4-6 wk) adjusted based on valve, organism and sensitivities
  - monitor for complications of IE (e.g. CHF, conduction block, new emboli) and complications for antibiotics (e.g. interstitial nephritis)
  - prophylaxis only for high risk individuals listed above with dental procedures that may lead to bleeding OR invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy OR procedures on infected skin, skin structure or musculoskeletal tissue
    - dental/respiratory: amoxicillin single dose 30-60 min prior; clindamycin if penicillin-allergic
    - skin/soft tissue: cephalaxin single dose 30-60 min prior; clindamycin if penicillin-allergic (modify based on etiology of skin/soft tissue infection)
  - surgical
    - most common indication is refractory CHF
    - other indications, include valve ring abscess, fungal etiology, valve perforation, unstable prosthesis, ≥ 2 major emboli, antimicrobial failure (persistently positive blood cultures), mycotic aneurysm, Staphylococci on a prosthetic valve

Prognosis

- adverse prognostic factors: CHF, prosthetic valve infection, valvular/myocardial abscess
- mortality: prosthetic valve IE (25-50%), non-IVDU S. aureus IE (30-45%), IVDU S. aureus or streptococcal IE (10-15%)
Neurological Infections

Meningitis

Definition

- inflammation of the meninges

Etiology

<table>
<thead>
<tr>
<th>Table 18. Common Organisms in Meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age 0-4 wk</strong></td>
</tr>
<tr>
<td>GBS</td>
</tr>
<tr>
<td>E. coli</td>
</tr>
<tr>
<td>Klebsiella</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>HSV-1, 2</td>
</tr>
<tr>
<td>Enteroviruses</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Risk Factors

- lack of immunization against *S. pneumoniae, H. influenzae type b*
- hematogenous spread after invasion from a mucosal surface (nasopharynx)
- parameningeal focus (otitis media, infection, sinusitis)
- penetrating head trauma
- anatomical meningeal defects – CSF leaks
- previous neurosurgical procedures, shunts
- immunocompromise (corticosteroids, HIV, asplenia, hypogammaglobulinemia, complement deficiency)
- contact with colonized or infected persons

Clinical Features

- neonates and children: fever, vomiting, lethargy, irritability, poor feeding
- older children and adults: fever, headache, neck stiffness, confusion, nausea and vomiting, lethargy, photophobia, altered level of consciousness, seizures, focal neurological signs, papilledema
- petechial rash on lower extremities with meningococcal meningitis

Investigations

- bloodwork: CBC and differential, electrolytes (for SIADH), blood C&S
- CSF: opening pressure, cell count + differential, glucose, protein, Gram stain, bacterial C&S
- AFB, fungal C&S, cryptococcal antigen in immunocompromised patients, subacute illness, suggestive travel history or TB exposure
- PCR for HSV, VZV, EBV, enteroviruses if viral cause suspected
- imaging/neurologic studies: CT, MRI, EEG if focal neurological signs present

Table 19. CSF Profiles for Meningitis

<table>
<thead>
<tr>
<th>CSF Analysis</th>
<th>Bacterial</th>
<th>Viral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Protein (g/L)</td>
<td>Markedly Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>White blood cell</td>
<td>500-10,000/µL</td>
<td>10-500/µL</td>
</tr>
<tr>
<td>Predominant WBC</td>
<td>Neutrophils</td>
<td>Lymphocytes</td>
</tr>
</tbody>
</table>

Treatment

- bacterial meningitis is a medical emergency: do not delay antibiotics before CT or LP
- empiric antibiotic therapy:
  - age <1 mo: ampicillin + cefotaxime ± gentamicin IV
  - age >1 mo: vancomycin + ceftriaxone IV
  - add ampicillin IV (or TMP-SMX) if risk factors for infection with *L. monocytogenes* present: age >50, alcoholism, immunocompromised
- steroids in acute bacterial meningitis: dexamethasone IV within 20 min prior to or with first dose of antibiotics (see sidebar)
- benefit in all adults (including with pneumococcal meningitis) now uncertain

Brudzinski’s Sign

Passive neck flexion causes involuntary flexion of hips and knees.

Kernig’s Sign

Resistance to knee extension when hip is flexed to 90°.

Jolt Accentuation of H/A

Headache worsens when head turned horizontally at 2-3 rotations/s.

CSF Gram Stain Findings

- *S. pneumoniae – GP diplococci*
- *N. meningitidis – GN diplococci*
- *H. influenzae – Pleomorphic GN coccobacilli*
- *L. monocytogenes – GP rods*

Adjuvant Dexamethasone in Bacterial Meningitis: A Meta-analysis of Individual Patient Data

- *Lancet 2010;9:254-8*
- *Meta-analysis of randomized, double blind, placebo controlled trial.*
- *Population: 2029 patients from 6 trials, 833 <15 yr, 489 in 580, bacterial meningitis confirmed in 1639.*
- *Intervention: Antibiotics vs. without dexamethasone (first dose given within 20 min prior to or with first dose of antibiotics).*
- *Outcome: Death, death or any neurological sequelae, and death or severe bilateral hearing loss at first follow-up, death or severe neurological sequelae at 1 mo.*
- *Results: There was no difference in death (OR 0.97 (95% CI, 0.79–1.19)), death or severe bilateral hearing loss (OR 0.89, 95% CI, 0.73–1.10)). Death or severe neurological sequelae or any hearing loss (OR 0.92 (95% CI, 0.76–1.11)), or death or any neurological sequelae or any hearing loss (OR 0.91 (95% CI, 0.74–1.10)). However, among survivors, dexamethasone may reduce hearing loss (OR 0.77 (95% CI, 0.60–0.99), p=0.01).*  
- *Conclusion: The benefit of dexamethasone in acute bacterial meningitis is questionable with seemingly little effect in death or neurological sequelae. There may be some benefit on prevention of hearing loss.*

Does this Adult Patient Have Acute Meningitis? From The Rational Clinical Examination

- *JAMA 2009;302:3482857*
- *Study: Systematic review of articles assessing the sensitivity and specificity of clinical exam maneuvers for the diagnosis of adult meningitis.*
- *Population: 2029 patients from 5 trials, 833 <15 yr, HIV in 580, bacterial meningitis confirmed in 1639.*
- *Patient Data: Meta-analysis of randomized, double blind, placebo controlled trial.*
- *Intervention: Antibiotics vs. without dexamethasone (first dose given within 20 min prior to or with first dose of antibiotics).*
- *Outcome: Death, death or any neurological sequelae, and death or severe bilateral hearing loss at first follow-up; death or severe neurological sequelae at 1 mo.*
- *Results: There was no difference in death (OR 0.97 (95% CI, 0.79–1.19)), death or severe bilateral hearing loss (OR 0.89, 95% CI, 0.73–1.10)). Death or severe neurological sequelae or any hearing loss (OR 0.92 (95% CI, 0.76–1.11)), or death or any neurological sequelae or any hearing loss (OR 0.91 (95% CI, 0.74–1.10)). However, among survivors, dexamethasone may reduce hearing loss (OR 0.77 (95% CI, 0.60–0.99), p=0.01).*  
- *Conclusion: The benefit of dexamethasone in acute bacterial meningitis is questionable with seemingly little effect in death or neurological sequelae. There may be some benefit on prevention of hearing loss.*
Prevention
- see Pediatrics, P3
- immunization
  - children: immunization against *H. influenzae* (Pentacel®), *S. pneumoniae* (Synflorix®, Prevenar-13®), *N. meningitidis* (Menjugate®, Menactra®)
  - adult: immunization against *N. meningitidis* in selected circumstances (outbreaks, travel, epidemics) and *S. pneumoniae* (Pneumovax®) for high-risk groups
- prophylaxis: close contacts of patients infected with *H. influenzae* should be treated with rifampin if they live with an inadequately immunized or immunocompromised child <4 yr; ciprofloxacin, rifampin or ceftriaxone if close or household contact of a patient with *N. meningitidis*

Prognosis
- complications
  - headache, seizures, cerebral edema, hydrocephalus, SIADH, residual neurological deficit (especially CN VIII), deafness, death
- mortality
  - *S. pneumoniae* 25%; *N. meningitidis* 5-10%; *H. influenzae* 5%
  - worse prognosis if: extremes of age, delays in diagnosis and treatment, stupor or coma, seizures, focal neurological signs, septic shock at presentation

Encephalitis

Definition
- inflammation of brain parenchyma

Etiology
- identified in only 40-70% of cases
  - when cause is identified, most common etiology is viral
  - e.g. HSV, VZV, EBV, enteroviruses, CMV, West Nile, HIV, mumps, measles, rabies, polio
  - bacteria: *L. monocytogenes*, *Mycobacteria*, spirochetes (Lyme, syphilis)
  - parasites: protozoa (e.g. *Toxoplasma*) and helminths (rare)
  - fungi: e.g. *Cryptococcus*
  - post-infectious (e.g. ADEM)

Pathophysiology
- acute inflammatory disease of the brain due to direct invasion or pathogen-initiated immune response
- viruses may reach CNS via peripheral nerves (e.g. rabies, HSV)
- herpes simplex encephalitis
  - acute, necrotizing, asymmetrical hemorrhagic process with lymphocytic and plasma cell reaction which usually involves the medial temporal and inferior frontal lobes
  - associated with HSV-1, but can also be caused by HSV-2

Clinical Features
- constitutional: fever, chills, malaise, nausea, vomiting
- meningeval involvement (meningoencephalitis): headache, nuchal rigidity
- parenchymal involvement: seizures, altered mental status, focal neurological signs
- herpes simplex encephalitis
  - acute onset (<1 wk) of focal neurological signs: hemiparesis, ataxia, aphasia, focal or generalized seizures
  - temporal lobe involvement: behavioural disturbance
  - usually rapidly progressive over several days and may result in coma or death
  - common sequelae: memory and behaviour disturbances

Investigations
- CSF: opening pressure, cell count + differential, glucose, protein, Gram stain, bacterial C&S, PCR for HSV, VZV, EBV, enteroviruses, and other less common viral etiologies
- serology: may aid diagnosis of certain causes of encephalitis (e.g. West Nile virus)
- imaging/neurologic studies: CT, MRI, EEG to define anatomical sites affected
- invasive testing: brain tissue biopsy may be required for culture, histological examination, and immunocytochemistry (if diagnosis not clear via non-invasive means)
- findings in herpes simplex encephalitis (must rule out due to high mortality)
  - CT/MRI: medial temporal lobe necrosis
  - EEG: early focal slowing, periodic discharges

Treatment
- general supportive care
- monitor vital signs carefully
- IV acyclovir empirically until HSV encephalitis ruled out
**Generalized Tetanus**

- see [Family Medicine, FM3](#)
- see [Pediatrics, P3](#)

**Etiology and Pathophysiology**

- caused by *Clostridium tetani*: motile, spore forming, anaerobic GP bacillus
- found in soil, splinters, rusty nails, GI tract (humans and animals)
- traumatic implantation of spores into tissues with low oxygenation (e.g. puncture wound, burns, nonsterile surgeries or deliveries)
- upon inoculation, spores transform into *C. tetani* bacilli that produce tetanus toxin
  - toxin travels via retrograde axonal transport to the CNS where it irreversibly binds presynaptic neurons to prevent the release of inhibitory neurotransmitters (e.g. GABA)
  - net effect is the disinhibition of spinal motor reflexes which results in tetany and autonomic hyperactivity

**Clinical Features**

- generalized tetanus
  - initially present with painful spasms of masseters (trismus or “lockjaw”)
  - sustained contraction of skeletal muscle with periodic painful muscle spasms (triggered by sensory stimuli, e.g. loud noises)
  - paralysis descends to involve large muscle groups (neck, abdomen)
  - apnea, respiratory failure, and death secondary to tonic contraction of pharyngeal and respiratory muscles
  - autonomic hyperactivity
    - diaphoresis, tachycardia, hypertension, fever as illness progresses

**Investigations**

- culture wounds, CK may be elevated, BUN usually normal

**Treatment**

- stop toxin production
  - wound debridement to clear necrotic tissue and spores

- antimicrobial therapy: IV metronidazole

- neutralize unbound toxin with TIg

- supportive therapy: intubation, spasmolytic medications (benzodiazepines), quiet environment, cooling blanket

- control autonomic dysfunction: α- and β-blockade (e.g. labetalol), magnesium sulfate

**Prevention**

- infection with *C. tetani* does not produce immunity – vaccinate patients on diagnosis
- tetanus toxoid vaccination (see [Pediatrics, P3](#)/[Emergency Medicine, ER17](#))

---

**Rabies**

**Definition**

- acute progressive encephalitis caused by RNA virus (family: *Rhabdoviridae*, genus *Lyssavirus*)

**Etiology and Pathophysiology**

- any mammal can transmit the rabies virus
  - most commonly transmitted by raccoon, skunk, bat, fox, cat, and dog; monkeys also a risk in the developing world
- transmission: breaching of skin by teeth or direct contact of infectious tissue (saliva, neural tissue) with skin or mucous membranes
- virus travels via retrograde axonal transport from PNS to CNS
- virus multiples rapidly in brain, then spreads to other organs, including salivary glands
- development of clinical signs occurs simultaneously with excretion of rabies virus in saliva
- infected animal can transmit rabies virus as soon as it shows signs of disease

**Clinical Features**

- 5 stages of disease:
  1. incubation period
  2. prodrome (<1 wk)
  3. influenza-like illness: low-grade fever, malaise, anorexia, N/V, headache, sore throat
  4. pain, pruritus, paresthesia may occur at wound site
  5. once prodromal symptoms develop, there is rapid, irreversible progression to death
- progression from prodrome to coma and death may occur without an intervening acute neurologic syndrome
3. acute neurologic syndrome: 3 types (<1 wk)
   A. encephalitic (most common): hyperactivity, fluctuating LOC, hydrophobia, aerophobia, 
   hypersalivation, fever, seizures
      • painful pharyngeal spasms on encountering gust of air or swallowing water cause 
   aerophobia and hydrophobia, respectively
   B. paralytic: quadriplegia, loss of anal sphincter tone, fever
   C. atypical: rare
4. coma
   ▪ complete flaccid paralysis, respiratory and cardiovascular failure
5. death (within days to weeks of initial symptoms)

Investigations
• purpose of diagnosis by investigations is to limit patient contact with others and to identify 
  others exposed to the infectious source
• ante-mortem: direct immunofluorescence or PCR on multiple specimens: saliva, skin biopsy, 
  serum, CSF
• post-mortem: direct immunofluorescence in nerve tissue, presence of Negri bodies (inclusion 
  bodies in neurons)

Treatment
• post-exposure prophylaxis depends on regional prevalence (contact Public Health) and 
  circumstances surrounding injury
• 3 general principles:
  ▪ wound care: clean wound promptly and thoroughly with soap and running water
  ▪ passive immunization: HRIg infiltrated into wound site, with any remaining volume 
    administered IM in anatomical site distant from vaccine administration
  ▪ active immunization: inactivated rabies virus vaccine (series of shots post-exposure)
• treatment is supportive once victim manifests signs and symptoms of disease

Prevention
• pre-exposure vaccination
  ▪ recommended for high risk persons: laboratory staff working with rabies, veterinarians, 
    animal and wildlife control workers, long-term travellers to endemic areas

Systemic Infections

Sepsis and Septic Shock

• see Respirology; R33

Definitions
• systemic inflammatory response syndrome (SIRS): 2 or more of
  (a) temperature <35ºC/95ºF or >38.5ºC/101.3ºF
  (b) heart rate >90 beats per minute
  (c) respiratory rate >20 breaths per minute or PaCO₂ <32 mmHg
  (d) WBC <4 x 10⁹/L or >12 x 10⁹/L or >10% bands
• sepsis: SIRS + proven or provable infection
• severe sepsis: sepsis + signs of end-organ dysfunction and hypoperfusion
• septic shock: severe sepsis + hypotension (<90 mmHg sBP), despite adequate fluid resuscitation

Pathophysiology
• causative agents are identified in only 50-70% of cases
• when organisms are identified, GP and GN organisms are the cause in 90% of cases (GP > GN > 
  fungal)
• primary bloodstream infection or secondary bacteremia → local immune response → immune 
  cells release pro-inflammatory cytokines that defend against pathogens → immune response 
  spreads beyond local environment → unregulated, exaggerated systemic immune response → 
  vasodilation and hypotension → involvement of tissues remote from the site of injury/infection 
  resulting in multiple major organ dysfunction → followed by a period immunoparalysis

Clinical Features
• history: fever, chills, dyspnea, cool extremities, fatigue, malaise, anxiety, confusion
• physical: abnormal vitals (fever, tachypnea, tachycardia, hypotension), local signs of infection

Investigations
• CBC and differential, electrolytes, BUN, creatinine, liver enzymes, ABG, lactate, INR, PTT, FDP, 
  blood C&S x3, urinalysis, urine C&S and cultures of any wounds or lines
• CXR (other imaging depends on suspicion of focus of infection)
**Treatment** (also see Respiratory, R33)  
- **respiratory support:** \( \text{O}_2 \) ± intubation  
- **cardiovascular support:** IV fluids, ± norepinephrine + ICU  
- **IV antibiotics** (empirical, depends on suspected source)  
  - start with broad spectrum antibiotics (piperacillin-tazobactam or meropenem) ± additional agents depending on patient risk factors, suspected etiology of infection, and local microbial susceptibilities (± aminoglycoside or vancomycin)  
  - if *Pseudomonas* unlikely: (ceftriaxone or piperacillin-tazobactam or meropenem) ± vancomycin  
  - if drug-resistant GN (e.g. *Pseudomonas*) possible: ceftazidime or meropenem or piperacillin-tazobactam + gentamicin  
  - narrow once susceptibilities are known  
- **hydrocortisone IV** in patients with septic shock unresponsive to fluid resuscitation and vasopressors

---

**Tuberculosis (TB)**

**Etiology, Epidemiology and Natural History**
- 1/3 of the world’s population is infected with TB  
- contracted by aerosolized inhalation of *Mycobacterium tuberculosis*, a slow growing aerobe (doubling time = 18 h) that can evade innate host defenses, survive and replicate in macrophages  
- inhalation and deposition in the lung can lead one of the following outcomes:  
  1. immediate clearance of the pathogen  
  2. latent TB: asymptomatic infection contained by host immune defenses (represents 95% of infected people)  
  3. primary TB: symptomatic, active disease (represents 5% of infected people)  
  4. secondary TB: symptomatic reactivation of previously dormant TB (represents 5-10% of those with latent TB, most often within the first 2-3 yr of initial infection) at a pulmonary or extra-pulmonary site

**Risk Factors**
- social and environmental factors  
  - travel or birth in country with high TB prevalence (e.g. Asia, Latin America, Sub-Saharan Africa, Eastern Europe)  
  - aboriginal, crowded living conditions, low SES/homeless  
  - personal or occupational contact  
- host factors  
  - immunocompromised/immunosuppressed (including extremes of age)  
  - silicosis  
  - chronic renal failure requiring dialysis  
  - malignancy and chemotherapy  
  - substance abuse (e.g. drug use, alcoholism, smoking)

**Clinical Features**
- primary infection usually asymptomatic, although progressive primary disease may occur, especially in children and immunosuppressed patients  
- secondary infection/reactivation usually produces constitutional symptoms (fatigue, anorexia, night sweats, weight loss) and site-dependent symptoms  
  1. pulmonary TB  
   - chronic productive cough ± hemoptysis  
   - CXR consolidation or cavitation, lymphadenopathy  
   - non-resolving pneumonia despite standard antimicrobial therapy  
  2. miliary TB  
   - widely disseminated spread especially to lungs, abdominal organs, marrow, CNS  
   - CXR: multiple small 2-4 mm millet seed-like lesions throughout lung  
  3. extrapulmonary TB  
   - lymphadenitis, pleurisy, pericarditis, hepatitis, peritonitis, meningoitis, osteomyelitis (vertebral = Pott’s disease), adrenal (causing Addison’s disease), renal, ovary

**Investigations**
- screening for latent TB  
  - PPD/Mantoux skin tests  
    - both tests diagnose prior TB exposure; neither can diagnose or exclude active disease  
    - IFN-\( \gamma \) release assay (IGRA):  
      - in patients previously infected with TB, T-cells produce increased amounts of IFN-\( \gamma \) when re-exposed to TB antigen  
      - detects antigen not present in the BCG vaccine or in most types of non-tuberculous-mycobacteria (NTM), therefore fewer false positives

---

**Tuberculous Polyserositis**  
= pleural + pericardial + peritoneal effusions (usually from granuloma breakdown that spills TB into pleural cavity – very rare)
Canadian TB guidelines recommend IGRA as a confirmatory test if false positive or false negative test results are suspected, while American guidelines treat IGRAs as equivalent to the TB skin test and preferable in patients with a history of BCG vaccination or who may not return for skin test reading

- diagnostic tests/investigations for active pulmonary TB:
  - morning sputum on 3 consecutive days for acid-fast bacilli smear and culture
  - BAL
  - CXR:
    - nodular or alveolar infiltrates with cavitation (middle/lower lobe if primary, apical if secondary)
    - pleural effusion (usually unilateral and exudative) may occur independently of other radiograph abnormalities
    - hilar/mediastinal adenopathy (especially in children)
    - tuberculoma (semi-calcified well-defined solitary coin lesion 0.5-4 cm that may be mistaken for lung CA)
    - miliary TB
    - evidence of past disease: calcified hilar and mediastinal nodes, calcified pulmonary focus, pleural thickening with calcification, apical scarring

**Prevention**

- primary prevention
  - airborne isolation for active pulmonary disease
  - BCG vaccine
    - ~80% effective against pediatric miliary and meningeal TB
    - effectiveness in adults debated (anywhere from 0-80%)
    - routine use rarely recommended in Canadian population, however widely used in other countries
  - secondary prevention (defer in pregnancy unless mother is high risk)
    - likely INH-sensitive: isoniazid (INH) + pyridoxine (vit B6 to help prevent INH-associated neuropathy) x 9 mo
    - likely INH-resistant: rifampin x 4 mo

**Treatment of Active Infection**

- empiric therapy: INH + rifampin + pyrazinamide + ethambutol + pyridoxine
- pulmonary TB: INH + rifampin + pyrazinamide + ethambutol + pyridoxine x 2 mo (initiation phase), then INH + rifampin + pyridoxine x 4 mo in fully susceptible TB (continuation phase), total 6 mo
- extrapulmonary TB: same regimen as pulmonary TB but increase to 12 mo in bone/joint, CNS, and miliary/disseminated TB + corticosteroids for meningitis, pericarditis
- empiric treatment of suspected MDR (multidrug resistant) or XDR (extensively drug-resistant) TB requires referral to a specialist
  - MDR = resistance to INH and rifampin ± others
  - XDR = resistance to INH + rifampin + fluoroquinolone + ≥1 of injectable, second-line agents
  - suspect MDR TB if previous treatment, exposure to known MDR index case, or immigration from a high-risk area
- note: TB is a reportable disease to Public Health (please see Public Health Agency of Canada website for more information: www.publichealth.gc.ca)

### Leprosy (Hansen’s Disease)

**Etiology**

- *Mycobacterium leprae*: obligate intracellular bacteria, slow-growing (doubling time 12.5 d), survives in macrophages
- bacteria transmitted from nasal secretions, potentially via skin lesions
- invades skin and peripheral nerves leading to chronic granulomatous disease

**Clinical Features**

- lesions involve cooler body tissues (e.g. skin, superficial nerves, nose, eyes, larynx)
- spectrum of disease determined by host immune response to infection
  - i. paucibacillary “tuberculoid” leprosy (intact cell-mediated immune response)
    - ≤5 hypoesthetic lesions, usually hypopigmented, well-defined, dry
    - early nerve involvement, enlarged peripheral nerves, neuropathic pain
    - may be self-limited, stable, or progress over time to multibacillary “lepromatous” form
  - ii. multibacillary “lepromatous” leprosy (weak cell-mediated immune response)
    - ≥6 lesions, symmetrical distribution
    - leonine facies (nodular facial lesions, loss of eyebrows, thickened ear lobes)
    - extensive cutaneous involvement, late and insidious nerve involvement causing sensory loss at the face and extremities
  - iii. borderline leprosy
    - lesions and progression lies between tuberculoid and lepromatous forms
Investigations
- skin biopsy down to fat or slit skin smears for AFB, PCR
- histologic appearance: intracellular bacilli in spherical masses (lepra cells), granulomas involving cutaneous nerves

Treatment (WHO Treatment Regimens)
- paucibacillary: dapsone + rifampin monthly x 6 mo
- single skin lesion paucibacillary: single dose of rifampicin, ofloxacin, and minocycline
- multibacillary and borderline: dapsone + rifampin monthly + clofazimine monthly x 12 mo and low dose clofazimide once daily x 12 mo
- treatment of leprosy can cause an immune reaction to killed bacteria (e.g. erythema nodosum leprosum and reversal reaction): symptomatic management with NSAIDs if mild, prednisone with 6-12 wk taper if severe; thalidomide for erythema nodosum leprosum

Prognosis
- curable with WHO-approved treatment regimens
- complications: muscle atrophy, contractures, trauma/superinfection of lesions, crippling/loss of limbs, erythema nodosum leprosum
- long post-treatment follow-up warranted to monitor for relapse and immune reactions

Syphilis

Etiology
- Treponema pallidum: thick motile spirochetes historically detectable by dark-field microscopy (rarely done now)
- transmitted sexually, vertically, or parenterally (rare)

Clinical Features
- see Dermatology, D31 and Gynecology, GY28
- multi-stage disease
  i. primary syphilis (3-90 d post-infection)
    - painless chancre at inoculation site (any mucosal surface)
    - regional lymphadenopathy
    - acute disease lasts 3-6 wk, 25% progress to secondary syphillis without treatment
  ii. secondary syphilis = systemic infection (2-8 wk following chancre)
    - maculo-papular non-pruritic rash including palms and soles
    - generalized lymphadenopathy, low grade fever, malaise, headaches, aseptic meningitis, ocular/otic syphilis
    - condylomata lata: painless, wart-like lesion on palate, vulva or scrotum (highly infectious)
  iii. latent syphilis
    - asymptomatic infection that follows untreated primary/secondary syphillis
    - early latent (<1 yr post-infection) or late latent/unknown duration (>1 yr post-infection)
    - increased transmission risk with early latent; longer treatment duration required for late latent
  iv. tertiary syphilis (1-30 yr post-infection)
    - gummatous syphilis: nodular granulomas of skin, bone, liver, testes, brain
    - aortic aneurysm and aortic insufficiency
    - neurosyphilis: dementia, personality changes, Argyll-Robertson pupils, tabes dorsalis
  v. congenital syphilis
    - causes spontaneous abortions, stillbirths, congenital malformations, developmental delay, deafness
    - infants may be asymptomatic until age 2-5 yr then present with rhinitis, lymphadenopathy, hepatosplenomegaly, bone and cartilage degeneration (including saddle nose, saber shins), CN VIII deafness

Investigations
- screening tests: VDRL and RPR (non-treponemal), EIA (treponemal)
- confirmatory tests: FTA-ABS, MHA-TP, TPPA, TPI, dark field microscopy with silver stain
- LP for 3rd syphilis if: seropositive and symptoms of neurosyphilis or treatment failure/other tertiary symptoms/RPR ≥1:32, or with HIV disease and late latent/unknown duration syphilis

Treatment
- for 1st, 2nd: early latent: benzathine penicillin G 2.4 million units IM x 1
- for 3rd: late latent: benzathine penicillin G 2.4 million units IM weekly x 3
- if allergic to penicillin: doxycycline 100 mg PO bid x 14 d
- neurosyphilis: aqueous Penicillin G 18-24 million units/d IV x 14 d

Generalized STI Workup
- see Family Medicine, FM46
Lyme Disease

Etiology/Epidemiology
- spirochete bacteria: *Borrelia burgdorferi* (N. America), *B. garinii, B. afzelii* (Europe and Asia)
- transmitted by Ixodes tick
- reported in 49 of the 50 U.S. states, but most cases occur in the Northeast, the Midwest, and Northern California
- in Canada, reported in southern and southeastern Quebec, southern and eastern Ontario, southeastern Manitoba, New Brunswick and Nova Scotia as well as southern British Columbia
- small rodents (mice) serve as primary reservoir, while larger animals (white tailed deer) serve as hosts for ticks
- human contact usually May-August in fields with low brush near wooded areas
- infection usually requires >36 h tick attachment

Clinical Features
- stage 1 (early localized stage: 7-14 d post-bite)
  - malaise, fatigue, headache, myalgias
  - erythema migrans (EM): expanding, non-pruritic bulls-eye (target) lesions (red with clear centre) on thigh/groin/axilla
- stage 2 (early disseminated stage): weeks post-infection
  - CNS: aseptic meningitis, CN palsies (CNVII palsy), peripheral neuritis
  - cardiac: transient heart block or myocarditis
- stage 3 (late persistent stage: months to years post-infection)
  - may not have preceding history of early stage infection
  - MSK: chronic monoarticular or oligoarticular arthritis
  - acrodermatitis chronica atrophicans (due to *B. afzelii*)
  - neurologic: encephalopathy, meningitis, neuropathy

Investigations
- serology: ELISA, Western Blot

Prevention
- use of protective clothing (tuck pants into socks), insect repellent, inspection for ticks and prompt removal of tick
- prophylaxis within 72 h of finding engorged attached nymphal tick that has been attached ≥36 h (approximately) in hyperendemic area (local rate of infection of ticks ≥20%): doxycycline

Treatment
- stage 1: doxycycline/amoxicillin/cefuroxime
- stage 2-3: ceftriaxone

Toxic Shock Syndrome (TSS)

Etiology
- superantigens produced by some strains of *S. aureus* or GAS cause widespread T-cell activation and pro-inflammatory cytokine release (IL-1, IL-6, TNF). Course of disease is precipitous and leads to acute fever, shock, multiorgan failure
- Staphylococcal TSS involves the production of superantigen TSST-1 (toxic shock syndrome toxin 1)
- Streptococcal TSS involves the production of superantigens SPEA, SPEB, SPEC

Risk Factors
- Staphylococcal: tampon use, nasal packing, wound infections (e.g. postpartum vaginal or caesarean or other surgical infections)
- Streptococcal: minor trauma, surgical procedures, preceding viral illness (chickenpox), use of NSAIDs

Clinical Features and Investigations
- acute onset, fever, sBP <90 mmHg
- Staphylococcal TSS:
  - rash with subsequent desquamation, especially on palms and soles
  - involvement of 3 or more organ systems: GI (vomiting, diarrhea), muscular (myalgia, increased CK), mucous membranes (hyperemia), renal, hepatic, hematologic (thrombocytopenia), CNS (disorientation)
  - isolation of *S. aureus* is not required for diagnosis (*S. aureus* is rarely recovered from blood in TSS)
- Streptococcal TSS:
  - erythematous macular rash
  - isolation of GAS (e.g. blood, pleural, tissue biopsy, or surgical wound)
  - ≥2 of coagulopathy, liver involvement, ARDS, soft tissue necrosis (necrotizing fasciitis, myositis, gangrene), renal impairment
Treatment
• supportive: fluid resuscitation
• Staphylococcal: for methicillin-susceptible S. aureus: clindamycin + cloxacillin (IV); for MRSA: vancomycin x 10-14 d
• Streptococcal: IV penicillin and clindamycin and IV Ig

Cat Scratch Disease

Etiology
• Bartonella henselae: intracellular bacteria
• cat-to-human transmission via cat scratch/bite

Clinical Features
• skin lesion appears 3-10 d post-inoculation
• may be followed by fever, tender regional lymphadenopathy
• in some patients, organism may disseminate causing hepatosplenomegaly, neurologic symptoms
• usually self-limited

Investigations
• serology, lymph node biopsy

Treatment
• supportive in most cases
• azithromycin x 10-14 d in patients with moderate-severe disease or immunocompromise

Rocky Mountain Spotted Fever

Etiology
• Rickettsia rickettsii: obligate intracellular GN organism
• reservoir hosts: rodents, dogs
• vectors: Dermacentor ticks
• organisms cause inflammation of endothelial lining of small blood vessels, causing small hemorrhages and thrombi
• can cause widespread vasculitis leading to headache, CNS changes and can progress to death if treatment is delayed

Clinical Features
• usually occurs in summer following tick bite
• influenza-like prodrome: acute onset fever, headache, myalgia, nausea/vomiting, anorexia
• macular rash appearing on day 2-4 of fever
  ▪ begins on wrists and ankles, then spreads centrally to arms/legs/trunk/palms/soles
  ▪ occasionally “spotless” (10% of patients)

Investigations
• skin biopsy and serology (indirect fluorescent antibody test)

Treatment
• doxycycline, usually 5-7 d course

West Nile Virus

Epidemiology
• virus has been detected throughout the United States and much of southern Canada
• overall case-fatality rates in severe cases are ~10%

Transmission
• primarily from mosquitoes that have fed on infected birds (crows, blue jays)
• transplacental, blood products (rare), organ transplantation

Clinical Features
• most are asymptomatic
• most symptomatic cases are mild (West Nile fever): acute onset of headache, back pain, myalgia, anorexia, maculopapular non-pruritic rash involving chest, back, arms
• severe complications: encephalitis, meningoencephalitis and acute flaccid paralysis (especially in those >60 yr)
Investigations
- IgM antibody in serum or CSF (cross reactivity with yellow fever and Japanese encephalitis vaccines, and with dengue fever and St. Louis virus infection); may not reflect current illness as IgM antibody can last for >6 mo
- Viral isolation by PCR from CSF, tissue, blood and fluids (all have low sensitivity)
- CSF: elevated lymphocytes and protein if CNS involvement

Treatment and Prevention
- treatment: supportive
- prevention: mosquito repellent (DEET), drain stagnant water, community mosquito control programs

Fungal Infections

Skin and Subcutaneous Infections

Superficial Fungal Infections
- see Dermatology, D25

Dermatophytes
- see Dermatology, D26

Subcutaneous Fungal Infection

Pathophysiology
- fungi that naturally reside in soil and enter skin via traumatic break
- *Sporothrix schenckii*: most commonly affects gardeners injured by a rose thorn or splinter
  - causes subcutaneous nodule at point of entry
  - fungi may migrate up lymphatic vessels creating nodules along the way – “nodular lymphangitis”

Treatment
- oral azole (e.g. itraconazole)
- IV amphotericin B for severe or disseminated infection

Endemic Mycoses

Basics
- three major endemic mycoses in North America
  - histoplasmosis
  - blastomycosis
  - coccidioidomycosis
- thermally dimorphic organisms: mold in cold temperature (e.g. soil) and yeast at higher temperature (e.g. tissue)
- infection occurs through inhalation of spores (soil, bird droppings, vegetation) or inoculation injury
- all can cause pneumonia and may disseminate hematogenously
- may reactivate or disseminate during immunocompromise

Treatment
- common to all systemic mycoses
  - oral azole (e.g. itraconazole for mild-moderate local infection)
  - IV amphotericin B for systemic infection

Histoplasmosis is commonly associated with exposure to chicken coops, bird roosts and bat caves.

High Risk for Dissemination
- Immuno compromised (e.g. AIDS, steroids, TNF-α inhibitors)
- Pregnancy (3rd trimester)
- Diabetes
### Table 20. Endemic Mycoses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Endemic Region</th>
<th>Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
</table>
| *Histoplasma capsulatum* | Ohio and Mississippi river valleys in central USA, Ontario, Quebec; widespread | Asymptomatic (in most people)  
Primary pulmonary  
- Fever, cough, chest pain, headache, myalgia, anorexia  
- CXR (acute): pulmonary infiltrates ± hilar lymphadenopathy  
- CXR (chronic): pulmonary infiltrates, cavitary disease  
Disseminated (rare)  
- Occurs primarily in immunocompromised patients  
- Spread to bone marrow (pancytopenia), GI tract (ulcers), lymph nodes (lymphadenitis), skin, liver, adrenals, CNS | Fungal culture, fungal stain  
Antigen detection (urine and serum) |
| *Blastomyces dermatitidis* | States east of Mississippi River, Northern Ontario and along the great lakes | May be asymptomatic  
Primary: acute or chronic pneumonia  
- Fever, cough, chest pain, chills, night sweats, weight loss  
- CXR (acute): lobar or segmental pneumonia  
- CXR (chronic): lobar infiltrates, fibronodular interstitial disease  
Disseminated  
- Spread to skin (verrucous lesions that mimic skin cancer, ulcers, subcutaneous nodules), bones (osteomyelitis, osteolytic lesions), GU tract (prostatitis, epididymitis) | Sputum smear and culture  
Direct examination of clinical specimens for characteristic broad-based budding yeast (sputum, tissue, purulent material) |
| *Coccidioides immitis*   | Deserts in southwest USA, northwest Mexico                                   | Primary  
- "Valley fever": subacute fever, chills, cough, chest pain, sore throat, fatigue that lasts for weeks to months  
- Can develop hypersensitivity with arthralgias, erythema nodosum  
Disseminated  
- Rare spread to skin (ulcers), joints (synovitis), bones (lytic lesions), meninges (meningitis)  
- Common opportunistic infection in patients with HIV | Sputum culture  
Direct examination of clinical specimens for characteristic yeast (sputum, tissue, purulent material) |

### Opportunistic Fungi

**Pneumocystis jiroveci (formerly P. carinii)**

**Microbiology**
- unicellular fungi
- previously classified as a protozoa

**Transmission**
- rarely person-to-person transmission
- most disease is due to reactivation of latent infection acquired by the respiratory route or reinfection by a different genotype
  - causes clinical disease in immunocompromised patients (steroid use, HIV)
  - 80% lifetime risk without prophylaxis in patients with CD4 count <200 cells/mm³

**Clinical Features**
- symptoms of pneumonia: fever, nonproductive cough, progressive dyspnea
- classic CXR (see sidebar)

**Investigations**
- demonstration of organism in induced sputum, bronchoalveolar lavage, or endotracheal aspirate (if intubated)

**Treatment and Prevention**
- oxygen to keep SaO₂ >90%
- antimicrobial options:
  - TMP/SMX (PO or IV) *First line*
  - dapsone and TMP
  - clindamycin and primaquine
  - pentamidine (IV)
  - atovaquone
- corticosteroids used as adjuvant therapy in those with severe hypoxia (pO₂ <70 mmHg or A-a gradient O₂ >35 mmHg)
- prophylactic TMP/SMX for those at high risk of infection (HIV patients when CD4 <200 cells/mm³ or non-HIV immunocompromised patients under specific conditions)

**CXR in P. jiroveci**
- Bilateral, diffuse opacities
- CXR may be normal (20-30% cases)
- CT shows cysts (hence the name Pneumo "cystis") but almost never pleural effusions
**Cryptococcus spp.**

**Microbiology**
- encapsulated yeast found worldwide
- 2 human pathogenic species: *C. gattii, C. neoformans*

**Transmission**
- inhalation of airborne yeast from soil contaminated with pigeon droppings (*C. neoformans*) or certain tree species such as Eucalyptus or Douglas fir (*C. gattii*) may cause local infection in lung, asymptomatic or pneumonia
- may also spread hematogenously to the CNS, skin, bones and other organs
- *C. neoformans* tends to affect immunocompromised hosts
- *C. gattii* tends to affect immunocompetent hosts

**Clinical Features**
- pulmonary
  - usually asymptomatic or self-limited pneumonitis
  - only 2% of HIV+ patients present with pulmonary symptoms including productive cough, chest tightness, and fever
- disseminated
  - frequently disseminates in HIV+ population
  - CNS: meningitis (leading cause of meningitis in patients with HIV)
  - skin: umbilicated papules that resemble large lesions of *Molluscum contagiosum*

**Investigations**
- serum cryptococcal antigen
- CSF for meningitis: India-ink stain, cryptococcal antigen test, culture to confirm
- blood C&S

**Treatment**
- in patients with HIV who have cryptococcal meningitis or severe pulmonary disease:
  - amphotericin B (+ flucytosine) is used in the first 2 wk for induction therapy; limited duration due to side effects
  - switch to fluconazole for at least 8 wk as consolidation therapy, then continue at lower dose for prolonged maintenance

**Candida albicans**

**Microbiology**
- yeast forms with pseudohyphae at 20°C and germ tube formation at 37°C

**Transmission**
- normal flora of skin, mouth, vagina and GI tract
- risk factors for overgrowth:
  - immunocompromised state (diabetes, corticosteroids)
  - ICU patients (broad-spectrum antibiotic use, central venous catheters, TPN)

**Clinical Features**
- mucocutaneous
  - oral thrush, esophagitis (chest pain, odynophagia), vulvovaginitis (see Gynecology, GY24), balanitis, cutaneous (diaper rash, skin folds, folliculitis), chronic mucocutaneous
  - small satellite lesions beyond the margin of the rash distinguish it from tinea or other conditions
- invasive
  - candidemia, endophthalmitis, endocarditis, UTI (upper tract), hepatosplenic disease

**Treatment**
- thrush: nystatin suspension or pastilles for mild disease, fluconazole for severe disease
- vulvovaginal candidiasis: topical agents (imidazole or nystatin), oral fluconazole for recurrent disease
- cutaneous infection: topical imidazole
- opportunistic infections in HIV, other systemic infections: fluconazole or echinocandin
- chronic mucocutaneous: azoles

**Aspergillus spp.**

**Microbiology**
- branching septate hyphae
- common species causing disease include *A. fumigatus, A. flavus*
Transmission
- ubiquitous in the air and the environment
- *Aspergillus* produces a toxin called aflatoxin that contaminates nuts, grains and rice

Clinical Features
- allergic bronchopulmonary aspergillosis (ABPA)
  - IgE-mediated asthma-type reaction with dyspnea, high fever and transient pulmonary infiltrates
  - occurs more frequently in patients with asthma and allergies
- aspergilloma (fungus ball)
  - ball of hyphae in a preexisting lung cavity
  - symptoms range from asymptomatic to massive hemoptysis
  - CXR: round opacity surrounded by a thin lucent rim of air, often in upper lobes (“air crescent” sign)
- invasive aspergillosis
  - associated with prolonged and persistent neutropenia
  - pneumonia – most common
  - may disseminate to other organs: brain, skin
  - severe symptoms with fever, cough, dyspnea, pleuritic pain, tends to cavitate; fatal if not treated early and aggressively
  - CXR: local or diffuse infiltrates ± pulmonary infarction, pulmonary nodules
- mycotoxicosis
  - aflatoxin produced by *A. flavus* (nuts, grains, rice)
  - results in liver hemorrhage, necrosis and hepatocellular carcinoma formation

Treatment Options
- for invasive aspergillosis: voriconazole or amphotericin B
- surgical resection for aspergilloma and hemorrhage
- corticosteroids for ABPA

Parasitic Infections

Protozoa – Intestinal/Genitourinal Infections

Entamoeba histolytica (Amoebas)

Transmission
- reservoir: infected humans
- cysts by fecal-oral and food/waterborne transmission in areas of poor sanitation
- seen in immigrants, travellers, institutionalized individuals, Aboriginal Canadians, MSM

Clinical Features
i. asymptomatic carriers
ii. amoebic dysentery
  - abdominal pain, cramping, colitis, dysentery, low grade fever with bloody diarrhea secondary to local tissue destruction and ulceration of large intestine
iii. amoebic abscesses
  - most common in liver (hematologic spread); presents with RUQ pain, weight loss, fever, hepatomegaly
  - can also occur in lungs and brain

Investigations
- serology, fecal/serum antigen testing, stool exam (for cysts and trophozoites), colon biopsy
- *E. histolytica* indistinguishable microscopically from the non-pathogen *E. dispar* (distinguish by specific stool antigen detection)

Treatment and Prevention
- metronidazole
- for invasive disease or cyst elimination: follow with iodoquinol or paromomycin
- aspiration of hepatic abscess if risk of cyst rupture, poor response to medical therapy, or diagnostic uncertainty
- asymptomatic cyst: iodoquinol or paromomycin alone
- good personal hygiene, purification of water supply by boiling, filtration (not chlorination)
**Giardia lamblia**

**Transmission**
- reservoir: infected humans and other mammals
- food/waterborne (especially in the Rockies) and fecal-oral transmission of infectious cysts
- risk factors: travel, camping, institutions, day care centres, MSM

**Clinical Features**
- giardiasis (“beaver fever”)
  - symptoms vary from asymptomatic to self-limited mild watery diarrhea to malabsorption syndrome (chronic giardiasis where the parasite coats small intestine and thus prevents fat absorption)
  - nausea, malaise, abdominal cramps, bloating, flatulence, fatigue, weight loss, steatorrhea
  - no hematochezia (no invasion into intestinal wall), no mucus in stool

**Investigations**
- multiple stool samples (daily x 3 d) for microscopy, stool antigen used occasionally
- occasionally small bowel aspirate or biopsy

**Treatment and Prevention**
- metronidazole, nitazoxanide if symptomatic
- good personal hygiene and sanitation, water purification (iodine better than chlorination), outbreak investigation

**Trichomonas vaginalis**

**Transmission**
- sexual contact

**Clinical Features**
- often asymptomatic (10-50%), especially males (occasionally urethritis, prostatitis)
- trichomonas vaginitis (see Gynecology, GY25)
  - vaginal discharge (profuse, malodorous, yellow-green or grey, frothy), pruritus, dysuria, dyspareunia

**Investigations**
- wet mount (motile parasites), antigen detection, culture
- urine PCR to detect in males

**Treatment**
- metronidazole for patient and partner(s)

**Cryptosporidium spp.**

**Transmission**
- reservoir: infected humans and a wide variety of young animals
- fecal-oral transmission by ingestion of cysts, waterborne
- risk factors: summer and fall, young children (day care), MSM, contact with farm animals, immunocompromise, immune reconstitution

**Clinical Features**
- range from self-limited watery diarrhea (immunocompetent) to chronic, severe, non-bloody diarrhea with nausea, vomiting, abdominal pain, and anorexia resulting in weight loss and death (immunocompromised)

**Investigations**
- modified acid-fast stain of stool specimen, microscopic identification of oocysts in stool or tissue, stool antigen detection by direct fluorescent antibody

**Treatment and Prevention**
- supportive care only for immunocompetent hosts
- in HIV, try HAART to restore immunity; if fails, try nitazoxanide
- good personal hygiene, water filtration
Blood and Tissue Infections

Plasmodium spp. (Malaria)

Microbiology
- species include: *P. falciparum* (most common and most lethal), *P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi* (new species isolated from primates in Malaysia, potentially fatal)
- complex life cycle: human host for asexual reproduction and mosquito for sexual reproduction
- sporozoite from mosquitoes infect liver cells in which parasites multiply and are released as merozoites which infect RBCs causing disease
- *P. ovale* and *P. vivax* can produce dormant hypnozoites in the liver that may cause relapsing malarial attacks by reactivating (entering the erythrocytic cycle) after many months

Transmission
- reservoir: infected human
- transmission by the bite of the female Anopheles mosquito, vertical transmission and blood transfusion
- occurs in tropical/subtropical regions (sub-Saharan Africa, Oceania, South Asia, Central America, Southeast Asia, South America)

Clinical Features
- flu-like prodrome
- paroxysms of high spiking fever and shaking chills (due to synchronous systemic lysis of RBCs)
  - *P. vivax* and *P. ovale*: chills and fever q48h but can be variable
  - *P. malariae*: chills and fever q72h but can be variable
  - *P. falciparum*: less predictable fever interval, can be highly variable (>90% ill within 30 d)
- abdominal pain, diarrhea, myalgia, headache, and cough
- hepatosplenomegaly and thrombocytopenia without leukocytosis

Complications
- *P. falciparum*: CNS involvement (cerebral malaria = seizures and coma), severe anemia, acute renal failure, ARDS, primarily responsible for fatal disease
- *P. knowlesi*, and rarely *P. vivax* can be fatal

Investigations
- microscopy: blood smear q12-24h (x3) to rule out infection
  - thick smear (Giemsa stain) for presence of organisms
  - thin smear (Giemsa stain) for species identification and quantification of parasites
- rapid antigen detection tests

Treatment and Prevention
- *P. vivax*, *P. ovale*: chloroquine (and primaquine to eradicate liver forms)
- *P. vivax*, chloroquine resistant: primaquine with quinine and doxycycline or tetracycline or mefloquine
- *P. malariae*, *P. knowlesi*: chloroquine
- *P. falciparum*: most areas of the world show chloroquine resistance
  - artesinin combination therapy (e.g. artesunate + doxycycline or clindamycin or atovaquone/proguanil)
  - atovaquone/proguanil combination (Malarone®)
  - quinine plus doxycycline, tetracycline or clindamycin
  - mefloquine and artesiminin resistance increasing in southeast Asia (check local resistance)
- prevented by antimalarial prophylaxis, bed nets, insect repellent

Trypanosoma cruzi

Transmission
- found in Mexico, South America and Central America
- transmission by Reduviid insect vector ("Kissing Bug"), which defecate on skin and tryptomastogotes in the stool usually rubbed into bite site by host (majority of infections)
- also transmitted via placental transfer, organ donation, blood transfusion and ingestion of contaminated food containing Reduviid insects (especially cane juice)

Clinical Features
- American trypanosomiasis (Chagas disease)
  - acute: usually asymptomatic, local swelling at site of inoculation ("Romanas sign"; usually around one eye) with variable fever, lymphadenopathy, cardiomegaly and hepatosplenomegaloy
  - intermediate phase: asymptomatic but increasing levels of parasite and antibody in blood; most infected persons remain in this phase
  - chronic: can lead to chronic dilated cardiomyopathy, esophagomegaly and megacolon 10-25 yr after acute infection in 30-40% of infected individuals

Trypanosoma cruzi

Transmission
- reservoir: infected human
- transmission by the bite of the female Anopheles mosquito, vertical transmission and blood transfusion
- occurs in tropical/subtropical regions (sub-Saharan Africa, Oceania, South Asia, Central America, Southeast Asia, South America)

Clinical Features
- acute: usually asymptomatic, local swelling at site of inoculation ("Romanas sign"; usually around one eye) with variable fever, lymphadenopathy, cardiomegaly and hepatosplenomegaloy
- intermediate phase: asymptomatic but increasing levels of parasite and antibody in blood; most infected persons remain in this phase
- chronic: can lead to chronic dilated cardiomyopathy, esophagomegaly and megacolon 10-25 yr after acute infection in 30-40% of infected individuals

Complications
- *P. falciparum*: CNS involvement (cerebral malaria = seizures and coma), severe anemia, acute renal failure, ARDS, primarily responsible for fatal disease
- *P. knowlesi*, and rarely *P. vivax* can be fatal

Investigations
- microscopy: blood smear q12-24h (x3) to rule out infection
  - thick smear (Giemsa stain) for presence of organisms
  - thin smear (Giemsa stain) for species identification and quantification of parasites
  - rapid antigen detection tests

Treatment and Prevention
- *P. vivax*, *P. ovale*: chloroquine (and primaquine to eradicate liver forms)
- *P. vivax*, chloroquine resistant: primaquine with quinine and doxycycline or tetracycline or mefloquine
- *P. malariae*, *P. knowlesi*: chloroquine
- *P. falciparum*: most areas of the world show chloroquine resistance
  - artesinin combination therapy (e.g. artesunate + doxycycline or clindamycin or atovaquone/proguanil)
  - atovaquone/proguanil combination (Malarone®)
  - quinine plus doxycycline, tetracycline or clindamycin
  - mefloquine and artesiminin resistance increasing in southeast Asia (check local resistance)
- prevented by antimalarial prophylaxis, bed nets, insect repellent

Figure 9. Life cycle of Plasmodium spp.
Investigations
• wet prep and Giemsa stain of thick and thin blood smear, serology, PCR

Treatment and Prevention
• acute: nifurtimox or benznidazole
• intermediate: increasing trend to treat as acute infection
• chronic: symptomatic therapy, surgery including heart transplant, or esophagectomy, colectomy, as necessary, may be a benefit to antiparasitic treatment
• insect control, bed nets

**Toxoplasma gondii**

Transmission
• acquired through exposure to cat feces (oocysts), ingestion of undercooked meat (tissue cysts), vertical transmission, organ transplantation, whole blood transfusions

Clinical Features
• congenital
  ▪ result of acute primary infection of mother during pregnancy (TORCH infection – see Obstetrics, OB20)
  ▪ stillbirth (rare), chorioretinitis, blindness, seizures, severe developmental delay, microcephaly
  ▪ initially asymptomatic infant may develop reactivation of chorioretinitis as adolescent or adult → blurred vision, scotoma, ocular pain, photophobia, epiphora, hearing loss, developmental delay
• acquired
  ▪ usually asymptomatic or mononucleosis-like syndrome in immunocompetent patient
  ▪ infection remains latent for life unless reactivation due to immunosuppression
• immunocompromised (most commonly AIDS with CD4 <200)
  ▪ encephalitis with focal CNS lesions seen as single or multiple ring-enhancing masses on CT (headache and focal neurological signs)
  ▪ lymph node, liver and spleen enlargement and pneumonitis
  ▪ chorioretinitis

Investigations
• serology, CSF Wright-Giemsa stain, antigen or DNA detection (PCR); pathology provides definitive diagnosis
• immunocompromised patients: consider CT scan (ring-enhancing lesion in cortex or deep nuclei) and ophthalmologic examination
• negative serology in many AIDS patients (false negative due to decreased lymphocyte population)

Treatment and Prevention
• no treatment if: immunocompetent, not pregnant, no severe organ damage
• pregnancy: spiramycin to prevent transplacental transmission or pyrimethamine + sulfadiazine (add folic acid), avoid undercooked meat and refrain from emptying cat litter boxes
• HIV: pyrimethamine + sulfadiazine, AIDS prophylaxis: see HIV section
• eye disease, meningitis: corticosteroids
• proper hand hygiene, cook meat thoroughly

**Helminths**

**Roundworms – Nematodes**

Table 21. Nematodes (roundworms)

<table>
<thead>
<tr>
<th>Nematode</th>
<th>Epidemiology</th>
<th>Transmission</th>
<th>Medical Importance</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascaris lumbricoides</td>
<td>Tropics</td>
<td>Human feces, ingestion of contaminated food or water</td>
<td>Abdominal pain and intestinal obstruction from high worm burden Cough, dyspnea, pulmonary infiltrates from larval migration through lungs (Löffler’s syndrome)</td>
<td>Mebendazole OR albendazole OR pyrantel pamoate</td>
</tr>
<tr>
<td>Trichuris trichuria</td>
<td>Tropics</td>
<td>Ingestion of eggs in soil</td>
<td>Diarrhea (± mucus, blood), abdominal pain, rectal prolapse, stunted growth</td>
<td>Mebendazole OR albendazole</td>
</tr>
<tr>
<td>Onchocerca volvulus</td>
<td>Africa, Latin America</td>
<td>Blackfly bite</td>
<td>River blindness (onchocerciasis), dermatitis</td>
<td>Ivermectin + doxycycline</td>
</tr>
</tbody>
</table>

Figure 10. Life cycle of *Toxoplasma gondii*
### Table 21. Nematodes (roundworms) (continued)

<table>
<thead>
<tr>
<th>Nematode</th>
<th>Epidemiology</th>
<th>Transmission</th>
<th>Medical Importance</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Wuchereria bancrofti</em></td>
<td>Tropics</td>
<td>Mosquito bite</td>
<td>Damage to lymphatics resulting in lymphadenopathy, lymphedema, and elephantiasis</td>
<td>Diethylcarbamazine + doxycycline</td>
</tr>
<tr>
<td><strong>Loa Loa</strong></td>
<td>Central Africa</td>
<td>Deer fly bite</td>
<td>Subcutaneous migration of worm, hyperresponsiveness in travelers</td>
<td>Diethylcarbamazine, removal of adult</td>
</tr>
<tr>
<td><em>Enterobius vermicularis</em> (Pinworm)</td>
<td>Worldwide</td>
<td>Human host: fecoral self-inoculation and fomite person-to-person transfer</td>
<td>Asymptomatic carriers or severe nocturnal perianal itching (pruritus ani) Occasional vaginitis Abdominal pain, nausea, vomiting with high worm burden</td>
<td>Sticky tape test: eggs adhere to tape applied to perianal skin (need 5-7 tests to rule out) Examination of perianal skin at night may reveal adult worms Usually no eosinophilia as no tissue invasion Mebendazole, albendazole; pyrantel in pregnancy Change underwear; bathe in morning, pajamas to bed, wash hands, trim fingernails Treat all family members simultaneously Reinfection common</td>
</tr>
<tr>
<td><strong>Strongyloides stercoralis</strong> (Threadworm)</td>
<td>Subtropical, tropical and temperate (including southern US)</td>
<td>Fecal contamination of soil. transmission via unbroken skin, walking barefoot Autoinfection: penetration of larva through GI mucosa or perianal skin Adult worms live in mucoza of small intestine</td>
<td>One of few worms able to multiple in human host Mostly asymptomatic infection or can have pruritic dermatitis at site of larval penetration Transient pulmonary symptoms during pulmonary migration of larvae (eosinophilic pneumonitis = Loffler’s syndrome) Abdominal pain, diarrhea, pruritis ani, larva currens (itchy rash) Hyperinfection: occasional fatal cases caused by massive auto-infection in immunocompromised host; immunosuppressive therapy, including high-dose corticosteroids, is the most common risk factor for disseminated infection</td>
<td>Ivermectin, 200 µg/kg/d PO x 2 doses (albendazole 40 mg PO bid x 7 d, less effective)</td>
</tr>
</tbody>
</table>

### Flatworms

#### Cestodes/Trematodes

### Table 22. Cestodes/Trematodes (flatworms)

<table>
<thead>
<tr>
<th></th>
<th>Epidemiology</th>
<th>Transmission</th>
<th>Medical Importance</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CESTODES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Taenia solium</em></td>
<td>Developing countries</td>
<td>Undercooked pork (larvae), human feces (eggs)</td>
<td>Taeniasis: mild abdominal symptoms Cysticercosis: mass lesions in CNS, eyes, skin, seizures</td>
<td>Corticosteroids + albendazole for cysticercosis Antiepileptics if seizures \ praaziquantel for adult tapeworm in gut (taeniasis)</td>
</tr>
<tr>
<td><em>Taenia saginata</em></td>
<td>Developing countries</td>
<td>Undercooked beef (larvae)</td>
<td>Mild GI symptoms</td>
<td>Praziquantel</td>
</tr>
<tr>
<td><em>Diphyllobothrium latum</em></td>
<td>Europe, North America, Asia</td>
<td>Raw fish</td>
<td>B12 deficiency leading to macrocytic anemia and posterior column deficits</td>
<td>Praziquantel</td>
</tr>
<tr>
<td><em>Echinococcus granulosus</em></td>
<td>Rural areas, sheep raising countries</td>
<td>Dog feces (eggs)</td>
<td>Liver/lung cysts (enlarge between 1-20 yr; may cause mass effect or rupture) Risk of anaphylaxis if cystic fluid released during surgical evacuation</td>
<td>Albendazole alone Surgery + perioperative albendazole Percutaneous aspiration + perioperative albendazole</td>
</tr>
<tr>
<td><strong>TREMATODES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Clonorchis sinensis</em></td>
<td>Japan, Taiwan, China, SE Asia</td>
<td>Raw fish</td>
<td>Exists in bile ducts, causes inflammation and sometimes cholangiocarcinoma</td>
<td>Praziquantel</td>
</tr>
<tr>
<td><em>Schistosoma spp.</em></td>
<td>Africa, SE Asia, focal in Western Hemisphere</td>
<td>Fresh water exposure</td>
<td>Chronic sequelae secondary to long-term infection (e.g. chronic liver disease, SCC of the bladder)</td>
<td>Praziquantel</td>
</tr>
</tbody>
</table>
### Trematodes/Flukes

#### Schistosoma spp.

**Species**
- *S. mansoni*, *S. hematobium*, *S. japonicum*

**Transmission**
- larvae (cercariae), released from snails, penetrate unbroken skin in infested fresh water (see Figure 13)
- adult worms live in terminal venules of bladder/bowel passing eggs into urine/stool
- eggs must reach fresh water to hatch; schistosomes cannot multiply in or pass between humans

**Clinical Features**
- most asymptomatic; symptoms seen in travelers (nonimmune)
- Swimmer’s itch: pruritic skin rash at site of penetration (cercarial dermatitis)
- acute schistosomiasis (Katayama fever): hypersensitivity to migrating parasites (4-8 wk after infection)
  - fever, hives, headache, weight loss, cough, abdominal pain, chronic diarrhea, eosinophilia

**Complications of Chronic Infection**
- caused by granulomatous response and fibrosis secondary to egg deposition by adults in the veins surrounding the intestine or bladder
- more common in individuals from sub-Saharan Africa, South America, Asia, Caribbean, Eastern Mediterranean/North Africa
- *S. mansoni*, *S. japonicum*
  - worms in mesenteric vein, eggs in portal tracts of liver and bowel
  - heavy infections: intestinal polyps, portal and pulmonary hypertension, splenomegaly (2o to portal HTN), hepatomegaly
- *S. hematobium*
  - worms in vesical plexus, eggs in distal ureter and bladder induce granulomas and fibrosis
  - hematuria and obstructive uropathy; associated with squamous cell bladder cancer
  - neurologic complications: spinal cord neuroschistosomiasis (transverse myelitis), cerebral or cerebellar neuroschistosomiasis (increased ICP, focal CNS signs, seizures)
  - pulmonary complications: granulomatous pulmonary endarteritis, pulmonary hypertension, cor pulmonale; especially in patients with hepatosplenic involvement

**Investigations**
- serology (high sensitivity and specificity), CBC (eosinophilia, anemia, thrombocytopenia)
- *S. mansoni*, *S. japonicum*: eggs in stool, liver U/S shows fibrosis, rectal biopsy
- *S. hematobium*: bladder biopsy, eggs in urine and occasionally stool, kidney and bladder U/S

**Treatment and Prevention**
- praziquantel
- add glucocorticoid if acute schistosomiasis or neurologic complications develop
- proper disposal of human fecal waste, molluscicide, avoidance of infested water

### Ectoparasites

- scabies, lice
- see Dermatology, D27

### Travel Medicine

**General Travel Precautions**
- vector-borne: long-sleeves, long pants, hats, repellents (containing permethrin) applied to clothes, belongings and bed nets, repellents applied to skin (DEET)
- food/water: avoid eating raw meats/seafood, uncooked vegetables and milk/dairy products; drink only bottled beverages, chlorinated water, boiled water
- recreation: caution when swimming in schistosomiasis-endemic regions, fresh water rafting/kayaking, beaches that may contain human/animal waste products, near storm drains, after heavy rainfalls
- prophylaxis: malaria (chloroquine, mefloquine, atovaquone + proguanil, doxycycline), traveller's diarrhea (bismuth salicylate)
• standard vaccines up to date (HepB, MMR, tetanus/diptheria, varicella, pertussis, polio)
• travel vaccines: Hepatitis A/B, Japanese encephalitis, typhoid fever, yellow fever, rabies, ETEC, cholera
• sexually transmitted and blood-borne infections: safe sex practices, avoidance of percutaneous injury through razors, tattoos, piercings

**Infectious Diseases to Consider**
- vector borne: malaria, dengue fever, Chikungunya fever, yellow fever, *Rickettsia*, West Nile virus, trypanosomiasis, Japanese encephalitis, tick-borne encephalitis, spotted fever, leishmaniasis
- sexually transmitted: HIV, HBV, syphilis, usual STIs
- zoonotic: rabies, hantavirus, tularemia, Q fever, anthrax, brucellosis
- airborne: TB
- food/water: HAV, HEV, brucellosis, typhoid, paratyphoid, amoebiasis, dysentery, traveller’s diarrhea, cholera, *Campylobacter* spp.
- soil/water: schistosomiasis, strongyloidiasis, leptospirosis, cutaneous larva migrans, histoplasmosis, paracoccidioidomycosis

### Fever in the Returned Traveller

**Etiology**
- commonly identified causes of fever in returning traveller
  - parasitic: malaria (20-30%)
  - viral: non-specific mononucleosis-like syndrome (4-25%), dengue (5%), viral hepatitis (3%)
  - bacterial: typhoid from *Salmonella* (2-7%), rickettsioses (3%)
  - diverse group of causative pathogens: traveller’s diarrhea (10-20%), RTI (10-15%), UTI/STI (2-3%)
- febrile illness in travellers can be caused by routine infections that are common in non-travellers (e.g. URTI, UTI)
- less commonly, fever can be due to non-infectious causes: e.g. DVT, PE

**History**
- pre-travel preparation
- travel itinerary: when, where, why, what, who, how?
  - dates of travel (determine incubation period)
  - season of travel: wet or dry
  - destination: country, region (urban or rural), environment (jungle, desert, etc.)
  - purpose of trip
- persons visiting friends and family more likely to be exposed to local population and pathogens
  - style of travel: lodgings, camping, adventure travelling
  - local population: sick contacts
  - transportation: use of animals
- exposure history
  - street foods, untreated water: increased risk of traveller’s diarrhea, enteric fever
  - uncooked meat/pasteurized dairy: increased risk of parasitic infection
  - body fluids (sexual contacts, tattoos, piercings, IVDU, other injections)
  - increased risk of HBV, HCV, HIV, GC, *C. trachomatis*, syphilis
  - animal/insect bites: increased risk of malaria, dengue, rickettsioses, rabies
- fever pattern
  - incubation period: use the earliest and latest possible dates of exposure to narrow the differential diagnosis and exclude serious infections
  - <21 d: consider malaria, typhoid fever, dengue fever, rickettsioses; exclude HBV, TB
  - >21 d: consider malaria, TB; exclude dengue fever, travellers’ diarrhea, rickettsioses
- body systems affected: GI, respiratory, CNS, skin

**Investigations**
- all travellers with fever should undergo the following tests:
  - bloodwork: CBC and differential, liver enzymes, electrolytes, creatinine, thick and thin blood smears x3 (for malaria), blood C&S
  - urine: urinalysis, urine C&S
  - special tests based on symptoms, exposure history, and geography
  - stool: C&S, O&P
  - CXR
  - dengue serology for IgM

---

**Important Exposures**

### Insect Bites
- *Mosquito*
  - *Plasmodium* spp. (Malaria)
  - Dengue
  - *Lymphatic filariasis* (Elephantiasis)
  - West Nile Encephalitis
  - *Yellow Fever*
  - *Japanese Encephalitis*
- *Tick*
  - *Borrelia burgdorferi* (Lyme Disease)
  - *Rickettsia rickettsii* (Rocky Mountain Spotted Fever)
- *Ry*
  - *Trypanosoma brucei* spp. (African sleeping sickness)
  - *Leishmania* spp. (Leishmaniasis)
  - *Bartonella bacilliformis* (Bartonellosis)
- *Rea*
  - *Vesicular Plague*
  - *Yersinio fermentans* (Plague)

### Mammal Bites
- *Dog/ Cat*
  - Rabies, Pasteurella, anerobes, *Streptococcus*, *S. aureus*
  - *Human*
  - *Streptococcus*, *S. aureus*, oral anerobes, *Eikenella*

### Oral Exposures
- *Unpasteurized milk*
  - *Listeria*
  - *Bacillus subtilis*, *non-tuberculosis mycobacteria*, *Salmonella*, *E. coli*, *Listeria*

### Undercooked meat
- *Entanobacteria*, *protozoa*
  - *Clostridium*
  - *Hep A/E*, *Norwalk*, *cholera*, *Salmonella*, *Shigella*, *Giardia*, *E. coli*, *Salmonella*

### Environmental Exposures
- *Freshwater*
  - *Leptospirosis*, *schistosomiasis*, *Acanthamoeba*, *Naegleria fowleri*
  - *Soil*
  - *Naegleria fowleri*, *Eikenella*

Adapted with permission from *Lancet* 2003;361:1459-69

For up to date information on geographic and seasonal patterns of disease and travel advisories, check the website for the United States Centers for Disease Control and Prevention (www.cdc.gov/travel) or Foreign Affairs Canada (travel.gc.ca).
Etiology of Classic FUO

- infectious causes (~30%)
  - TB: extra-pulmonary (most common), miliary, pulmonary (if pre-existing disease)
  - abscess: subphrenic, liver, splenic, pancreatic, perinephric, diverticular, pelvis, psoas
  - osteomyelitis
  - bacterial endocarditis (culture negative)
  - uncommon: viral (CMV, EBV), fungal (histoplasmosis, cryptococcosis), parasitic (toxoplasmosis, leishmaniasis, amoebiasis, malaria)
- neoplastic causes (~20%)
  - most commonly lymphomas (especially non-Hodgkin’s) and leukemias, also multiple myeloma, myelodysplastic syndrome
  - solid tumours: RCC (most common), also breast, liver (hepatoma), colon, pancreas or liver metastases
- collagen vascular diseases (~30%)
  - SLE, RA, rheumatic fever, vasculitis (temporal arteritis, PAN), JRA, Still’s disease
- miscellaneous (~20%)
  - drugs, factitious fever
  - sarcoidosis, granulomatous hepatitis, IBD
  - hereditary periodic fever syndromes (such as familial Mediterranean fever)
  - venous thromboembolic disease: PE, DVT
  - endocrine: thyroiditis, thyroid storm, adrenal insufficiency, pheochromocytoma
- unknown despite investigations in 30-50% despite detailed work-up

Table 23. Fever in the Returned Traveller

<table>
<thead>
<tr>
<th>Illness</th>
<th>Geography/Timing</th>
<th>Pathogen</th>
<th>Incubation Period</th>
<th>Clinical Manifestations</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>Africa India SE Asia Usually rural, night-biting mosquitoes</td>
<td>Plasmodium falciparum Plasmodium vivax P. malariae P. ovale P. knowlesi</td>
<td>10 d to 40 yr</td>
<td>Fever and flu-like illness, shaking chills, headache, muscle aches, and fatigue Nausea, vomiting, and diarrhea Anemia and jaundice</td>
<td>Blood smear (thick and thin) x3 Antigen detection PCR (mostly a research tool)</td>
<td>Artesunate (for severe disease) + malarone, doxycycline, or clindamycin Quinine sulfate + doxycycline or clindamycin Chloroquine + primaquine</td>
</tr>
<tr>
<td>Dengue</td>
<td>South East Asia Caribbean Usually rural, day-biting mosquitoes</td>
<td>Dengue viruses</td>
<td>3 d to 2 wk</td>
<td>Sudden onset of fever, headache, retro-orbital pain, myalgias and arthralgias</td>
<td>Anti-dengue IgM positivity</td>
<td>Symptom relief: Acetaminophen (avoid using NSAIDs because of anti-coagulant properties)</td>
</tr>
<tr>
<td>Typhoid (enteric fever)</td>
<td>Global but mostly Indian subcontinent</td>
<td>Salmonella typhi Salmonella paratyphi</td>
<td>3 to 60 d</td>
<td>Sustained fever 39° to 40°C (103° to 104°F) Abdominal pain, headache, loss of appetite, cough, constipation</td>
<td>Stool, urine or blood sample positive for S. typhi or S. paratyphi</td>
<td>Quinolone antibiotic (e.g. ciprofloxacin), ceftriaxone or macrolide</td>
</tr>
<tr>
<td>Tick typhus</td>
<td>Mediterranean South Africa India</td>
<td>Rickettsia</td>
<td>1 to 2 wk</td>
<td>Fever, headache, fatigue, muscle aches, occasionally rash Eschar at site of tick bite Thrombocytopenia Elevated liver enzymes</td>
<td>Serology Presence of classic tick eschar</td>
<td>Doxycycline</td>
</tr>
<tr>
<td>TB</td>
<td>Global</td>
<td>M. tuberculosis</td>
<td>Variable</td>
<td>Fever, cough, hemoptysis</td>
<td>CXR Sputum culture and acid-fast stain</td>
<td>Ethambutol, isoniazid, pyrazinamide, rifampin</td>
</tr>
<tr>
<td>Mononucleosis</td>
<td>Caribbean, C. and S. America</td>
<td>EBV or CMV</td>
<td>30 to 50 d</td>
<td>Malaise, fatigue, pharyngitis, lymphadenopathy, splenomegaly</td>
<td>Atypical lymphocytes on blood smear and positive heterophilic antibody (monospot) test</td>
<td>Acetaminophen or NSAIDs, fluids</td>
</tr>
</tbody>
</table>

Table 24. Classification of Fever of Unknown Origin (FUO) – Temp >38.3°C/101°F on several occasions

<table>
<thead>
<tr>
<th>Classical FUO</th>
<th>Nosocomial FUO</th>
<th>Neutropenic FUO</th>
<th>HIV-associated FUO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration &gt;3 wk</td>
<td>Hospitalized patient Infection not present/ incubating on admission</td>
<td>Neutrophil count &lt;500/mL or is expected to fall to that level in 1-2 d</td>
<td>HIV infections Duration &gt;4 wk for outpatients, &gt;3 d for hospitalized patients</td>
</tr>
<tr>
<td>Diagnosis uncertain after 3 outpatient visits or 3 d in hospital or 1 wk of intensive ambulatory investigation</td>
<td>Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures</td>
<td>Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures</td>
<td>Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures</td>
</tr>
</tbody>
</table>

Etiology of Classic FUO

- infectious causes (~30%)
  - TB: extra-pulmonary (most common), miliary, pulmonary (if pre-existing disease)
  - abscess: subphrenic, liver, splenic, pancreatic, perinephric, diverticular, pelvis, psoas
  - osteomyelitis
  - bacterial endocarditis (culture negative)
  - uncommon: viral (CMV, EBV), fungal (histoplasmosis, cryptococcosis), parasitic (toxoplasmosis, leishmaniasis, amoebiasis, malaria)
- neoplastic causes (~20%)
  - most commonly lymphomas (especially non-Hodgkin’s) and leukemias, also multiple myeloma, myelodysplastic syndrome
  - solid tumours: RCC (most common), also breast, liver (hepatoma), colon, pancreas or liver metastases
- collagen vascular diseases (~30%)
  - SLE, RA, rheumatic fever, vasculitis (temporal arteritis, PAN), JRA, Still’s disease
- miscellaneous (~20%)
  - drugs, factitious fever
  - sarcoidosis, granulomatous hepatitis, IBD
  - hereditary periodic fever syndromes (such as familial Mediterranean fever)
  - venous thromboembolic disease: PE, DVT
  - endocrine: thyroiditis, thyroid storm, adrenal insufficiency, pheochromocytoma
- unknown despite investigations in 30-50% despite detailed work-up

Causes of Nosocomial FUO

- B, C, D, E
- Bacterial and fungal infections of respiratory tract and surgical sites
- Catheters (intravascular and urinary)
- Drugs
- Emboli

Anti-Drugs that may Cause Fever:
- Anti-microbials (sulfonamides, penicillins, nitrofurantoin, antimicrobials)
- Anti-hypertensives (hydralazine, methylxanthine)
- Anti-epileptics (barbiturate, phenytoin)
- Anti-arrhythmics (quinine, procainamide)
- Anti-inflammatory (NSAIDs)
- Anti-thrombotic (ASA)
- Anti-histamines
- Anti-thyroid
Approach to Classic FUO
- careful history: travel, environmental/occupational exposures, infectious contacts, medication history, immunizations, TB history, sexual history, past medical history, comprehensive review of systems (including symptoms that resolved before interview)
- thorough physical exam: fever pattern, rashes (skin, mucous membranes), murmurs, arthritis, lymphadenopathy, organomegaly
- initial investigations as appropriate
  - bloodwork: CBC and differential, electrolytes, BUN, Cr, calcium profile, LFTs, ESR, CRP, muscle enzymes, RF, ANA, serum protein electrophoresis (SPEP), blood smear
  - cultures: blood (x 2 sets), urine, sputum, stool C&S, O&P, other fluids as appropriate
  - serology: HIV, monospot, CMV IgM
  - imaging: CXR, abdominal imaging
- if there are diagnostic clues from any of the above steps, proceed with directed exam, biopsies or invasive testing as required, followed by directed treatment once a diagnosis is established
- if no diagnosis with the above, consider empiric therapy vs. watchful waiting
  - without intervention: patients that remain undiagnosed despite extensive work-up have good prognosis

Infections in the Immunocompromised Host
- immunocompromised hosts have increased susceptibility to infections from pathogens that are typically low virulence, commensal, or latent
- type of immunsuppression predicts probable spectrum of agents

Factors that Compromise the Immune System
- general: age (very young or elderly), malnutrition
- immune disease: HIV/AIDS, malignancies, asplenia (functional or anatomic), hypogammaglobulinemia, neutropenia
- DM
- iatrogenic: corticosteroids, chemotherapy, radiation treatment, anti-TNF therapy, other immunosuppressive drugs (e.g. in transplant patients)

Table 25. Types of Immunocompromise

<table>
<thead>
<tr>
<th>Type</th>
<th>Conditions</th>
<th>Vulnerable To</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell-Mediated Immunity</td>
<td>HIV, Hodgkin’s, hairy cell leukemia, cytotoxic drugs, SCID, DiGeorge syndrome</td>
<td>Latent viruses, Fungi, Parasites</td>
</tr>
<tr>
<td>Humoral Immunity</td>
<td>CLL, lymphosarcoma, multiple myeloma, nephrotic syndrome, protein-losing enteropathy, burns, sickle cell anemia, asplenia, splenectomy, selective Ig deficiencies, Wiskott-Aldrich syndrome</td>
<td>Encapsulated organisms (S. pneumoniae, H. influenzae, N. meningitidis, Salmonella typhi, GBS)</td>
</tr>
<tr>
<td>Neutrophil Function</td>
<td>Myelodysplasia, paroxysmal nocturnal hemoglobinuria, radiation, cytotoxic drug therapy, C3 or C5 deficiencies, chronic granulomatous disease</td>
<td>Catalase-producing organisms (Staphylococcus, Serratia, Nocardia, Aspergillus)</td>
</tr>
</tbody>
</table>

Febrile Neutropenia (FN)

Definition
- fever (≥38.3°C/101°F or ≥38.0°C/100.4°F for ≥1 h) and one of:
  - ANC <0.5 OR ANC <1.0 but trending down to 0.5

Pathophysiology
- decreased neutrophil production
  - marrow: infection, aplastic/myelophthisic anemia, leukemia, lymphoma, myelodysplastic syndromes
  - iatrogenic: cancer chemotherapy, radiation, drugs
  - deficiencies: vitamin B₁₂, folate
  - increased peripheral neutrophil destruction
  - autoimmune: Felty’s syndrome, SLE, antineutrophil antibodies
  - splenic sequestration

Epidemiology/Etiology
- most common life-threatening complication of cancer therapy
- 8 cases per 1000 cancer patients per year in the US
- causative organism identified only 1/3 of the time
- GN (especially Pseudomonas) historically most common
- GP more common now
- fungal superinfection if neutropenia prolonged or if concurrent antibiotic use (especially Candida, Aspergillus)
Investigations
- examine for potential sites of infection: mucositis and line infections are most common
- do NOT perform DRE; examine perianal region
- blood C&S (x2 sets), urine C&S, culture all indwelling catheter ports, ± sputum C&S and NP swab for respiratory viruses
- CBC and differential, Cr, BUN, electrolytes, AST/ALT, total bilirubin

Treatment
- most hospitals have their own specific protocol; one example is presented below

**Figure 14. Example of treatment protocol for febrile neutropenia**

### Infections in Solid Organ Transplant Recipients
- infection is a leading cause of early morbidity/mortality in transplant recipients
- infection depends on degree of immunosuppression
- common infections <1 mo post-transplant:
  - bacterial infection of wound/lines/lungs, herpetic stomatitis
- common infections >1 mo post-transplant:
  - viral (especially CMV, EBV, VZV)
  - fungal (especially *Aspergillus, Cryptococcus, P. jiroveci*)
  - protozoan (especially *Toxoplasma*"
  - unusual bacterial/mycobacterial infections (especially TB, *Nocardia, Listeria*)

Prophylactic Vaccinations Given Before Transplant
- to all transplant patients: DTaP, pneumococcal, influenza, hepatitis A and B vaccines
- if low titre or poor documentation: MMR, polio, varicella vaccination (with booster 4-8 wk later)

### Immune Reconstitution Syndrome (IRS)

**Definition**
- a harmful inflammatory response directed against a previously acquired infection following a recovery of the immune system
Etiology
- paradoxical worsening of a successfully or partially treated opportunistic infection
- new onset response to a previously unidentified opportunistic infection
- the majority of cases are in HIV/AIDS or immunosuppressed patients starting antiretroviral therapy or discontinuing immunosuppressive therapy; sudden recovery from an immunosuppressive state towards a pro-inflammatory state directed towards subclinical infection results in fever and inflammation
- can occur in response to multiple infections:
  - Mycobacteria (tuberculosis, avium complex)
  - Cryptococcus
  - Pneumocystis
  - Toxoplasma
  - HBV and HCV
  - Herpes viruses (VZV reactivation, HSV, CMV)
  - JC virus (progressive multifocal leukoencephalopathy)
  - Molluscum contagiosum
- clinical features are dependent on the type and location of the pre-existing infection
- thought to be worse with quick increase in CD4 count and with lower pre-treatment CD4 count
- non-HIV conditions with documented IRS: solid organ transplant recipients, post-partum women, neutropenic patients, anti-TNF therapy

Epidemiology
- in HIV patients starting HAART, IRS reported to affect ~10%

Investigations
- IRS is a diagnosis of exclusion
- rule out drug reaction, patient non-adherence, drug resistance

Treatment
- continue HAART therapy in HIV patients with mild-moderate symptoms, but consider discontinuation if symptoms are life-threatening or potentially irreversible
- treat underlying infection; initiate treatment for some infections prior to HAART initiation
- consider starting corticosteroids/NSAIDs to decrease inflammatory response

HIV and AIDS

Epidemiology

Canadian Situation (Public Health Agency of Canada, 2012)
- estimated 71,300 Canadians living with HIV infection at the end of 2011, 25% unaware of HIV-positive status
- estimated 3,175 new infections occurred in 2011: MSM account for 47% of cases, IVDU 17%

Global Situation (WHO Global Summary of the HIV/AIDS Epidemic, December 2010)
- estimated 34.0 million people living with HIV/AIDS in 2010
- estimated 2.7 million newly infected in 2010
- estimated 1.8 million AIDS-related deaths in 2010

Definition and Pathophysiology
- human immunodeficiency virus (HIV) is a retrovirus that causes progressive immune system dysfunction which predisposes patients to various opportunistic infections and malignancies
- HIV virion includes an envelope (gp1 and gp120 glycoproteins), matrix (p17) and capsid (p24) enclosing 2 single-stranded copies of RNA + enzymes in its core (see Figure 15)
- virion glycoproteins bind CD4 and CXCR4/CCR5 on CD4+ T lymphocytes (T-helper cells) to fuse and enter the cells
- RNA converted to dsDNA by reverse transcriptase; dsDNA is integrated into host genome
- virus DNA transcribed during host replication and new virions are produced
- virions bud out of host cell, incorporating host cell membrane
- exact mechanisms of CD4 depletion incompletely characterized but likely include direct viral cytopathic effects, apoptosis, increased cell turnover

Figure 15. HIV viral particle
**Modes of Transmission**

Table 26. Modes of Transmission by Site and Medium

<table>
<thead>
<tr>
<th>HIV Invasion Site</th>
<th>Sub-location</th>
<th>Transmission Medium</th>
<th>Transmission Probability per Exposure Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female genital tract</td>
<td>Vagina, ectocervix, endocervix</td>
<td>Semen</td>
<td>1 in 200 to 1 in 2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cervicovaginal and rectal secretions and desquamations</td>
<td>1 in 700 to 1 in 3000</td>
</tr>
<tr>
<td>Male genital tract</td>
<td>Inner foreskin, penile urethra</td>
<td>Semen</td>
<td>1 in 20 to 1 in 300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maternal blood/genital secretions (intrapartum)</td>
<td>1 in 5 to 1 in 10</td>
</tr>
<tr>
<td>Intestinal tract</td>
<td>Rectum</td>
<td>Semen</td>
<td>1 in 250</td>
</tr>
<tr>
<td></td>
<td>Upper GI tract</td>
<td>Semen</td>
<td>1 in 2500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maternal blood (intrauterine)</td>
<td>1 in 5 to 1 in 10</td>
</tr>
<tr>
<td>Placenta</td>
<td>Chorionic villi</td>
<td>Maternal blood (intrauterine)</td>
<td>1 in 10 to 1 in 20</td>
</tr>
<tr>
<td>Blood stream</td>
<td></td>
<td>Contaminated blood products</td>
<td>95 in 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sharp/needlestick injuries</td>
<td>1 in 150</td>
</tr>
</tbody>
</table>

Adapted with permission from Macmillan Publishers Ltd. Nat Rev Immunology 2008;8:447-457.

**Natural History**

![Figure 16. Relationships between CD4 T cell count, viral load, and anti-HIV antibodies](image)

**Acute (Infection) Retroviral Syndrome (ARS)**
- 40-90% experience an acute "mononucelosis like" illness (fever, pharyngitis, lymphadenopathy, rash, arthralgias, myalgias, headaches, GI symptoms, oral ulcers, weight loss) 2-6 wk post-exposure lasting 10-15 d
- hematologic disturbances (lymphopenia, thrombocytopenia)
- 10-20% present with aseptic meningitis; HIV RNA and/or p24 may be detected in CSF
- associated with a high level of plasma viremia and therefore high risk of transmission

**Asymptomatic (Latent) Stage**
- during latent phase, HIV infects and replicates in CD4+ T lymphocytes (lymph nodes)
- normal CD4 count: 500-1100 cells/mm³
- CD4 count drops 60-100 cells/mm³ per year
- by 10 yr post-infection, 50% have AIDS, 30% demonstrate milder symptoms and <20% are asymptomatic if left untreated

**AIDS Definition in Canada**
- HIV-positive AND
- one or more clinical illnesses that characterize AIDS, including: opportunistic infections (e.g. PJP (previously PCP), esophageal candidiasis, CMV, MAC, TB, toxoplasmosis), malignancy (Kaposi's sarcoma, invasive cervical cancer), wasting syndrome OR
- first CD4 <200 (or <15%)
Table 27. Symptomatic Stage (CD4 count thresholds for classic clinical manifestations)

<table>
<thead>
<tr>
<th>CD4 Counts</th>
<th>Possible Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;500 cells/mm³</td>
<td>Constitutional symptoms: fever, night sweats, fatigue, weight loss</td>
</tr>
<tr>
<td></td>
<td>Mucocutaneous lesions: seborrheic dermatitis, HSV, VZV (shingles), oral hairy leukoplakia (EBV), candidiasis (oral, esophageal, vaginal), Kaposi’s sarcoma (KS)</td>
</tr>
<tr>
<td></td>
<td>Recurrent bacterial infections, especially pneumonia</td>
</tr>
<tr>
<td></td>
<td>Pulmonary and extrapulmonary tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>Pneumocystis jiroveci pneumonia (formerly PCP)</td>
</tr>
<tr>
<td></td>
<td>KS</td>
</tr>
<tr>
<td></td>
<td>Oral thrush</td>
</tr>
<tr>
<td>&lt;100 cells/mm³</td>
<td>Progressive multifocal leuкоencephalopathy (PML) – JC virus</td>
</tr>
<tr>
<td></td>
<td>CNS toxoplasmosis</td>
</tr>
<tr>
<td>&lt;50 cells/mm³</td>
<td>CMV infection: retinitis, colitis, cholangiopathy, CNS disease</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium avium complex (MAC)</td>
</tr>
<tr>
<td></td>
<td>Bacillary angiomatosis (disseminated Bartonella)</td>
</tr>
<tr>
<td></td>
<td>Primary central nervous system lymphoma (PCNSL)</td>
</tr>
</tbody>
</table>

Laboratory Diagnosis

- anti-HIV antibodies detectable after a median of 3 wk, virtually all by 3 mo
- initial screening test: enzyme linked immunosorbent assay (ELISA) detects serum antibody to HIV; sensitivity >99.5%
  - some jurisdictions (e.g. Ontario) use combination Ag/Ab test as screen (tests for p24 antigen and HIV antibody)
- confirmatory test: if positive screen, Western blot confirmation by detection of antibodies to at least two different HIV protein bands (p24, gp41, gp120/160); specificity >99.99%
- rapid (point of care) antibody tests: higher false positives, therefore need to confirm positive results with traditional serology
- p24 antigen: detection by ELISA may be positive during "window period" before antibodies become detectable; combined with standard antibody test in some jurisdictions

Management of the HIV-Positive Patient

- verify positive HIV test
- complete baseline history and physical examination, then follow-up every 3 mo
- laboratory evaluation
  - routine CD4 count to measure status of the immune system
  - routine HIV-RNA levels (viral load)
    - also important indicator of effect of anti-retroviral (ARV) therapy
  - baseline HIV resistance testing to guide ARV therapy
  - HLA-B*5701 to reduce risk of abacavir hypersensitivity
  - baseline tuberculin skin test (PPD): induration greater than 5 mm is positive
  - baseline serologies (hepatitis A, B and C, syphilis, toxoplasma, CMV, VZV)
  - routine biochemistry and hematology; CXR
  - annual fasting lipid profile and fasting glucose (due to HAART side effects)
- education
  - regular follow-up on CD4 counts and viral loads (q3-4mo) as well as strict adherence with ARVs improves prognosis
  - prevention of further transmission through safer sex and clean needles for injection drug use
  - HIV superinfection (transmission of different HIV strains from another HIV+ person) can rarely occur so barrier protection during sex is still recommended
- health care maintenance
  - assessment for counseling needs and referral for psychiatric or social concerns
  - vaccines: influenza annually, 23-valent pneumococcal every 5 yr, HBV (if not immune), HAV (if seronegative)
  - annual screening (PAP smear, STIs as applicable)
  - management of comorbid conditions (e.g. blood pressure monitoring, smoking cessation, alcohol/drug use)

Table 28. Prophylaxis Against Opportunistic Infections in HIV-infected Patients

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Indication for Prophylaxis</th>
<th>Prophylactic Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystis jiroveci</td>
<td>CD4 count &lt;200 cells/mm³ or history of oral candidiasis</td>
<td>TMP-SMX 1 SS or DS OD</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>IgG antibody to Toxoplasma and CD4 count &lt;100 cells/mm³</td>
<td>As per prophylaxis for pneumocystis</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>PPD reaction &gt;5 mm or contact with case of active TB</td>
<td>INH + pyridoxine daily x 9 mo</td>
</tr>
<tr>
<td>Mycobacterium avium complex</td>
<td>CD4 count &lt;50 cells/mm²</td>
<td>Azithromycin 1200 mg q2wk</td>
</tr>
</tbody>
</table>

SS = single strength; DS = double strength
Highly Active Antiretroviral Treatment (HAART)

Overall Treatment Principles
• in asymptomatic patients: initiate HAART when CD4 <350; ongoing debate about when to initiate HAART when CD4 is between 350-500 or >500
• current guidelines differ in various industrialized countries – see 2008 OARAC Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents
  http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf
• other indications for initiating therapy include opportunistic infection/malignancy, pregnancy, HIV-associated nephropathy, HIV-associated thrombocytopenia, need for hepatitis B therapy in HBV co-infected patients
• consider starting treatment early if HCV co-infection, high HIV viral load, co-morbid conditions (e.g. cardiovascular disease)
• consider results of baseline resistance testing and complete ARV treatment history before (re-) initiating HAART
• goal: keep viral load <40 copies/mL; viral load should decrease 10-fold within 4-8 wk and be undetectable by 6 mo and restore immunological function
• secondary benefit of initiating therapy is 96% reduction in risk of transmitting HIV to sexual partners

HAART Recommendations for Treatment of Naïve Patients
• 2 NRTIs + 1 NNRTI/PI (boosted with ritonavir) or INSTI

Treatment Failure
• defined clinically (HIV progression), immunologically (failure to increase CD4 count by 25-50 over first year of treatment or CD4 decrease >100 over 1 yr), or virologically (failure to achieve viral load <40 copies/mL after 6 mo)
• ensure that viral load >40 is not just a transient viremia or ‘blip’

Table 29. Antiretroviral Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside reverse transcriptase inhibitors (NRTIs)</td>
<td>zidovudine (AZT)</td>
<td>Incorporated into the growing viral DNA chain, thereby competitively inhibiting reverse transcriptase and terminating viral DNA growth</td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td></td>
<td>lamivudine (3TC)</td>
<td></td>
<td>Lipodystrophy</td>
</tr>
<tr>
<td></td>
<td>stavudine (d4T)</td>
<td></td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td>didanosine (ddI)</td>
<td></td>
<td>N/V/diarrhea</td>
</tr>
<tr>
<td></td>
<td>abacavir (ABC)</td>
<td></td>
<td>Bone marrow suppression (AZT)</td>
</tr>
<tr>
<td></td>
<td>emtricitabine (FTC)</td>
<td></td>
<td>Peripherial neuropathy (ddI, d4T)</td>
</tr>
<tr>
<td>Combination Tablets:</td>
<td>AZT/3TC (Combivir®)</td>
<td></td>
<td>Drug-induced hypersensitivity (ABC)</td>
</tr>
<tr>
<td></td>
<td>AZT/3TC/ABC (Trizivir®)</td>
<td></td>
<td>Panreatitis (ddI/d4T)</td>
</tr>
<tr>
<td></td>
<td>ABC/3TC (Kivexa®)</td>
<td></td>
<td>Myopathy (AZT)</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC (Truvada®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tenofor disoprox fumarate (TDF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</td>
<td>efavirenz (EFZ)</td>
<td>Non-competitively inhibit function of reverse transcriptase, thereby preventing viral RNA replication</td>
<td>Rash, Stevens-Johnson syndrome</td>
</tr>
<tr>
<td></td>
<td>nevirapine (NVP)</td>
<td></td>
<td>CNS: dizziness, insomnia, somnolence, abnormal dreams (efavirenz)</td>
</tr>
<tr>
<td></td>
<td>delavirdine (DLV)</td>
<td></td>
<td>Hepatotoxicity (nevirapine – avoid in females with CD4 &gt;250, men with CD4 &gt;400)</td>
</tr>
<tr>
<td></td>
<td>etravirine (ETR)</td>
<td></td>
<td>CYP3A4 interactions</td>
</tr>
<tr>
<td></td>
<td>rilpivirine (RPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors (PIs)*</td>
<td>ritonavir (RTV)</td>
<td>Prevent maturation of infectious virions by inhibiting the cleavage of polypeptides</td>
<td>Lipodystrophy, metabolic syndrome</td>
</tr>
<tr>
<td></td>
<td>saquinavir (SQV)</td>
<td></td>
<td>N/V/diarrhea</td>
</tr>
<tr>
<td></td>
<td>amprenavir (APV)</td>
<td></td>
<td>Nephrolithiasis (indinavir)</td>
</tr>
<tr>
<td></td>
<td>nelfinavir (NFV)</td>
<td></td>
<td>Rash (APV)</td>
</tr>
<tr>
<td></td>
<td>indinavir (IDV)</td>
<td></td>
<td>Hyperlipidemia (azatnavir, indinavir)</td>
</tr>
<tr>
<td></td>
<td>atazanavir (ATV)</td>
<td></td>
<td>CYP3A4 interactions</td>
</tr>
<tr>
<td></td>
<td>fosamprenavir (FPV)</td>
<td></td>
<td>Hyperlipemia</td>
</tr>
<tr>
<td></td>
<td>lopinavir/ritonavir (Kalatra®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tipranavir (TPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>darunavir (DRV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusion inhibitor</td>
<td>enfuviride (T-20)</td>
<td>Inhibit viral fusion with T-cells by inhibiting gp41, preventing cell infection</td>
<td>Injection site reactions, rash, infection, diarrhea, nausea, fatigue</td>
</tr>
<tr>
<td>CCR5 antagonist</td>
<td>maraviroc</td>
<td>Inhibit viral entry by blocking host CCR5 co-receptor</td>
<td>Fever, cough, dizziness</td>
</tr>
<tr>
<td>Integrase strand tranfer inhibitors (INSTIs)</td>
<td>raltegravir</td>
<td>Inhibits integration of HIV DNA into the human genome thus preventing HIV replication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>elvitegravir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Standard of care is to pharmacology boost most PIs with ritonavir to increase concentrations
Figure 17. Mechanism of HIV replications

**TARGET SITES FOR ANTIRETROVIRAL DRUGS**
- (A) Fusion inhibitor
- (B) CCR5 antagonist
- (C) Nucleoside reverse transcriptase inhibitors (NRTIs)
- (D) Integrase strand transfer inhibitors (INSTIs)
- (E) Protease inhibitors (PIs)

**PROCESS OF MULTIPLICATION**
1. Binding
2. Fusion and uncoating
3. Reverse transcription
4. Integration
5. Translation
6. Assembly and budding
7. Maturation

**Tropism Testing**
- In addition to CD4, HIV requires a co-receptor (either CCR5 or CXCR4) to enter cells
- CCR5 antagonists (e.g. Maraviroc) only work if virus is CCR5-tropic
- Tropism test required prior to initiating CCR5 antagonists

**Prevention of HIV Infection**
- education, including harm-reduction:
  - safer sexual practices: condoms for vaginal and anal sex, barriers for oral sex
  - harm prevention for injection drug users: avoid sharing needles
- treatment of HIV+ women with HAART during the 2nd and 3rd trimester of pregnancy and AZT during delivery followed by AZT treatment of the infant for 6 wk (decreases maternal-fetal transmission from 25% to <3%)
- universal blood and body precautions for health care workers
  - post-exposure prophylaxis (PEP) after occupational (e.g. needle-stick injury) and non-occupational (e.g. consensual sex, sexual assault) exposure to HIV: 2- or 3-drug regimen initiated immediately (<72 h) after exposure and continuing for 4 wk
- recent data has demonstrated efficacy of pre-exposure prophylaxis (oral PrEP or topical microbicides) in preventing HIV although additional data needed
- HAART associated with 96% reduction in risk of transmitting HIV to sexual partners
- screening of blood and organ donation
Types of Testing

1. Nominal/name-based HIV testing
   - the person ordering the test knows the identity of the person being tested for HIV
   - the HIV test is ordered using the name of the person being tested
   - person ordering the test is legally obligated to notify Public Health officials if test results are positive for HIV
   - the test result is recorded in the health care record of the person being tested

2. Non-nominal/non-identifying HIV testing
   - similar to nominal/name-based testing on all points except:
     - the HIV test is ordered using a code or the initials of the person being tested

3. Anonymous testing
   - available at specialized clinics
   - the person ordering the HIV test does not know the identity of the person being tested
   - the HIV test is carried out using a unique non-identifying code that only the person being tested for HIV knows
   - test results are not recorded on the health care record of the person being tested

HIV Pre- and Post-test Counselling

- a diagnosis of HIV can be overwhelming and is often associated with stigma and discrimination
- consider pre- and post-test counselling, regardless of the results
- goals include: assessing risk, making informed decision to be tested, education to protect themselves and others from virus exposure, where to go for more information and support
- HIV+ patients should be connected with local support services

A Simplified Look at Antibiotics

- general overview, see Table 30 for more details

1. Penicillins (most Streptococcus, N. meningitidis, many oral anaerobes except B. fragilis)

   - [Image: Figure 18. Penicillins]

   Penicillin G (IV)/Penicillin V (PO)
   - Ampicillin (IV)/Amoxicillin (PO)
     - + Enterococcus and HiPLESS*
   - Cloxacillin
     - + MSSA but ↓ Streptococci
   - Amoxicillin-clavulanate
     - + Pseudomonas and Enterobacter
   - Piperacillin
     - Piperacillin-tazobactam

   *HiPLESS = H. influenza, Proteus, Listeria, E. coli, Salmonella, Shigella

2. Cephalosporins (PO/IV)
   - 1st generation: cephalaxin/cefazolin (mostly GP, some GN)
   - 2nd generation: cefuroxime/cefuroxime (some GP and some GN, *anaerobes)
   - 3rd generation: cefixime/cefotaxime, ceftriaxone (good Streptococcal coverage, mostly GN) and ceftazidime (no GP, mostly GN, *Pseudomonas*)
   - 4th generation: --/cefepeime (most GP, most GN, *Pseudomonas*)

3. Aminoglycosides (GN aerobic bacilli)
   - gentamicin
   - tobramycin
   - amikacin

4. Macrolides [GP, Hemophilus, and atypical bacteria (Legionella, Chlamydia, Mycoplasma)]
   - erythromycin
   - clarithromycin
   - azithromycin

Early identification of HIV is essential for patients to receive the maximal benefit from ARVs.
5. Fluoroquinolones (GN – although resistance becoming a huge problem)
   - ciprofloxacin (+ Pseudomonas)
   - norfloxacin (for UTI only)
   - respiratory fluoroquinolones (some GP, GN, "atypicals", Legionella, Mycoplasma, Chlamyphila)
   - levofloxacín
   - moxifloxacin (+ anaerobes)

6. Carbapenems (broad coverage: GP, GN and anaerobes)
   - imipenem (+ Pseudomonas)
   - meropenem (+ Pseudomonas)
   - ertapenem

7. Others
   - doxycycline/tetracycline (GP, syphilis, Chlamyphila, Rickettsia, Mycoplasma)
   - vancomycin (all GP and C. difficile – the oral form)
   - linezolid (for resistant GP infections)
   - clindamycin (most GP, GN anaerobes)
   - TMP/SMX (most S. aureus incl. MRSA, GN aerobes, Pneumocystis)
   - nitrofurantoin (GN bacilli, S. saprophyticus, Enterococcus)
   - linezolid (for resistant GP infections)
   - treatment for C. Difficile: metronidazole OR oral vancomycin; consider both in serious infection

Antimicrobials

Antibiotics

- empiric antibiotic therapy
  - choose antibiotic(s) to cover for most likely and lethal organisms for the type of infection prior to obtaining laboratory results (usually reserved for serious infections)
  - adjust antibiotic(s) based on C&S
    - if causative organism identified, use antibiotic to which organism is sensitive
    - if causative organism not identified, re-evaluate need for ongoing antimicrobial therapy (and continue with empiric antibiotic(s) if indicated)

Reasons for Combination Therapy

- Polymicrobial infection
- Empiric therapy pending culture results
- Synergy for difficult to treat pathogens (e.g. Enterococcus spp. causing endocarditis)
- To prevent emergence of resistance

Figure 19. Mechanism of action of antibiotics

©Stuart Jantzen 2012
### Table 30. Antibiotics

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CELL WALL INHIBITORS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzyl penicillin</td>
<td>GP except Staphylococcus, Enterococcus, Oral anaerobes</td>
<td>Bactericidal: (\beta)-lactam inhibits cell wall synthesis by binding penicillin binding protein (PBP) preventing cross-linking of peptidoglycan</td>
<td>Immediate allergy (e.g.: anaphylaxis, urticaria), Late-onset allergy (e.g.: urticaria, rash, serum sickness), Interstitial nephritis, Dose related toxicity: seizures, Diarrhea</td>
<td>Mild to moderately severe infections caused by susceptible organisms including actinomycosis, streptococcal pharyngitis, streptococcal skin and soft tissue infections, pneumococcal pneumonia, syphilis</td>
<td>Hypersensitivity to penicillin</td>
</tr>
<tr>
<td>- penicillin G IV/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- penicillin V PO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminopenicillin</td>
<td>Same as penicillin AND Enterococcus Listeria</td>
<td>See above</td>
<td>See above</td>
<td>Bacterial meningitis and endocarditis (IV ampicillin), acute otitis media (AOM), streptococcal pharyngitis, sinusitis, acute exacerbations of COPD, part of multidrug therapy for H. pylori treatment, Lyme disease, pneumococcal pneumonia; UTI (amoxicillin and ampicillin) for most enterococci and susceptible gram-negative pathogens</td>
<td>Hypersensitivity to penicillin or (\beta)-lactam antibiotics</td>
</tr>
<tr>
<td>- ampicillin IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- amoxicillin PO (Amoxicillin®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoxazol penicillin</td>
<td>Methicillin-sensitive Staphylococcus aureus; streptococci</td>
<td>See above</td>
<td>See above</td>
<td>Bacterial infections caused by staphylococci and streptococci including skin soft-tissue infections</td>
<td>Hypersensitivity to cloxacillin or any penicillin</td>
</tr>
<tr>
<td>- cloxacillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- methicillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- natocillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- oxacillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\beta)-lactam/(\beta)-lactamase Inhibitor combinations</td>
<td>Same as penicillin AND Staphylococcus H. influenzae Enterococcus Anaerobes (oral and gut)</td>
<td>(\beta)-lactamases produced by certain bacteria inactivate (\beta)-lactams</td>
<td>See above</td>
<td>Various (\beta)-lactamase producing bacteria, Clavulin® sensitive bacteria including RTI, sinusitis, AOM, skin and soft tissue infections, UTI, and severe intra-abdominal and pelvic infections</td>
<td>Hypersensitivity to penicillin or cephalosporin History of Clavulin®-associated jaundice or hepatic dysfunction</td>
</tr>
<tr>
<td>- amoxicillin clavulanate (Clavulin®, Augmentin®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- piperacillin/ tazobactam (Tazocin®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO</td>
<td>IV</td>
<td>cefazolin (Ancef®)</td>
<td>GP Good with the exception of Enterococcus and MRSA</td>
<td>Bactericidal: (\beta)-lactam inhibits PBP prevents cross-linking of peptidoglycan, less susceptible to penicillinases</td>
<td>10% penicillin allergy cross-reactivity Nephrotoxicity</td>
</tr>
<tr>
<td>1°</td>
<td></td>
<td>cefuroxime (Zinacef®) cefamandole (Cefobid®)</td>
<td>Weaker activity than 1° More coverage than 1° (Includes anaerobes)</td>
<td>See above</td>
<td>See above</td>
</tr>
<tr>
<td>2°</td>
<td></td>
<td>cefuroxime (Zinacef®) cefixime (Suprax®) cefotaxime (Ceftin®) cefazolin (Ancef®) ceftriaxone (Rocephin®)</td>
<td>(\beta)-lactamase sensitive pathway (cambicillin and cefotaxime especially S. pneumoniae) Broad coverage (Includes Pseudomonas for ceftriaxone only)</td>
<td>See above</td>
<td>See above</td>
</tr>
<tr>
<td>3°</td>
<td></td>
<td>cefotaxime (Suprax®)</td>
<td>(\beta)-lactamase sensitive pathway (cambicillin and cefotaxime especially S. pneumoniae) Broad coverage (Includes Pseudomonas for ceftriaxone only)</td>
<td>See above</td>
<td>See above</td>
</tr>
<tr>
<td>4°</td>
<td></td>
<td>cefepime (Maxipime®)</td>
<td>Broad spectrum Broad coverage including Pseudomonas</td>
<td>See above</td>
<td>See above</td>
</tr>
</tbody>
</table>
### Table 30. Antibiotics (continued)

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CELL WALL INHIBITORS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>imipenem (Primaxin®)</td>
<td>GP except MRSA, GN including Pseudomonas + Enterobacter, ESBLS, anaerobes</td>
<td>β-lactam inhibits PBP and prevents cross-linking of peptidoglycan</td>
<td>Penicillin allergy cross-reactivity, Seizures</td>
<td>Treatment of infections caused by GNB producing extended-spectrum β-lactamases, serious infections caused by susceptible organisms</td>
<td>Hypersensitivity to imipenem</td>
</tr>
<tr>
<td>meropenem (Merrem®)</td>
<td>See above. Does not cover Enterococcus.</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>Hypersensitivity to β-lactams</td>
</tr>
<tr>
<td>ertapenem (Invanz®)</td>
<td>GP except Enterococcus, MRSA GN including Enterobacter (but not Pseudomonas), anaerobes</td>
<td>See above</td>
<td>See above</td>
<td>See above. Once-daily administration makes it convenient for outpatient IV therapy</td>
<td>Hypersensitivity to β-lactams</td>
</tr>
<tr>
<td><strong>Glycopeptides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin (Vancocin®)</td>
<td>GP including MRSA, not VRE C. difficile if PO</td>
<td>Glycopeptide sterically inhibits cell wall synthesis</td>
<td>Red Man Syndrome, Nephrotoxicity, Ototoxicity, Thrombocytopenia</td>
<td>Severe or life-threatening GP infections, patients with β-lactam allergy</td>
<td>May only be taken orally for severe C. difficile infection</td>
</tr>
<tr>
<td><strong>PROTEIN SYNTHESIS INHIBITORS (50S RIBOSOME)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>erythromycin (Erybid®, Eryc®)</td>
<td>GP except Enterococcus GN: Legionella, B. pertussis “Atypicals”: Chlamydia, Mycoplasma</td>
<td>Binds to 50S ribosomal subunit inhibiting protein synthesis</td>
<td>GI upset, Acute cholestatic hepatitis, Prolonged QT</td>
<td>Susceptible RTI, pertussis, diphtheria, Legionnaires’ disease, skin and soft tissue infections</td>
<td>Hypersensitivity to erythromycin, Concurrent therapy with astemizole, terfenadine</td>
</tr>
<tr>
<td>clarithromycin (Biaxin®)</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>Susceptible RTI, skin infections, non-tuberculous mycobacterial infections, part of multidrug therapy for H. pylori treatment</td>
<td>Hypersensitivity to macrolides</td>
</tr>
<tr>
<td>azithromycin (Zithromax®)</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>Susceptible RTI, acute exacerbations of COPD, community-acquired pneumonia, skin infections, Campylobacter infections if treatment indicated, chlamydia</td>
<td>Hypersensitivity to macrolides</td>
</tr>
<tr>
<td><strong>Lincosamides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clindamycin (Dalacin®)</td>
<td>GP except Enterococcus, most community-acquired MRSA Anaerobes</td>
<td>Inhibits peptide bond formation at 50S ribosome</td>
<td>Pseudomembranous colitis, GI upset</td>
<td>Treatment of suspected or proven infections caused by GP, anaerobes including skin and skin structure infections, oropharyngeal infections, in combination with GN coverage for intra-abdominal and pelvic infections</td>
<td>Hypersensitivity to clindamycin, Infants &lt; 30 d</td>
</tr>
<tr>
<td>chloramphenicol</td>
<td>GP GN Anaerobes</td>
<td>Inhibits peptidyl transferase action of tRNA at 50S ribosome</td>
<td>Aplastic anemia, Grey Baby Syndrome</td>
<td>Serious infections by susceptible organisms when suitable alternatives are not available including meningococcal disease in patients with anaphylaxis to β-lactams</td>
<td>Hypersensitivity to chloramphenicol</td>
</tr>
<tr>
<td>linezolid (Zyvoxam®)</td>
<td>GP including VRE + MRSA</td>
<td>Binds 50S ribosome and prevents functional 70S initiation complex</td>
<td>HTN (acts as MAOI), Risks with prolonged use: myelosuppression, optic neuropathy, peripheral neuropathy</td>
<td>Vancomycin-resistant Enterococcus faecium infections including intra-abdominal, skin and skin-structure, and urinary tract infections, MRSA infections as out patient therapy</td>
<td>Hypersensitivity to linezolid</td>
</tr>
<tr>
<td>Class and Drugs</td>
<td>Coverage</td>
<td>Mechanism of Action</td>
<td>Adverse Effects</td>
<td>Indications</td>
<td>Contraindications</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------</td>
<td>---------------------</td>
<td>----------------</td>
<td>-------------</td>
<td>------------------</td>
</tr>
<tr>
<td>PROTEIN SYNTHESIS INHIBITORS (30S RIBOSOME)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gentamicin</td>
<td>GN (includes Pseudomonas)</td>
<td>Binds 30S subunit of ribosome inhibiting protein synthesis</td>
<td>Nephrotoxicity (reversible), Vestibular and ototoxicity (irreversible). Vestibular toxicity is the most important aminoglycoside toxicity</td>
<td>GN infections when alternatives do not exist, UTIs, used in low doses for synergy with β-lactams or with vancomycin for the treatment of serious enterococcal infections</td>
<td>Pre-existing hearing loss and renal dysfunction</td>
</tr>
<tr>
<td>tobramycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amikacin (Amikin®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tetracycline (Apo-Tetra®, Nu-Tetra®)</td>
<td>GP</td>
<td>Binds 30S subunit of ribosome inhibiting protein synthesis</td>
<td>GI upset</td>
<td>Rickettsial infections, Chlamyphilia, acne (tetracycline, minocycline), PID (step-down), malaria prophylaxis (doxycycline)</td>
<td>Severe renal or hepatic dysfunction</td>
</tr>
<tr>
<td>minocycline (MinocinT®)</td>
<td>Anaerobes, “Atypicals”: Chlamydophila, Mycoplasma, Rickettsia, Borreli burgdorferi, Treponema</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>doxycycline (Doxycin®)</td>
<td>Malaria prophylaxis (doxycycline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOPOISOMERASE INHIBITORS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones (FQs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ciprofloxacin (Cipro®)</td>
<td>Poor GP activity GN (includes Pseudomonas)</td>
<td>Inhibits DNA gyrase</td>
<td>H/A, dizziness</td>
<td>Upper and lower RTI (not ciprofloxacin unless susceptible organism isolated), UTI, prostatitis (not moxifloxacin), bone and joint infections for susceptible organisms, skin and soft tissue infections (levofloxacin, moxifloxacin), infectious diarrhea, meningococcal prophylaxis, intra-abdominal infections (moxifloxacin, ciprofloxacin in combination with metronidazole or clindamycin), febrile neutropenia prophylaxis (ciprofloxacin, levofloxacin) or ciprofloxacin in combination with amoxicillin/clavulanate low management of “low-risk” febrile neutropenia</td>
<td>Jaundice</td>
</tr>
<tr>
<td>norfloxacin (Apo-Norflox®)</td>
<td>Anaerobes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ofloxacin (Floxin®)</td>
<td>Respiratory FQs: levofloxacin (Levaquin®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oxofloxacin (Avelox®)</td>
<td>Moxifloxacin also covers many anaerobes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>GP cocci</td>
<td>Inhibits RNA polymerase</td>
<td>Hepatic dysfunction, P450 enzyme induction</td>
<td>Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment of other mycobacterial infections, endocarditis involving prosthetic valve or other prosthetic device infections in combination with other antibiotic agents, prophylaxis for those exposed to people with N. meningitidis or HiB meningitis</td>
<td>Jaundice</td>
</tr>
<tr>
<td>N. meningitidis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. influenzae</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycobacteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole (Flagyl®)</td>
<td>Anaerobes</td>
<td>Forms toxic metabolites in bacterial cell which damage microbial DNA</td>
<td>Disulfiram-type reaction</td>
<td>Protozoal infections (trichomoniases, amebiasis, giardiasis), bacterial vaginosis, anaerobic bacterial infections</td>
<td></td>
</tr>
<tr>
<td>Protozoa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANTI-METABOLITE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprin- Sulfamethoxazole (TMP-SMX) (Septra®, Bactrim®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP, esp. S. aureus (incl. most MRSA) GN: enteric Nocardia Other: Pneumocystis, Toxoplasmosis</td>
<td>Inhibits folic acid pathway (TMP inhibits DHFR and SMX competes with PABA)</td>
<td>Hepatitis Stevens Johnson syndrome Bone marrow suppression Hyperkalemia Drug toxicity (increases free levels of many drugs, including glyburide, warfarin)</td>
<td>Susceptible UTI, RTI, GI infections, skin and soft tissue infections caused by staphylococcal species, treatment and prophylaxis of P. jiroveci pneumonia</td>
<td></td>
<td>Hypersensitivity to TMP-SMX, sulfam drugs</td>
</tr>
</tbody>
</table>
### Table 30. Antibiotics (continued)

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-METABOLITE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitrofurantoin (MacroBID®, MacroDantin®)</td>
<td>Enteroococcus, S. saprophyticus GN (coliforms)</td>
<td>Reactive metabolites inhibit ribosomal protein synthesis</td>
<td>Cholestasis, hepatitis Hemolysis if G6PD deficiency Interstitial lung disease with chronic use</td>
<td>Lower UTI; not pyelonephritis or bacteremia</td>
<td>Hypersensitivity to nitrofurantoin Anuria, oliguria or significant renal impairment Pregnant patients during labour and delivery or when labour imminent Infants &lt; 1 mo of age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANTI-MYCOBACTERIALS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>isoniazid (INH)</td>
<td>Mycobacteria</td>
<td>Inhibits mycolic acid synthesis</td>
<td>Hepatotoxicity Hepatitis Drug-induced SLE Peripheral neuropathy</td>
<td>Part of multidrug treatment for active TB, alone for treatment of latent TB</td>
<td>Drug-induced hepatitis or acute liver disease</td>
</tr>
<tr>
<td>rifampin (RIF)</td>
<td>Mycobacteria</td>
<td>Inhibits RNA polymerase</td>
<td>Hepatotoxicity P450 enzyme inducer Orange tears, saliva, urine</td>
<td>Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment of other mycobacterial infections</td>
<td>Jaundice Not to be used monotherapy (except for prophylaxis)</td>
</tr>
<tr>
<td>ethambutol</td>
<td>Mycobacteria</td>
<td>Inhibits mycolic acid synthesis</td>
<td>Loss of central and colour vision</td>
<td>Part of multidrug treatment for active TB and other mycobacterial infections</td>
<td>Renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pyrazinamide (PZA)</td>
<td>Mycobacteria</td>
<td>Unknown</td>
<td>Hepatotoxicity Gout Gastric irritation</td>
<td>Part of multidrug treatment for active TB</td>
<td>Severe hepatic damage or acute liver disease Patients with acute gout</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SULFONES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dapsone sulfone</td>
<td>M. Leprae, part of treatment for P. jiroveci pneumonia (with TMP), P. jiroveci pneumonia prophylaxis, toxoplasmosis prophylaxis with pyrimethamine</td>
<td>Inhibit folic acid synthesis by competition with PABA</td>
<td>Rash Drug fever Agranulocytosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 31. Antibiotics for Selected Bacteria

<table>
<thead>
<tr>
<th>Pseudomonas</th>
<th>S. aureus</th>
<th>Enterococcus</th>
<th>H. influenzae</th>
<th>Anaerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ciprofloxacin</td>
<td>cloxacillin (MSSA)</td>
<td>ampicillin</td>
<td>amoxicillin-clavulanate</td>
<td>metronidazole</td>
</tr>
<tr>
<td>gentamicin, tobramycin</td>
<td>1° cephapirin (MSSA)</td>
<td>amoxicillin</td>
<td>2°/3° cephalosporin</td>
<td>clindamycin</td>
</tr>
<tr>
<td>piperacillin/tazobactam</td>
<td>clindamycin</td>
<td>vancomycin (incl. MRSA)</td>
<td>vancomycin macrodil (clarithromycin, azithromycin)</td>
<td>amoxicillin-clavulanate</td>
</tr>
<tr>
<td>ceftazidime</td>
<td>vancomycin (incl. MRSA)</td>
<td>linezolid (incl. MRSA)</td>
<td>linezolid for VRE</td>
<td>cefoxitin</td>
</tr>
<tr>
<td>cefepime</td>
<td>daptomycin (incl. MRSA)</td>
<td>daptomycin for VRE</td>
<td>daptomycin for VRE</td>
<td>piperacillin-tazobactam</td>
</tr>
<tr>
<td>meropenem</td>
<td></td>
<td></td>
<td>tigecycline for VRE</td>
<td>moxifloxacin</td>
</tr>
<tr>
<td>imipenem</td>
<td></td>
<td></td>
<td></td>
<td>etrapenam, imipenem, meropenem</td>
</tr>
</tbody>
</table>

### Antivirals

### Table 32. Antivirals

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-HERPESVIRUS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acyclovir</td>
<td>HSV-1,2 VZV</td>
<td>Guanosine analog inhibits viral DNA polymerase</td>
<td>PO well-tolerated IV: nephrotoxicity, CNS</td>
<td>Hypersensitivity to acyclovir or valacyclovir</td>
</tr>
<tr>
<td>valacyclovir (Valtrex®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>penciclovir</td>
<td>HSV-1,2 VZV</td>
<td>See above</td>
<td>H/A, nausea</td>
<td>Hypersensitivity to famiclovir or penciclovir</td>
</tr>
<tr>
<td>foscarnet</td>
<td>CMV HSV-1,2, VZV</td>
<td>See above</td>
<td>Heme: neutropenia, thrombocytopenia, anemia Gl: N/V, diarrhea</td>
<td>Hypersensitivity to ganciclovir or valganciclovir Possible cross-hypersensitivity between acyclovir and valacyclovir</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANTI-HIV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antimicrobials/Antivirals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toronto Notes 2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 32. Antivirals (continued)

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OTHER ANTIVIRALS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>interferon-PEG interferon-α</td>
<td>Chronic hep B, hep C</td>
<td>Inhibits viral protein synthesis</td>
<td>“Flu-like” syndrome</td>
<td>Hypersensitivity to any interferon</td>
</tr>
<tr>
<td>2a, 2b</td>
<td>HPV</td>
<td>Depression</td>
<td>Bone marrow suppression</td>
<td>Cannot use in combination with ribavirin if renal impairment</td>
</tr>
<tr>
<td>ribavirin (Virazole®)</td>
<td>Chronic hep C</td>
<td>Guanosine analog with multiple postulated mechanisms of action</td>
<td>Hemolytic anemia</td>
<td>Pregnancy or woman who may become pregnant</td>
</tr>
<tr>
<td>RSV</td>
<td>Lassa fever</td>
<td>Rash, conjunctivitis</td>
<td>Highly teratogenic</td>
<td></td>
</tr>
<tr>
<td>lamivudine (3TC®, Heptovir®)</td>
<td>Chronic hep B</td>
<td>See HIV/AIDS, ID41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M2 inhibitors:</td>
<td></td>
<td>Inhibits viral uncoating after infection of cell</td>
<td>Anti-cholinergic effects</td>
<td>Hypersensitivity to lamivudine</td>
</tr>
<tr>
<td>amantadine (Endantadine®, Symmetrel®)</td>
<td>Influenza A treatment</td>
<td></td>
<td>CNS: anxiety, insomnia, H/A, dizziness, difficulty concentrating</td>
<td></td>
</tr>
<tr>
<td>rimantadine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuraminidase inhibitors:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>zanamavir (Relenza®)</td>
<td>Influenza A and B: treatment and prophylaxis</td>
<td>Inhibits neuraminidase, an enzyme required for release of virus from infected cells and prevention of viral aggregation</td>
<td>GI: N/V, diarrhea</td>
<td></td>
</tr>
<tr>
<td>oseltamavir (Tamiflu®)</td>
<td></td>
<td></td>
<td>Bronchospasm in zanamavir</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 20. Mechanism of action of antivirals**

© Olivia Toronto Shim 2012
## Antifungals

### Table 33. Antifungals

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POLYENES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amphotericin B</td>
<td>Endemic mycoses: Histoplasmosis, blastomycosis, coccidiomycosis Pulmonary; Aspergillosis CNS: Cryptococcus</td>
<td>A polyene antimicrobial: inserts into fungal cytoplasmic membrane causing altered membrane permeability and cell death</td>
<td>Nephrotoxicity Hypo/hyperkalemia Infusion reactions: chills, fevers, H/A Peripheral phlebitis</td>
<td>Renal impairment</td>
</tr>
<tr>
<td>nystatin (oral, topical)</td>
<td>Candidiasis: mucocutaneous, GI, oral (thrush), vaginal</td>
<td>See above Not absorbed from the GI tract</td>
<td>GI: N/V, diarrhea Highly toxic if given IV</td>
<td></td>
</tr>
<tr>
<td><strong>IMIDAZOLES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clotrimazole (Canesten®)</td>
<td>Oral and vulvovaginal candidiasis Dermatomycoses</td>
<td>All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability</td>
<td>Pruritis, skin irritation</td>
<td></td>
</tr>
<tr>
<td>miconazole (Monistat®, Micazol®)</td>
<td>Vulvovaginal candidiasis Dermatomycoses</td>
<td>Vaginal burning Nausea and vomiting</td>
<td>Cross-sensitivity with other azoles possible Hepatic dysfunction Pregnant women or those that may become pregnant</td>
<td></td>
</tr>
<tr>
<td>ketoconazole (Nizoral®)</td>
<td>Dermatomycoses Seborrheic dermatitis</td>
<td>Pruritis, skin irritation GI nonspecific Results in decreased androgen and testosterone synthesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TRIAZOLES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluconazole (Diflucan®)</td>
<td>Candida infections (mucosal and invasive) Cryptococcal meningitis (step-down therapy)</td>
<td>All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability</td>
<td>Elevated liver enzymes GI nonspecific</td>
<td>Cross-sensitivity with other azoles unknown Concurrent use of terfenadine if dose of fluconazole &gt;400 mg</td>
</tr>
<tr>
<td>itraconazole (Sporanox®®)</td>
<td>Porotrichosis Onychomycoses Endemic mycoses: Histoplasmosis, blastomycosis, coccidiomycosis</td>
<td>Elevated liver enzymes Rash GI nonspecific</td>
<td>Cross-sensitivity with other azoles unknown Severe ventricular dysfunction</td>
<td></td>
</tr>
<tr>
<td>voriconazole (Vfend®)</td>
<td>Aspergillosis Candidiasis</td>
<td>Visual disturbance (30%) Hepatotoxicity Cutaneous photosensitivity Cutaneous squamous cell carcinoma Long term use in immunosuppressed patients</td>
<td>Cross-sensitivity with other azoles unknown May avoid or alter doses if co-administered with other CYP3A4 substrates, rifampin, carbamazepine, long-acting barbiturates, ritonavir, efavirenz, sirolimus, rifabutin, ergot alkaloids</td>
<td></td>
</tr>
<tr>
<td>posaconazole (Posanoz®, Noxafil®)</td>
<td>Candidiasis Aspergillosis Mucormycosis</td>
<td>GI nonspecific Elevated liver enzymes Headache</td>
<td>Coadministration of cisapride, ergot alkaloids, pimozide, quinidine, or sirolimus</td>
<td></td>
</tr>
<tr>
<td><strong>ALLYLAMINES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>terbinafine (Lamisil®)</td>
<td>Dermatomycoses Onychomycoses</td>
<td>Inhibits enzyme needed for ergosterol synthesis</td>
<td>Rash, local irritation GI nonspecific, transaminits</td>
<td>Active liver disease</td>
</tr>
<tr>
<td><strong>ECHINOCANDINS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>caspofungin micafungin anidulafungin</td>
<td>Refractory aspergillosis, candidemia (azole-resistant)</td>
<td>Inhibits 1-3 ß-glycan synthesis (needed for fungal cell wall)</td>
<td>Hepatotoxicity</td>
<td></td>
</tr>
</tbody>
</table>
**Antiparasitics**

**Table 34. Antiparasitics**

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIMALARIALS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>chloroquine</td>
<td>Malaria: treatment of erythrocytic phase of all five species of <em>Plasmodium</em> that infect humans</td>
<td>Inhibits parasite heme polymerase</td>
<td>CNS: blurred vision, retinopathy, dizziness, Nonspecific GI</td>
<td>Hypersensitivity to chloroquine or other 4-aminquinoline, Retinal or visual field changes due to 4-aminquinoline</td>
</tr>
<tr>
<td></td>
<td>Note: High resistance of <em>P. falciparum</em> and <em>P. vivax</em> in certain geographic areas</td>
<td></td>
<td>(rare with prophylaxis)</td>
<td></td>
</tr>
<tr>
<td>quinine</td>
<td>Malaria: treatment of all five species of <em>Plasmodium</em> that infect humans, including chloroquine-resistant <em>P. falciparum</em></td>
<td></td>
<td>Cinchonism: ears (tinnitus, vertigo), eyes (visual disturbance), GI (N/V, diarrhea), CNS (H/A, fever)</td>
<td>Hypersensitivity to quinine, may have cross-sensitivity with quinidine, Patients with G6PD deficiency, tinnitus, optic neuritis, hypoglycemia, history of blackwater fever or thrombocytopenic purpura due to quinine use</td>
</tr>
<tr>
<td>mefloquine (Lariam®)</td>
<td>Malaria: treatment and prophylaxis of all four species of <em>Plasmodium</em> that infect humans</td>
<td></td>
<td>CNS/Psych: irritability, nightmares, psychoses, suicide, depression, seizures, H/A</td>
<td>History of seizures, psychosis, severe anxiety or depression</td>
</tr>
<tr>
<td>primaquine</td>
<td>Malaria: treatment of liver hypnozoites of <em>P. vivax</em> and <em>P. ovale.</em> Prophylaxis of all <em>Plasmodium</em> spp. <em>Plasmodium jiroveci</em> (with clindamycin)</td>
<td>Interferes with mitochondrial function</td>
<td>Hemolytic anemia in G6PD deficient GI upset (take with food)</td>
<td>G6PD nonspecific G6PD deficiency, Concurrent or recent use of quinacrine Pregnancy</td>
</tr>
<tr>
<td>atovaquone/proguanil (Malarone®)</td>
<td>Malaria: treatment and prophylaxis of <em>P. falciparum</em></td>
<td>Inhibits mitochondrial electron transport and dhtydrofolate reductase</td>
<td>N/V, anorexia, diarrhea, abdo pain (take with food)</td>
<td>Hypersensitivity to atovaquone or proguanil, Severe renal impairment</td>
</tr>
<tr>
<td>artemisinin derivatives (artemeter, artesunate, etc.) Note: marketed primarily in endemic countries</td>
<td>Malaria: treatment of all <em>Plasmodium</em> species Severe malaria (IV artesunate) Typically used in combination with a longer-acting agent from above</td>
<td>Binds iron, leading to formation of free radicals that damage parasite proteins</td>
<td>Transient neurologic deficits (nystagmus, balance disturbance) Transient neuropenia (at high doses of oral artesunate)</td>
<td>Hypersensitivity to artemisinins</td>
</tr>
<tr>
<td>Class and Drugs</td>
<td>Coverage</td>
<td>Mechanism of Action</td>
<td>Adverse Effects</td>
<td>Contraindications</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------</td>
<td>---------------------</td>
<td>----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Other Anti-Protozoal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iodoquinol (Diodoquin®)</td>
<td>T. vaginalis, giardiasis</td>
<td>Contact amoebicide that acts in intestinal lumen by uncertain mechanism</td>
<td>GI: N/V, diarrhea, abdo pain</td>
<td>Hypersensitivity to any 8-hydroxy-quinoline or iodine Patients with hepatic damage or optic neuropathy Pregnancy</td>
</tr>
<tr>
<td>metronidazole</td>
<td>Amebiasis, T. vaginalis, giardiasis</td>
<td>See Antibiotics, ID47</td>
<td>N/V, diarrhea, abdo pain, headache</td>
<td>Hypersensitivity to metronidazole</td>
</tr>
<tr>
<td>nitazoxanide</td>
<td>Cryptosporidium, giardiasis</td>
<td>Interferes with parasite anaerobic metabolism</td>
<td>N/V, diarrhea, abdo pain, headache</td>
<td>Hypersensitivity to nitazoxanide</td>
</tr>
<tr>
<td>Anti-Helminthics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>praziquantel</td>
<td>Schistosomiasis and other flukes</td>
<td>Increases Ca&lt;sup&gt;2+&lt;/sup&gt; permeability of helminth cell membrane, causing paralysis and detachment</td>
<td>N/V, fever, dizziness</td>
<td>Ocular cysticercosis</td>
</tr>
<tr>
<td>albendazole</td>
<td>Intestinal roundworms Neurocysticercosis Microsporidiosis Echinococcus → Hydatid disease</td>
<td>Inhibits glucose uptake into susceptible parasites</td>
<td>Elevated liver enzymes Alopecia GI nonspecific Agranulocytosis</td>
<td>Pregnancy, Ocular cysticercosis or intraventricular cysticercosis</td>
</tr>
<tr>
<td>mebendazole (Vermox®)</td>
<td>Intestinal roundworms: - pinworm - whipworm - hookworm - roundworm (e.g. Ascaris)</td>
<td>Inhibits microtubule formation and glucose uptake</td>
<td>Nonspecific GI</td>
<td>Pregnancy, infants</td>
</tr>
<tr>
<td>ivermectin</td>
<td>Strongyloides Onchocerciasis Scabies</td>
<td>Interferes with polarization of nerve and muscles cells in susceptible parasites leading to paralysis</td>
<td>Nausea, bloating, diarrhea, myalgias, lightheadedness, headache</td>
<td>Hypersensitivity to ivermectin Pregnancy</td>
</tr>
<tr>
<td>diethylcarbamazine</td>
<td>Wuchereria bancrofti Loa loa</td>
<td></td>
<td>Anorexia, N/V, headache, drowsiness, encephalitis, retinal hemorrhage Mazotti reaction if coinfected with onchocerciasis</td>
<td></td>
</tr>
</tbody>
</table>

Quick Reference: Common Infections and their Antibiotic Management

<table>
<thead>
<tr>
<th>Infection</th>
<th>Bacteria</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Community-acquired</td>
<td>S. pneumonia, H. influenzae, M. catarrhalis, Mycoplasma, Chlamyphila, Legionella, S. aureus</td>
<td>Outpatient: amoxicillin-clavulanate OR doxycycline Hospitalized: antipseudomonal respiratory fluoroquinolone OR 3rd generation cephalosporin ± macrolide</td>
</tr>
<tr>
<td>• Hospital-acquired: GNR (including Pseudomonas in special settings such as ICU)</td>
<td></td>
<td>ceftriaxone (if not at risk for Pseudomonas) OR pip/tazo OR meropenem</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Mycobacterium tuberculosis</td>
<td>isoniazid + rifampin + pyrazinamide + ethambutol + pyridoxine (for initial empiric therapy)</td>
</tr>
<tr>
<td>UTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystitis</td>
<td>KEEP²S</td>
<td>fluoroquinolone OR TMP/SMX OR nitrofurantoin</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>KEEP²S</td>
<td>ciprofloxacin OR 3rd gen. ceph</td>
</tr>
<tr>
<td>Urethritis</td>
<td>Neisseria gonorrhoea Chlamydia</td>
<td>ceftriaxone azithromycin OR doxycycline</td>
</tr>
<tr>
<td>Soft Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td>β-hemolytic streptococci, MSSA</td>
<td>cephalaxin OR cefazolin</td>
</tr>
<tr>
<td>Necrotizing Fasciitis</td>
<td>Type I: polymicrobial (GNR and anaerobes)</td>
<td>pip/tazo + clindamycin</td>
</tr>
<tr>
<td>Type II: β-hemolytic streptococci Unknown organism</td>
<td></td>
<td>penicillin G + clindamycin</td>
</tr>
</tbody>
</table>

KEEP²S = Klebsiella, E. Coli, Enterococi, Proteus mirabilis, Pseudomonas, S. saprophyticus
### Table 35. Common Infections and their Empiric Antibiotic Management (continued)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Bacteria</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteomyelitis</td>
<td>MSSA</td>
<td>clindamycin OR cefoxitin</td>
</tr>
<tr>
<td>Diabetic Foot</td>
<td>• Mild</td>
<td>cephalxin OR clindamycin</td>
</tr>
<tr>
<td></td>
<td>• Moderate or severe</td>
<td>clindamycin + ciprofloxacin OR pip/tazo ± vancomycin if MRSA suspected</td>
</tr>
<tr>
<td>Septic Arthritis</td>
<td><em>N. gonorrhoeae</em> (sexually active adults)</td>
<td>vancomycin + ceftriaxone</td>
</tr>
<tr>
<td></td>
<td><em>S. aureus, S. pyogenes</em></td>
<td></td>
</tr>
<tr>
<td>OTHER</td>
<td>Meningitis</td>
<td>ceftriaxone + vancomycin (+ ampicillin for Listeria in very young, old, immunocompromised)</td>
</tr>
<tr>
<td>Bacterial Endocarditis</td>
<td>• Native valve</td>
<td>Usually non urgent and can wait for confirmation of etiology</td>
</tr>
<tr>
<td></td>
<td><em>S. viridans, S. aureus, Enterococcus</em></td>
<td>Empirical therapy if patient unstable, vancomycin and gentamycin or ceftriaxone. Take multiple blood cultures prior to initiating therapy</td>
</tr>
</tbody>
</table>

### References

Principles of Microbiology

Neurological Infections

Respiratory Infections

Cardiac Infections

Gastrointestinal Infections
Gottlieb T, Heathcris CS. Diarrhoea in adults (acute). Clinical Evidence 2011;02:301.

Respiratory Infections

Cardiac Infections

Gastrointestinal Infections
Gottlieb T, Heathcris CS. Diarrhoea in adults (acute). Clinical Evidence 2011;02:301.

Reference Sources
Quick Reference: Common Infections/References

To view the full reference list, please refer to the original source.
HIV and AIDS

Fungal Infections

Parasitic Infections

Infections in the Immunocompromised Host

Fever of Unknown Origin

Nosocomial Infections

Travel Medicine

Antimicrobials

Antivirals
Medical Imaging

Ashley Leckie, Laura Quigley and Erin Wong, chapter editors
Maria Jogova and Howard Meng, associate editors
Melini Gupta, EBM editor
Dr. Taebong Chung, Dr. Nasir Jaffer and Dr. Eugene Yu, staff editors

Imaging Modalities .................................. 2
Ultrasound (U/S)
Magnetic Resonance Imaging (MRI)
Positron Emission Tomography Scans (PET)
Contrast Enhancement

Chest Imaging ............................................ 4
Chest X-Ray (CXR)
Computed Tomography (CT) Chest
Lung Abnormalities
Pulmonary Vascular Abnormalities
Pleural Abnormalities
Mediastinal Abnormalities
Tubes, Lines, and Catheters

Abdominal Imaging ................................. 10
Abdominal X-Ray (AXR)
Approach to Abdominal X-Ray (AXR)
Approach to Abdominal Computed Tomography (CT)
Contrast Studies
Specific Visceral Organ Imaging
"itis" Imaging
Angiography of GI Tract

Genitourinary System and Adrenal ............... 16
Urological Imaging
Gynecological Imaging
Adrenal Mass

Neuroradiology ................................. 18
Modalities
Approach to CT Head
Selected Pathology

Musculoskeletal System (MSK) ............... 22
Modalities
Approach to Interpretation of Bone X-Rays
Trauma
Arthritis
Bone Tumour
Infection
Metabolic Bone Disease

Nuclear Medicine ............................... 26
Brain
Thyroid
Respiratory
Cardiac
Abdomen and Genitourinary System
Bone

Interventional Radiology ....................... 28
Vascular Procedures
Nonvascular Interventions

Breast Imaging .................................... 30
Modalities
Breast Interventional Procedures
Breast Findings

References ..................................... 32

Acronyms

AXR  abdominal x-ray
CT  computed tomography
CTA  computed tomographic angiogram
DEXA  dual-energy x-ray absorptiometry
DSA  digital subtraction angiography
DWI  diffusion-weighted image
ERCP  endoscopic retrograde cholangiopancreatography
FLAIR  fluid-attenuated inversion recovery
HIDA  hepatobiliary iminodiacetic acid
HSQ  hysterosalpingogram
IVP  intravenous pyelogram
MRA  magnetic resonance angiogram
MRCP  magnetic resonance cholangiopancreatography
MRI  magnetic resonance imaging
MUGA  multiple gated acquisition scan
PBD  percutaneous biliary drainage
PET  positron emission tomography scan
PTA  percutaneous transluminal angioplasty
RAIU  radioactive iodine uptake
SPECT  single photon emission computed tomography
TRUS  transrectal ultrasound
TVUS  transvaginal ultrasound
VCUG  voiding cystourethrogram
Imaging Modalities

X-Ray Imaging
- x-rays, or Roentgen rays, are a form of electromagnetic energy of short wavelength
- as x-ray photons traverse matter, they can be absorbed (a process known as “attenuation”) and/or scattered
  - the density of a structure determines its ability to attenuate or “weaken” the x-ray beam
  - air < fat < water < bone < metal
- structures that have high attenuation, e.g. bone, appear white on the resulting images

Plain Films
- x-rays pass through the patient and interact with a detection device to produce a 2-dimensional projection image
- structures closer to the film appear sharper and less magnified
- contraindications: pregnancy (relative)
- advantages: inexpensive, non-invasive, readily available
- disadvantages: radiation exposure, generally poor at distinguishing soft tissues

Fluoroscopy
- continuous x-rays allow real-time visualization
- used for guiding angiographic and interventional procedures, in contrast examinations of the GI tract, and in the OR for certain surgical procedures (e.g. orthopedic, urological)
- on the fluoroscopic image black and white are reversed so that bone and contrast agents appear dark and radiolucent structures appear light

Computed Tomography (CT)
- x-ray beam opposite a detector moves in a continuous 360 degree arc as patient is advanced through the imaging system
  - subsequent computer assisted reconstruction of anatomical structures from the axial plane
  - attenuation is quantified in Hounsfield units:
    - adjusting the “window width” (range of Hounsfield units displayed) and “window level” (midpoint value of the window width) can maximally visualize certain anatomical structures
    - e.g. CT chest can be viewed using “lung”, “soft tissue” and “bone” settings
- contraindications: pregnancy (relative), contraindications to contrast agents (e.g. allergy, renal failure)
- advantages: delineates surrounding soft tissues, excellent at delineating bones and identifying lung/liver masses, may be used to guide biopsies, spiral CT has fast data acquisition, helical CT allows 3D reconstruction, CT angiography is less invasive than conventional angiography
- disadvantages: high radiation exposure, IV contrast injection, anxiety of patient when going through scanner, higher cost and less available than plain film

Ultrasound (U/S)
- high frequency sound waves are transmitted from a transducer and passed through tissues; reflections of the sound waves are picked up by the transducer and transformed into images
- reflection (or “echo”) occurs when the sound waves pass through tissue interfaces of different acoustic densities
- structures are described based on their echogenicity; hyperechoic structures appear bright whereas hypoechoic structures appear dark
- higher ultrasound frequencies result in greater resolution but greater attenuation (i.e. deeper structures more difficult to visualize)
- artifacts: acoustic shadowing refers to the echo-free area located behind an interface that strongly reflects (i.e. tissue/air) or absorbs (tissue/bone) sound waves; enhancement refers to the increase in reflection amplitude (increased brightness) from objects that lie below a weakly attenuating structure (e.g. cyst)
- Doppler: determines the velocity of blood flowing past the transducer based on the Doppler effect
- Duplex scan: Doppler + visual images
- advantages: relatively low cost, non-invasive, no radiation, real time imaging, may be used for guided biopsies, many different imaging planes (axial, sagittal), determines cystic versus solid
- disadvantages: highly operator-dependent, air in bowel may prevent imaging of midline structures in the abdomen, may be limited by patient habitus

## Typical Effective Doses from Diagnostic Medical Exposures (in adults)**

<table>
<thead>
<tr>
<th>Diagnostic Procedure</th>
<th>Equivalent Number of Chest X-rays</th>
<th>Approximate Equivalent Period of Natural Background Radiation** (~3 mSv/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>X-ray examinations:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skull</td>
<td>5</td>
<td>12 d</td>
</tr>
<tr>
<td>Cervical spine</td>
<td>10</td>
<td>3 wk</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>50</td>
<td>4 mo</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>75</td>
<td>6 mo</td>
</tr>
<tr>
<td>Chest (single PA film)</td>
<td>1</td>
<td>2 d</td>
</tr>
<tr>
<td>Shoulder</td>
<td>0.5</td>
<td>1 d</td>
</tr>
<tr>
<td>Mammoigraphy</td>
<td>20</td>
<td>1 wk</td>
</tr>
<tr>
<td>Abdomen</td>
<td>35</td>
<td>3 mo</td>
</tr>
<tr>
<td>Hip</td>
<td>35</td>
<td>3 mo</td>
</tr>
<tr>
<td>Pelvis</td>
<td>30</td>
<td>10 wk</td>
</tr>
<tr>
<td>Knee</td>
<td>0.25</td>
<td>&lt;1 d</td>
</tr>
<tr>
<td>IVU</td>
<td>190</td>
<td>1 yr</td>
</tr>
<tr>
<td>Dual-energy x-ray densitometry (without/with CT)</td>
<td>0.5/2</td>
<td>&lt;1/0.4 d</td>
</tr>
<tr>
<td>Upper GI series</td>
<td>300</td>
<td>2 yr</td>
</tr>
<tr>
<td>Small bowel series</td>
<td>250</td>
<td>20 mo</td>
</tr>
<tr>
<td>Barium enema</td>
<td>400</td>
<td>2.7 yr</td>
</tr>
<tr>
<td><strong>CT procedures:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>100</td>
<td>8 mo</td>
</tr>
<tr>
<td>Neck</td>
<td>150</td>
<td>1 yr</td>
</tr>
<tr>
<td>Spine</td>
<td>300</td>
<td>2 yr</td>
</tr>
<tr>
<td>Chest</td>
<td>350</td>
<td>2.3 yr</td>
</tr>
<tr>
<td>Chest (pulmonary embolism)</td>
<td>750</td>
<td>5 yr</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>800</td>
<td>5.3 yr</td>
</tr>
<tr>
<td>Abdomen</td>
<td>400</td>
<td>2.7 yr</td>
</tr>
<tr>
<td>Pelvis</td>
<td>300</td>
<td>2 yr</td>
</tr>
<tr>
<td><strong>Radionuclide studies:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain (18FDG)</td>
<td>705</td>
<td>4.7 yr</td>
</tr>
<tr>
<td>Bone (99mTc)</td>
<td>315</td>
<td>2.1 yr</td>
</tr>
<tr>
<td>Thyroid (131I)</td>
<td>240</td>
<td>1.6 yr</td>
</tr>
<tr>
<td>Thyroid (131I)</td>
<td>95</td>
<td>8 mo</td>
</tr>
<tr>
<td>Cardiac rest-stress test (123I)</td>
<td>470</td>
<td>3 yr</td>
</tr>
<tr>
<td>(123I) 1-d</td>
<td>640</td>
<td>4 yr</td>
</tr>
<tr>
<td>Lung ventilation</td>
<td>25</td>
<td>2 mo</td>
</tr>
<tr>
<td>(133Xe) 1-d</td>
<td>100</td>
<td>8 mo</td>
</tr>
<tr>
<td>Lung perfusion (133Xe)</td>
<td>90-165</td>
<td>7-13 mo</td>
</tr>
<tr>
<td>Renal (131I)</td>
<td>105</td>
<td>8.4 yr</td>
</tr>
<tr>
<td>Liver-spleen (99mTc)</td>
<td>135</td>
<td>1 yr</td>
</tr>
<tr>
<td>Biliary tract (99mTc)</td>
<td>150</td>
<td>&lt;1 d</td>
</tr>
</tbody>
</table>

*Source: Radiology 2008; 248:254-263
**Calculated using average natural background exposure in Canada (Health Canada: http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/environ/expos-eng.php)

## Attenuation
- Bone (= bright) > grey matter > white matter (“fatty” myelin) > CSF > air (= dark)
**Magnetic Resonance Imaging (MRI)**

- Non-invasive technique that does not use ionizing radiation
- Able to produce images in virtually any plane
- Patient is placed in a magnetic field; protons (H+) align themselves along the plane of magnetization due to intrinsic polarity. A pulsed radiofrequency beam is subsequently turned on which deflects all the protons off their aligned axes due to absorption of energy from the radiofrequency beam. When the radiofrequency beam is turned off, the protons return to their pre-excitation axis, giving off the energy they absorbed. This energy is measured with a detector and interpreted by a computer to generate MR images.
- The MR image reflects the signal intensity picked up by the receiver. This signal intensity is dependent on:
  1. Hydrogen density: tissues with low hydrogen density (e.g. cortical bone, lung) generate little to no MR signal compared to tissues with high hydrogen density (e.g. water)
  2. Magnetic relaxation times (T1 and T2): reflect quantitative alterations in MR signal strength due to intrinsic properties of the tissue and its surrounding chemical and physical environment (see Table 1)

<table>
<thead>
<tr>
<th>Imaging Techniques</th>
<th>Contrast Enhancements</th>
<th>Main Application</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion Weighted</td>
<td>Contrast dependent on the molecular motion of water. Decreased diffusion is hyperintense (bright), whereas increased diffusion is hypointense (dark)</td>
<td>Neuroradiology</td>
<td>Sensitive for detection of acute ischemic stroke and differentiating an acute stroke from other neurologic pathologies. An acute infarction will appear hyperintense</td>
</tr>
<tr>
<td>T1-Weighted</td>
<td>Fluid is hypointense (dark) and fat is hyperintense (bright)</td>
<td>Body soft tissues</td>
<td>Often considered an anatomic scan since they provide a reference for functional imaging</td>
</tr>
<tr>
<td>T2-Weighted</td>
<td>Fluid is hyperintense (bright) and fat is hypointense (dark)</td>
<td>Body soft tissues</td>
<td>Often considered a pathologic scan since they will highlight edematous areas associated with certain pathologies</td>
</tr>
</tbody>
</table>

**Positron Emission Tomography Scans (PET)**

- Non-invasive technique that involves exposure to ionizing radiation (~7 mSv)
- Nuclear medicine imaging technique that produces images of functional processes in the body
- Current generation models integrate PET and CT technologies into a single imaging device (PET-CT) that collects both anatomic and functional information during a single acquisition
- Positron-producing radioisotope, such as 18-fluorodeoxyglucose (18-FDG) is chemically incorporated into a metabolically active molecule (glucose), injected into patient, which travels to target organ, accumulates in tissues of interest, and as radioactive substance begins to decay, gamma rays are produced which are detected by PET scanner
- Advantages: shows metabolism and physiology of tissues (not only anatomic), in oncology allows diagnosis, staging, restaging (lung, breast, colorectal, lymphoma, melanoma, esophageal, head and neck), has predictive and prognostic value (breast, lymphoma), can evaluate cardiac viability
- Disadvantages: cost, ionizing radiation
- Contraindications: pregnancy

**Table 2. Contrast Agents**

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Types</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray/CT</td>
<td>1. Barium (oral or rectal)</td>
<td>Radiopaque substance which helps to delineate intraluminal anatomy, may demonstrate patency, lumen integrity, or large filling defects</td>
<td>Risk of nephrotoxicity</td>
<td>Previous adverse reaction to contrast; barium enema is contraindicated in toxic megacolon, acute colitis, and suspected perforation</td>
</tr>
<tr>
<td></td>
<td>2. Iodine (IV injection)</td>
<td>Delineates intraluminal anatomy, may demonstrate patency, lumen integrity, or large filling defects; under fluoroscopy, may also give information on function of an organ</td>
<td></td>
<td>Previous adverse reaction to contrast, renal failure, diabetes, pregnancy, multiple myeloma, severe heart failure and dehydration</td>
</tr>
<tr>
<td>MRI</td>
<td>1. Gadolinium-Chelates (IV injection)</td>
<td>Shortens T1 relaxation time, thereby increasing signal intensity in T1-weighted sequences; gadolinium has some effect on T2-relaxation time; highlights highly vascular structures (i.e. tumours)</td>
<td>Risk of nephrogenic systemic fibrosis in patients with end-stage renal disease</td>
<td>Previous adverse reaction to contrast or if end-stage renal disease (relative contraindication)</td>
</tr>
<tr>
<td>U/S</td>
<td>1. Microbubbles (IV injection)</td>
<td>Since gas is highly echogenic, the microbubbles allow for echo-enhancement of a tissue</td>
<td></td>
<td>Contraindicated in individuals with right-to-left cardiac shunts or people with known hypersensitivity reactions</td>
</tr>
</tbody>
</table>
Chest Imaging

Chest X-Ray (CXR)

Standard Views
- posteroanterior (PA): anterior chest against film plate to minimize magnification of the heart size
  - helps localize lesions when combined with PA view
- lateral: better visualization of retrocardiac space and thoracic spine (more sensitive at picking up pleural effusions)
  - enlarged cardiac silhouette
- anteroposterior (AP): for bedridden patients (generally a lower quality film than PA)
- lateral decubitus: to assess for pleural effusion and pneumothorax in bedridden patients
- lordotic: angled beam allowing better visualization of apices normally obscured by the clavicles and anterior ribs

![CXR views](image)

Figure 1. CXR views

Approach to CXR

Basics
- ID: patient name, MRN, sex, age
- date of exam
- markers: Right and/or Left
- technique: view (e.g. PA, AP, lateral), supine or erect
- indications for the study
- comparison: date of previous study for comparison (if available)
- quality of film: inspiration (6th anterior and 10th posterior ribs should be visible), penetration (thoracic spine should be visible) and rotation (clavicles vs. spinous process)

Analysis
- tubes and lines: check position and be alert for pneumothorax or pneumomediastinum
- soft tissues: neck, axillae, pectoral muscles, breasts/nipples, chest wall
  - nipple markers can help identify nipples (may mimic lung nodules)
  - amount of soft tissue, presence of masses and air (subcutaneous emphysema)
- abdomen (see Abdominal Imaging, MI10):
  - free air under the diaphragm, air-fluid levels, distention in small and large bowels
  - herniation of abdominal contents (i.e. diaphragmatic hernia)
- bones: C-spine, thoracic spine, shoulders, ribs, sternum, clavicles
  - lytic and blastic lesions and fractures
- mediastinum: trachea, heart, great vessels, mediastinum
  - cardiomegaly (cardiothoracic ratio >0.5), tracheal shift, tortuous aorta, widened mediastinum
- hila: pulmonary vessels, mainstem bronchi, and segmental bronchi, lymph nodes
- lungs: lung parenchyma, pleura, diaphragm
  - spine sign: on lateral films, vertebral bodies should appear progressively radiolucent as one moves down the thoracic vertebral column. If they appear more radiopaque, it is an indication of pathology (i.e. consolidation in overlying left lower lobe)
  - comment on abnormal lung opacity, pleural effusions or thickening
  - right hemidiaphragm usually higher than left due to liver
  - right vs. left hemidiaphragm can be discerned on lateral CXR due to heart resting directly on left hemidiaphragm

Sodium Bicarbonate plus N-acetylcysteine Prophylaxis: A Meta-analysis

*JACC Cardiovasc Interv* 2009;2:1116-1124

**Study:** A meta-analysis of 10 RCTs.

**Objective:** To compare N-acetylcysteine (NAC) + sodium bicarbonate (NaHCO$_3$) to NAC + normal saline hydration in prevention of acute kidney injury (AKI) from IV contrast.

**Patients:** Those receiving IV contrast for various indications (PCI, angiography, catheterization)

**Results:** Combination treatment of NAC with intravenous NaHCO$_3$, reduced contrast-induced AKI by 35% (relative risk: 0.65; 95% confidence interval: 0.40 to 1.05). However, the combination of N-acetylcysteine plus NaHCO$_3$, did not significantly reduce renal failure requiring dialysis.

**Conclusion:** Combination prophylaxis should be considered for all high-risk patients (emergency cases or patients with chronic kidney disease).
**Anatomy**

**Localizing Lesions**
- silhouette sign: loss of normal interfaces due to lung pathology (consolidation, atelectasis, mass), which can be used to localize disease in specific lung segments (see Table 3)
  - note that pleural or mediastinal disease can also produce the silhouette sign

<table>
<thead>
<tr>
<th>Interface Lost</th>
<th>Location of Lung Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior vena cava/right superior mediastinum</td>
<td>RUL</td>
</tr>
<tr>
<td>Right heart border</td>
<td>RML</td>
</tr>
<tr>
<td>Right hemidiaphragm</td>
<td>RLL</td>
</tr>
<tr>
<td>Aortic knob/left superior mediastinum</td>
<td>LUL</td>
</tr>
<tr>
<td>Left heart border</td>
<td>Lingula</td>
</tr>
<tr>
<td>Left hemidiaphragm</td>
<td>LLL</td>
</tr>
</tbody>
</table>

Table 3. Localization Using the Silhouette Sign

- **Legend**
  - a1: anterior 1st rib
  - a2: anterior 2nd rib
  - aa: aortic arch
  - apw: aorto-pulmonary window
  - as: anterior airspace
  - ca: carina
  - cl: clavicle
  - co: coracoid process
  - cpa: costophrenic angle
  - di: diaphragm
  - g: gastric bubble
  - ivc: inferior vena cava
  - la: left atrium
  - lpa: left pulmonary artery
  - lv: left ventricle
  - mf: major fissure
  - mi: minor fissure
  - p3: posterior 3rd rib
  - p4: posterior 4th rib
  - pa: main pulmonary artery
  - ra: right atrium
  - rbr: right mainstem bronchus
  - rpa: right pulmonary artery
  - rv: right ventricle
  - sc: scapula
  - sp: spinous process
  - st: sternum
  - svc: superior vena cava
  - vb: vertebral body

**Figure 2.** Location of fissures, mediastinal structures and bony landmarks

**Figure 3.** Location of lobes of the lung

---

© Anas Nader 2009
Computed Tomography (CT) Chest

Approach to CT Chest
- soft tissue window
  - thyroid, chest wall, pleura
  - heart: chambers, coronary artery calcifications, pericardium
  - vessels: aorta, pulmonary artery, smaller vasculature
  - lymph nodes: mediastinal, axillary
- bone window
  - look at vertebral, sternum, manubrium, ribs for fractures, lytic lesions, sclerosis
- lung window
  - central-trachea: patency, secretions
  - bronchial trees: anatomic variants, mucus plugs, airway collapse
  - lung parenchyma: fissures, nodules, fibrosis/interstitial changes
  - pleural space: effusions

Table 4. Types of CT Chest

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>High Resolution</th>
<th>Low Dose</th>
<th>CT Angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantage</strong></td>
<td>Scans full lung very quickly (&lt;1 min)</td>
<td>Thinner slices provide high definition of lung parenchyma</td>
<td>1/5th the radiation</td>
<td>Iodinated contrast highlights vasculature</td>
</tr>
<tr>
<td><strong>Disadvantage</strong></td>
<td>Poor at evaluating diffuse disease</td>
<td>Only 5-10% lung is sampled</td>
<td>Decreased detail</td>
<td>Contrast can cause severe allergic reaction and is nephrotoxic</td>
</tr>
<tr>
<td><strong>Contrast</strong></td>
<td>± No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>CXR abnormality, Pleural and mediastinal abnormality</td>
<td>Hemoptysis, Diffuse lung disease (e.g. sarcoidosis, hypersensitivity pneumonitis, pneumoconiosis)</td>
<td>Screening Follow up infections, lung transplant, metastases</td>
<td>Pulmonary embolism, Aortic aneurysms</td>
</tr>
</tbody>
</table>

Lung Abnormalities

Atelectasis
- pathogenesis: collapse of alveoli due to restricted breathing, blockage of bronchi, external compression or poor surfactant
- findings:
  - increased opacity of involved segment/lobe, vascular crowding, silhouette sign, air bronchograms
  - volume loss: fissure deviation, hilar/mediastinal displacement, diaphragm elevation
  - compensatory hyperinflation of remaining normal lung
- differential diagnosis:
  - obstructive (most common): air distal to obstruction is reabsorbed causing alveolar collapse
    - endobronchial lesion, foreign body, inflammation (granulomatous infections, pneumoconiosis, sarcoidosis, radiation injury) or mucus plug (cystic fibrosis)
  - compressive:
    - tumour, bulla, effusion, enlarged heart, lymphadenopathy
  - traction (cicatrization): due to scarring, which distorts alveoli and contracts the lung
  - adhesive: due to lack of surfactant
    - hyaline membrane disease, prematurity
  - passive (relaxation): a result of air or fluid in the pleural space
    - pleural effusion, pneumothorax
- management: in the absence of a known etiology, persisting atelectasis must be investigated (CT thorax) to rule out a bronchogenic carcinoma

Consolidation
- pathogenesis: fluid (water, blood), inflammatory exudates, protein, or tumour in alveoli
- findings:
  - air bronchograms: lucent branching bronchi visible through opacification
  - airspace nodules: fluffy, patchy, poorly defined margins with later tendency to coalesce, may take on lobar or segmental distribution
  - silhouette sign

Figure 4. CT thorax windows

DDx of Airspace Disease
- Pus (e.g. infections such as pneumonia, non-infectious inflammatory process)
- Fluid (e.g. pulmonary edema)
- Blood (e.g. pulmonary hemorrhage)
- Cells (e.g. bronchioalveolar carcinoma, lymphoma)
- Protein (e.g. alveolar proteinosis)

Figure 5. Atelectasis: RML collapse
**Pulmonary Nodule**
- **findings**:
  - fluid: pulmonary edema, blood (trauma, vasculitis, bleeding disorder, pulmonary infarct)
  - inflammatory exudates: bacterial infections, TB, allergic hypersensitivity alveolitis, bronchiolitis obliterans organizing pneumonia (BOOP), allergic bronchopulmonary aspergillosis (ABPA), aspiration, sarcoidosis
  - protein: pulmonary alveolar proteinosis
  - tumour: bronchoalveolar carcinoma, lymphoma
- **management**: varies depending on the pattern of consolidation, which can suggest different etiologies. Management should also be done in the context of clinical picture

**Interstitial Disease**
- **pathogenesis**: pathological process involving the interlobular connective tissue (i.e. “scaffolding of the lung”)
- **findings**:
  - linear: fine lines caused by thickened connective tissue septae
  - Kerley B: short horizontal lines extending from lateral lung margin
  - Kerley C: diffuse linear pattern throughout lung
  - seen in pulmonary edema, lymphangitic carcinomatosis and atypical interstitial pneumonias
  - nodular: 1-5 mm well-defined nodules distributed evenly throughout lung
  - seen in malignancy, pneumoconiosis and granulomatous disease (sarcoidosis, miliary TB)
  - reticular (honeycomb): parenchyma replaced by thin-walled cysts suggesting extensive destruction of pulmonary tissue and fibrosis (see Figures 7 and 8)
  - seen in interstitial pulmonary fibrosis (IPF), asbestosis and CVD
  - NOTE: watch for pneumothorax as a complication
  - reticulonodular: combination of reticular and nodular patterns
  - may also see signs of airspace disease (atelectasis and consolidation)
- **differential diagnosis**:
  - occupational/environmental exposure
  - inorganic: asbestosis, coal miner’s pneumoconiosis, silicosis, berylliosis, talc pneumoconiosis
  - organic: hypersensitivity pneumonitis, bird fancier’s lung, farmer’s lung (moldy hay), and other organic dust
  - autoimmune: CVD (e.g. rheumatoid arthritis, scleroderma, SLE, polymyositis, mixed connective tissue disease), IBD, celiac disease, vasculitis
  - drug-related: antibiotics (cephalosporins, nitrofurantoin), NSAIDs, phenytoin, carbamazepine, fluoxetine, amiodarone, chemotherapy (e.g. methotrexate), heroin, cocaine, methadone
  - infections: non-tuberculous mycobacteria, certain fungal infections
  - idiopathic: hypersensitivity pneumonitis, IPF, BOOP
- **for Causes of Interstitial Lung Disease Classified by Distribution**, see Respirology, R12
- **management**: high resolution CT thorax and biopsy

**Pulmonary Nodule** (see Table 5)
- **findings**: round opacity ± silhouette sign
- **note**: do not mistake nipple shadows for nodules; if in doubt, repeat CXR with nipple markers
- **differential diagnosis**:
  - extrapulmonary density: nipple, skin lesion, electrode, pleural mass, bony lesion
  - solitary nodule:
    - tumour: carcinoma, hamartoma, metastasis, bronchial adenoma
    - inflammation: histioplasmosis, tuberculosis, coccidiodomycosis
  - vascular: AV fistula, pulmonary varix (dilated pulmonary vein), infarct, embolism
  - multiple nodules: metastases, abscess, granulomatous lung disease [TB, fungal, sarcoid, rheumatoid nodules, silicosis, granulomatosis with polyangiitis (GPA)]
- **management**: clinical information and CT appearance determine level of suspicion of malignancy
  - if high probability of malignancy, invasive testing (fine needle aspiration, transbronchial/ transthoracic biopsy) is indicated
  - if low probability of malignancy, repeat CXR or CT in 1-3 mo and then every 6 mo for 2 yr; if no change, then >99% chance benign

**DDx for Cavitating Lung Nodule**
- **WEIRD HOLES**
  - GPA (Wegener’s)
  - Embolic (pulmonary, septic)
  - Infection (anaerobes, pneumocystis, TB)
  - Rheumatoid (neurobiotic nodules)
  - Developmental cysts (sequestration)
  - Histiocytosis
  - Oncological
  - Lymphangioleiomyomatosis
  - Environmental, occupational
  - Sarcoïdosis

**DDx of Interstitial Lung Disease**
- **FASSTEN** (upper lung disease)
  - Farmer’s lung (hypersensitivity pneumonitis)
  - Ankylosing spondylitis
  - Sarcoidosis
  - Silicosis
  - TB
  - Eosinophilic granuloma (Langerhans cell histiocytosis)
  - Neurofibromatosis
- **BAD RASH** (lower lung disease)
  - Bronchiolitis obliterans with organizing pneumonia (BOOP)
  - Asbestos
  - Drugs (nitrofurantoin, hydroxyzine, INH, amiodarone, many chemo drugs)
  - Rheumatological disease
  - Aspiration
  - Scleroderma
  - Hamman Rich (interstitial pulmonary fibrosis) and idiopathic pulmonary fibrosis

**Figure 6. Consolidation: bacterial pneumonia**

**Figure 7. Interstitial disease: fine reticular pattern**

**Figure 8. Interstitial disease: medium reticular pattern**
Table 5. Characteristics of Benign and Malignant Pulmonary Nodules

<table>
<thead>
<tr>
<th></th>
<th>Malignant</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin</td>
<td>Ill-defined/spiculated (“corona radiata”)</td>
<td>Well-defined</td>
</tr>
<tr>
<td>Contour</td>
<td>Lobulated</td>
<td>Smooth</td>
</tr>
<tr>
<td>Calcification</td>
<td>Eccentric or stippled</td>
<td>Diffuse, central, popcorn, concentric</td>
</tr>
<tr>
<td>Doubling Time</td>
<td>20-460 d</td>
<td>&lt;20 d or &gt;460 d</td>
</tr>
<tr>
<td>Other Features</td>
<td>Cavitation, collapse, adenopathy, pleural effusion, lytic bone lesions, smoking history</td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td>&gt;3 cm</td>
<td>&lt;3 cm</td>
</tr>
<tr>
<td>Cavitation</td>
<td>Yes, especially with wall thickness &gt;15 mm, eccentric cavity and shaggy internal margins</td>
<td>No</td>
</tr>
<tr>
<td>Satellite Lesions</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Pulmonary Edema
- **Pathogenesis:** fluid accumulation in the airspaces of the lungs
- **Findings:**
  - Vascular redistribution/enlargement, cephalization, pleural effusion, cardiomegaly (may be present in cardiogenic edema and fluid overloaded states)
  - Fluid initially collects in interstitium:
    - Loss of definition of pulmonary vasculature
    - Peribronchial cuffing
    - Kerley B lines
    - Reticulonodular pattern
    - Thickening of interlobar fissures
  - As pulmonary edema progresses, fluid begins to collect in alveoli causing diffuse air space disease often in a “bat wing” or “butterfly” pattern in perihilar regions with tendency to spare the outermost lung fields
- **Differential diagnosis:** cardiogenic (CHF), renal failure, volume overload, non-cardiogenic (ARDS)

Pulmonary Embolism
- **Pathogenesis:** arterial blockage in the lungs
- **Findings:** Westermark sign (localized pulmonary oligemia), Hampton’s hump (triangular peripheral infarct), enlarged RV and RA, atelectasis, pleural effusion, and rarely pulmonary edema
- **Management:** V/Q scan, CT angiography (look for filling defect)

Pleural Abnormalities

Pleural Effusion
- **Pathogenesis:** gas/air accumulation within the pleural space resulting in separation of the lung from the chest wall
- **Findings:**
  - Upright chest film allows visualization of visceral pleura as curvilinear line paralleling chest wall, separating partially collapsed lung from pleural air
  - More obvious on expiratory (increased contrast between lung and air) or lateral decubitus films (air collects superiorly)
  - More difficult to detect on supine film; look for the “deep (costophrenic) sulcus” sign, “double diaphragm” sign (dome and anterior portions of diaphragm outlined by lung and pleural air, respectively), hyperlucent hemithorax, sharpening of adjacent mediastinal structures
  - Mediastinal shift may occur if air is under tension (i.e. tension pneumothorax)

Pneumothorax
- **Pathogenesis:** gas/air accumulation within the pleural space resulting in separation of the lung from the chest wall
- **Findings:**
  - Upright chest film allows visualization of visceral pleura as curvilinear line paralleling chest wall, separating partially collapsed lung from pleural air
  - More obvious on expiratory (increased contrast between lung and air) or lateral decubitus films (air collects superiorly)
  - More difficult to detect on supine film; look for the “deep (costophrenic) sulcus” sign, “double diaphragm” sign (dome and anterior portions of diaphragm outlined by lung and pleural air, respectively), hyperlucent hemithorax, sharpening of adjacent mediastinal structures
  - Mediastinal shift may occur if air is under tension (i.e. tension pneumothorax)
• differential diagnosis: spontaneous (tall and thin males, smokers), iatrogenic (lung biopsy, ventilation, CVP line insertion), trauma (associated with rib fractures), emphysema, malignancy, honeycomb lung
• management: needle decompression or chest tube insertion, repeat CXR to ensure resolution

Asbestos
• asbestos exposure may cause various pleural abnormalities including benign plaques (most common) that may calcify, diffuse pleural fibrosis, effusion, and malignant mesothelioma

**Mediastinal Abnormalities**

**Mediastinal Mass**
• the mediastinum is divided into three compartments; this provides the approach to the differential diagnosis of a mediastinal mass
• anterior (anterior border formed by anterior trachea and posterior border by the heart and great vessels)
  - 4 Ts: see sidebar
  - cardiophrenic angle mass differential: thymic cyst, epicardial fat pad, foramen of Morgagni hernia
• middle (extending behind anterior mediastinum to a line 1 cm posterior to the anterior border of the thoracic vertebral bodies)
  - esophageal carcinoma, esophageal duplication cyst
  - metastatic disease
  - lymphadenopathy (all causes)
  - hiatus hernia
  - bronchogenic cyst
• posterior (posterior to the middle line described above)
  - neurogenic tumour (e.g. neurofibroma, schwannoma)
  - multiple myeloma
  - pheochromocytoma
  - neurenteric cyst
  - thoracic duct cyst
  - lateral meningocele
  - Bochdalek hernia
  - extramedullary hematopoiesis
• in addition, any compartment may give rise to lymphoma, lung cancer, aortic aneurysm or other vascular abnormalities, abscess, and hematoma

**Enlarged Cardiac Silhouette**
• heart borders
  - on PA view, right heart border is formed by right atrium; left heart border is formed by left atrium and left ventricle
  - on lateral view, anterior heart border is formed by right ventricle; posterior border is formed by left atrium (superior to left ventricle) and left ventricle
• cardiothoracic ratio = greatest transverse dimension of the central shadow relative to the greatest transverse dimension of the thoracic cavity
  - using a good quality erect PA chest film in adults, cardiothoracic ratio of >0.5 is abnormal
  - differential of ratio >0.5
    - cardiomegaly (myocardial dilatation or hypertrophy)
    - pericardial effusion
    - poor inspiratory effort/low lung volumes
    - pectus excavatum
  - ratio <0.5 does not exclude enlargement (e.g. cardiomegaly + concomitant hyperinflation)
• pericardial effusion
• globular heart with loss of indentations on left mediastinal border
• right atrial enlargement
  - increase in curvature of right heart border and enlargement of SVC
• left atrial enlargement
  - straightening of left heart border
  - increased opacity of lower right side of cardiovascular shadow (double heart border)
  - elevation of left main bronchus (specifically, the upper lobe bronchus on the lateral film), distance between left main bronchus and “double” heart border >7 cm, splayed carina (late sign)
• right ventricular enlargement
  - elevation of cardiac apex from diaphragm
  - anterior enlargement leading to loss of retrosternal air space on lateral
  - increased contact of RV against sternum
• left ventricular enlargement
  - displacement of cardiac apex inferiorly and posteriorly – “boot-shaped” heart
Tubes, Lines, and Catheters

- ensure appropriate placement and assess potential complications of lines and tubes
- avoid mistaking a line/tube for pathology (e.g. oxygen rebreather mask for pneumothoraces)

Central Venous Catheter
- used for fluid and medication administration, vascular access for hemodialysis, and central venous pressure (CVP) monitoring
- tip must be located distal to (above) right atrium to prevent inducing arrhythmias or perforating wall of atrium
  - if monitoring CVP, catheter tip must be proximal to venous valves
- tip of well positioned central venous catheter projects over silhouette of SVC in a zone demarcated superiorly by the anterior first rib end and clavicle and inferiorly by top of RA
- course should parallel course of SVC – if appears to bend as it approaches wall of SVC or appears perpendicular, catheter may damage and ultimately perforate wall of SVC
- complications: pneumothorax, bleeding (mediastinal, pleural), air embolism

Endotracheal Tube
- frontal chest film: tube projects over trachea and shallow oblique or lateral chest radiograph will help determine position in 3 dimensions
- progressive gaseous distention of stomach on repeat imaging is concerning for esophageal intubation
- tip should be located 4 cm above tracheal carina – avoids bronchus intubation and vocal cord irritation
- maximum inflation diameter <3 cm to avoid necrosis of tracheal mucosa and rupture – ensure diameter of balloon is less than tracheal diameter above and below balloon
- complications: aspiration (parenchymal opacities), pharyngeal perforation (subcutaneous emphysema, pneumomediastinum, mediastinitis)

Nasogastric Tube (NG Tube)
- tip and sideport of NG tube should be positioned distal to esophagogastric junction and proximal to gastric pylorus
- radiographic confirmation of tube is mandatory because clinical techniques for assessing tip position may be unreliable
- complications: aspiration (parenchymal opacities), intracranial perforation (trauma patients), pneumothorax

Swan-Ganz Catheter
- to monitor pulmonary capillary wedge pressure and to measure cardiac output for suspected left ventricular dysfunction
- tip should be positioned within right or left main pulmonary arteries or in one of their large, lobar branches
- if tip is located more distally, increased risk of prolonged pulmonary artery occlusion resulting in pulmonary infarction or, rarely, pulmonary artery rupture
- complications: pneumothorax, bleeding (mediastinal, pleural), air embolism

Chest Tube
- in dorsal and caudal portion of pleural space to evacuate fluid usually
- in ventral and cephalad portions of pleural space to evacuate pneumothoraces
- tube may lie in fissure as long as functioning
- complications: lung perforation (mediastinal opacities)

Abdominal Imaging

Abdominal X-Ray (AXR)

- indications:
  - acute abdomen: bowel perforation, toxic megacolon, bowel ischemia, small bowel obstruction (SBO), large bowel obstruction (LBO)
  - chronic symptoms: constipation, calcifications (gallstones, renal stones, urinary bladder stones, etc.)
  - not useful in: GI bleeds, chronic anemia, vague GI symptoms
- AXR 3 most common views: left lateral decubitus (LLD), supine, erect upright
Anatomy

- abdomen divided into 2 cavities:
  - peritoneal cavity: lined by peritoneum that wraps around most of the bowel, the spleen, and most of the liver; forms a recess lateral to both the ascending and descending colon (paracolic gutters)
  - retroperitoneal cavity: contains several organs situated posterior to the peritoneal cavity; the contour of these can often be seen on radiographs

Table 7. Differentiating Small and Large Bowel

<table>
<thead>
<tr>
<th>Property</th>
<th>Small Bowel</th>
<th>Large Bowel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal Folds</td>
<td>Uninterrupted valvulae conniventes (or plicae</td>
<td>Interrupted haustra extend only partway</td>
</tr>
<tr>
<td></td>
<td>circularis)</td>
<td>across lumen</td>
</tr>
<tr>
<td>Location</td>
<td>Central</td>
<td>Peripheral (picture frame)</td>
</tr>
<tr>
<td>Maximum diameter</td>
<td>3 cm</td>
<td>6 cm (9 cm at cecum)</td>
</tr>
<tr>
<td>Maximum fold thickness</td>
<td>3 mm</td>
<td>5 mm</td>
</tr>
<tr>
<td>Other</td>
<td>Rarely contains solid fecal material</td>
<td>Commonly contains solid fecal material</td>
</tr>
</tbody>
</table>

Approach to Abdominal X-Ray (AXR)

- mnemonic: “Free ABDO”
- Free = free fluid
  - small amounts of fluid: increased distance between lateral fat stripes and adjacent colon may indicate free peritoneal fluid in the paracolic gutters
  - large amounts of fluid: diffuse increased opacification on supine film; bowel floats to centre of anterior abdominal wall
  - ascites and blood (hemoperitoneum) are the same density on the radiograph and therefore cannot be differentiated
- A = air
  - volvulus – twisting of the bowel upon itself; from most to least common:
    - sigmoid: “coffee bean” sign (massively dilated sigmoid projects to right or mid-upper abdomen) with proximal large bowel dilation
    - cecal: massively dilated bowel loop projecting to left or mid-upper abdomen with small bowel dilation
    - gastric: rare
    - small bowel: “corkscrew sign” (rarely diagnosed on plain films, seen best on CT)
- toxic megacolon
  - manifestation of fulminant colitis
  - extreme dilatation of colon (>6.5 cm) with mucosal changes including foci of edema, ulceration and pseudopolyps, loss of normal haustral pattern
- B = bowel wall thickening
  - increased soft tissue density in bowel wall, thumb-like indentations in bowel wall (“thumb-printing”), or a picket-fence appearance of the valvulae conniventes (“stacked coin” appearance)
  - may be seen in IBD, infection, ischemia, hypoproteinemic states, and submucosal hemorrhage
- D = densities
  - bones: look for gross abnormalities of lower ribs, vertebral column, and bony pelvis
  - abnormal calcifications: approach by location
    - RUQ: renal stone, adrenal calcification, gallstone, porcelain gallbladder
    - RLQ: ureteral stone, appendicolith, gallstone ileus
    - LUQ: renal stone, adrenal calcification, tail of pancreas
    - LLQ: ureteral stone
    - central: aorta/aortic aneurysm, pancreas, lymph nodes
    - pelvis: phleboliths (calcified veins), uterine fibroids, bladder stones
- O = organs
  - kidney, liver, gallbladder, spleen, pancreas, urinary bladder, psoas shadow
  - outlines can occasionally be identified because they are surrounded by more lucent fat, but all are best visualized with other imaging modalities (CT, MRI)
Figure 13. Normal AXRs: (left) supine anteroposterior AXR, (middle) upright anteroposterior AXR, and (right) left lateral decubitus AXR

Table 8. Abnormal Air on Abdominal X-Ray

<table>
<thead>
<tr>
<th>Air</th>
<th>Appearance</th>
<th>Common Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraluminal</td>
<td>Upright film: air under diaphragm</td>
<td>Perforated viscus</td>
</tr>
<tr>
<td></td>
<td>Supine film: gas outlines of structures not normally seen:</td>
<td>Postoperative (up to 10 d to be resorbed)</td>
</tr>
<tr>
<td></td>
<td>• Inner and outer bowel wall (Rigler’s sign)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Falciform ligament</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Peritoneal cavity (“football” sign)</td>
<td></td>
</tr>
<tr>
<td>Intraperitoneal (pneumoperitoneum)</td>
<td>Gas outlining retroperitoneal structures allowing increased visualization:</td>
<td>Perforation of retroperitoneal segments of bowel: duodenal ulcer, post-colonoscopy</td>
</tr>
<tr>
<td></td>
<td>• Psoas shadows</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Renal shadows</td>
<td></td>
</tr>
<tr>
<td>Intramural (pneumatoasis intestinals)</td>
<td>Lucent air streaks in bowel wall, 2 types:</td>
<td>1. Linear: ischemia, necrotizing enterocolitis</td>
</tr>
<tr>
<td></td>
<td>1. Linear</td>
<td>2. Rounded (cystoides type)</td>
</tr>
<tr>
<td>Intraluminal</td>
<td>Dilated loops of bowel, air-fluid levels</td>
<td>Adynamic (paralytic) ileus, mechanical bowel obstruction (see Table 9)</td>
</tr>
<tr>
<td>Loculated</td>
<td>Mottled, localized in abnormal position without normal bowel features</td>
<td>Abscess (evaluate with CT)</td>
</tr>
<tr>
<td>Biliary</td>
<td>Air centrally over liver</td>
<td>Sphincterotomy, gallstone ileus, erosive peptic ulcer, cholangitis, emphysematous cholecystitis</td>
</tr>
<tr>
<td>Portal Venous</td>
<td>Air peripherally over liver in branching pattern</td>
<td>Bowel ischemia/Infarction</td>
</tr>
</tbody>
</table>

Table 9. Adynamic Ileus vs. Mechanical Obstruction

<table>
<thead>
<tr>
<th>Feature</th>
<th>Adynamic Ileus</th>
<th>Mechanical Obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calibre of Bowel Loops</td>
<td>Normal or dilated</td>
<td>Usually dilated</td>
</tr>
<tr>
<td>Air-Fluid Levels (erect and LLD films only)</td>
<td>Same level in the same single loop</td>
<td>Multiple air fluid levels giving “step ladder” appearance, dynamic (indicating peristalsis present), “string of pearls” (row of small gas accumulations in the dilated valvulae conniventes)</td>
</tr>
<tr>
<td>Distribution of Bowel Gas</td>
<td>Air throughout GI tract is generalized or localized \</td>
<td>Dilated bowel up to the point of obstruction \</td>
</tr>
<tr>
<td></td>
<td>• In a localized ileus (e.g. pancreatitis, appendicitis); dilated “sentinel loop” remains in the same location on serial films, usually adjacent to the area of inflammation</td>
<td>No air distal to obstructed segment \</td>
</tr>
<tr>
<td></td>
<td>“Hairpin” (180°) turns in bowel</td>
<td>“Hairpin” (180°) turns in bowel</td>
</tr>
</tbody>
</table>

Abdominal CT
- indications for plain CT: renal colic, hemorrhage
- indications for CT with contrast:
  - IV contrast given immediately before or during CT to allow identification of arteries and veins
  - portal venous phase: indicated for majority of cases
  - biphasic (arterial and portal venous phases): liver, pancreas, bile duct tumours
  - oral contrast: barium or water soluble (water soluble if suspected perforation) given in most cases to demarcate GI tract
  - rectal contrast: given for investigation of colonic lesions
- caution: contrast allergy (may premedicate with steroids and antihistamine)
- contraindication: impaired renal function, based on eGFR
**Approach to Abdominal Computed Tomography (CT)**

- look through all images in gestalt fashion to identify any obvious abnormalities
- look at each organ/structure individually, from top to bottom evaluating size and shape of each area of increased or decreased density
- evaluate the following
  - soft tissue window
    - liver, gallbladder, spleen and pancreas
    - adrenals, kidneys, ureters and bladder
    - stomach, duodenum, small bowel mesentery and colon/appendix
    - retroperitoneum: aorta, vena cava and mesenteric vessels; look for adenopathy in vicinity of vessels
    - peritoneal cavity for fluid or masses
    - abdominal wall and adjacent soft tissue
  - lung window
    - visible lung (bases)
  - bone window
    - vertebræ, spinal cord, and bony pelvis

**CT and Bowel Obstruction**

- cause of bowel obstruction rarely found on plain films – CT is best choice for imaging
- the “3,6,9” rule is a very useful guide to determining when the bowel is dilated. The maximum diameter of the bowel is 3 cm for small bowel, 6 cm for large bowel and 9 cm for cecum. This can also be useful in distinguishing between small and large bowel and when assessing for ‘impending’ cecal perforation (post-untreated Ogilvie’s syndrome)

**CT Colonography (virtual colonoscopy)**

- emerging imaging technique for evaluation of intraluminal colonic masses (i.e. polyps, tumours)
- two CT scans of the abdomen (prone and supine) after the instillation of carbon dioxide into a prepped colon
- computer reconstruction of 2D CT images into a 3D intraluminal view of the colon in order to look for masses
- lesions seen on 3D images correlated with 2D axial images
- indications: surveillance in low-risk patients, incomplete colonoscopy, staging of obstructing colonic lesions

**Contrast Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Indications</th>
<th>Assessment</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cine Esophagogram</strong></td>
<td>Contrast agent swallowed Recorded for later playback and analysis</td>
<td>Dysphagia, swallowing incoordination, recurrent aspiration, post-op cleft palate repair</td>
<td>Cervical esophagus</td>
<td>Aspiration, webs (partial occlusion), Zenker’s diverticulum, criopharyngeal bar, laryngeal tumour</td>
</tr>
<tr>
<td><strong>Barium Swallow</strong></td>
<td>Contrast agent swallowed under fluoroscopy, selective images captured</td>
<td>Dysphagia, r/o GERD, post esophageal surgery</td>
<td>Thoracic esophagus</td>
<td>Achalasia, hiatus hernia, esophagitis, cancer, esophageal tear</td>
</tr>
<tr>
<td><strong>Upper GI Series</strong></td>
<td>Double contrast study: 1. Barium to coat mucosa, then 2. Gas pills for distention Patient NPO after midnight</td>
<td>Dyspepsia, investigate possible UGI bleed, weight loss/anemia, post gastric surgery</td>
<td>Thoracic esophagus, stomach, or duodenum</td>
<td>Ulcers, neoplasms, filling defects</td>
</tr>
<tr>
<td><strong>Barium Enema</strong></td>
<td>Colon filled retrograde with barium and air or CO₂, Bowel prep the night before procedure</td>
<td>Altered bowel habits, suspected LGI bleed, weight loss/anemia, r/o large bowel obstruction, suspected perforation, check surgical anastomosis, history of polyps</td>
<td>Large bowel Rectum may be obscured by tube – therefore must do sigmoidoscopy to exclude rectal lesions</td>
<td>Diverticulosis, neoplasms, IBD, intussusception (can be reduced with barium or air enema), volvulus</td>
</tr>
<tr>
<td><strong>Small Bowel Follow Through</strong></td>
<td>Single contrast images following UGI series</td>
<td>GI bleed with nondiagnostic upper GI series/barium enema, weight loss/anemia, diarrhea, IBD, malabsorption, abdominal pain, post small bowel surgery</td>
<td>Entire small bowel</td>
<td>Neoplasms, IBD, malabsorption, infection</td>
</tr>
<tr>
<td><strong>Small Bowel Enema (enteroclysis)</strong></td>
<td>Duodenal intubation: 1. Barium/methyl cellulose infusion and fluoroscopic evaluation 2. CT enteroclysis with water infusion</td>
<td>IBD, malabsorption, weight loss/anemia, Meckel’s diverticulum</td>
<td>Entire small bowel</td>
<td>Neoplasms, IBD, malabsorption, infection</td>
</tr>
</tbody>
</table>
Specific Visceral Organ Imaging

Liver
- U/S: assessment of cysts, abscesses, tumours, biliary tree
- CT ± IV: most popular procedure for imaging the liver parenchyma (primary liver tumours, metastases, cysts, abscesses, trauma, cirrhosis)
- MR: also excellent in evaluation of primary liver tumours, liver metastases, and other parenchymal conditions. It is particularly helpful in differentiating common benign hepatic hemangiomas from primary liver tumours and metastases
- findings:
  - altered liver size, contour, density
  - advanced cirrhosis: liver small and irregular (fibrous scarring, segmental atrophy, regenerating nodules)
  - portal hypertension: increased portal vein diameter, collateral veins, splenomegaly (≥12 cm), portal vein thrombosis, recanalization of the umbilical vein
  - varices (caput medusa, esophageal varices, porto-systemic shunts, dilated splenic vein)
  - splenomegaly and ascites
- U/S: cirrhosis appears nodular and hypechoic with irregular areas of atrophy of the right lobe and hypertrophy of the caudate or left lobes
- CT: fatty infiltration appears hypodense
- investigation of liver masses
- require contrast to visualize certain hepatic masses

Table 11. Phases of Enhancement Following IV Contrast Bolus

<table>
<thead>
<tr>
<th>Phase</th>
<th>Time Frame</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial Phase</td>
<td>20-30 s</td>
<td>• Early and late arterial phase possible on multidetector CT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Late arterial phase best for discriminating hypervascular HCC</td>
</tr>
<tr>
<td>Portal Venous Phase</td>
<td>60-70 s</td>
<td>• Provides maximum enhancement of hepatic tissue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Most tumours supplied by hepatic artery are relatively hypovascular, therefore appear as low-attenuation masses in portal venous phase</td>
</tr>
<tr>
<td>Equilibrium Phase</td>
<td>120-180 s</td>
<td>• Hypervascular tumours wash out (HCC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Persistent enhancement suggests blood pool (hemangioma) or fibrous/scar tissue (HCC capsule, focal nodular hyperplasia, cholangiocarcinoma)</td>
</tr>
</tbody>
</table>

Table 12. Imaging of Liver Masses

<table>
<thead>
<tr>
<th>Mass</th>
<th>U/S</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastases</td>
<td>Multiple masses of variable echotexture</td>
<td>Usually low attenuation on contrast enhanced scan</td>
</tr>
<tr>
<td>HCC</td>
<td>Single/multiple masses, or diffuse infiltration</td>
<td>Hypervascular enhances in arterial and washes out venous phase with portal venous tumour thrombus</td>
</tr>
<tr>
<td>Abscess</td>
<td>Poorly defined, irregular margin, hypechoic contents</td>
<td>Low-attenuation lesion with an irregular enhancing wall</td>
</tr>
<tr>
<td>Hydatid Cyst</td>
<td>Simple/multiloculated cyst</td>
<td>Low-attenuation simple or multiloculated cyst; calcification</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>Homogenous hypechoic mass</td>
<td>Peripheral global enhancement in arterial phase scans; central-filling and persistent enhancement on delayed scans</td>
</tr>
<tr>
<td>Focal Nodular Hyperplasia</td>
<td>Well-defined mass, central scar seen in 50%</td>
<td>Hypervascular mass in arterial phase and iso-attenuation to liver in portal venous phase</td>
</tr>
<tr>
<td>Hepatic Adenoma</td>
<td>Most common in young women taking oral contraceptives. Well-defined mass with hypechoic areas due to hemomarghe</td>
<td>Well-defined hypervascular lesion with enlarged central vessel becoming slightly isoattenuating in venous phase</td>
</tr>
</tbody>
</table>

Spleen
- U/S, CT, and/or nuclear medicine scan
- CT for splenic trauma (hemorrhage)

Biliary Tree
- U/S
  - bile ducts usually visualized only if dilated, secondary to obstruction (e.g. choledocholithiasis, benign stricture, mass)
- CT
  - dilated intrahepatic ductules seen as branching, tubular structures following pathway of portal venous system
- ERCP, MRCP, PTC: further evaluation of obstruction and possible intervention

Figure 15. ERCP: biliary tree

Revised Estimates of Diagnostic Test Sensitivity and Specificity in Suspected Biliary Tract Disease
Arch Intern Med 1999;159:2573-2581
Purpose: To assess the sensitivity and specificity of tests used to diagnose cholelithiasis and acute cholecystitis, including ultrasonography, oral cholecystography, radionucleotide scanning with Technetium, MRI, CT.
Study Characteristics: Meta-analysis of 30 studies evaluating the use of different imaging modalities in the diagnosis of biliary tract disease.
Participants: No limits.
Main Outcomes: Sensitivity and specificity of the different imaging modalities, using the gold standard of surgery, autopsy, or 3 mo clinical follow-up for cholelithiasis. For acute cholecystitis, pathologic findings, confirmation of an alternate disease, or clinical resolution during hospitalization for cholecystitis were used as the standard.
Results: For evaluating cholelithiasis, U/S had the best unadjusted sensitivity (0.97; 95% CI, 0.95 to 0.99) and specificity (0.96, 95% CI, 0.93 to 0.98), and adjusted (for verification bias) sensitivity (0.84, 95% CI, 0.76 to 0.92) and specificity (0.90; 95% CI, 0.90 to 1.00). For evaluating acute cholecystitis, radionucleotide scanning has the best sensitivity (0.97; 95% CI, 0.96 to 0.98) and specificity (0.90; 95% CI, 0.86 to 0.95).
Conclusions: U/S is the test of choice for diagnosing cholelithiasis and radionucleotide scanning is the superior test for diagnosing acute cholecystitis.

Liver Mass DDx
- 5 hs
  - HCC
  - Hydatid cyst
  - Hemangioma
  - Hepatic adenoma
  - Hyperplasia (focal nodular)
Pancreas
- tumours
  - U/S: mass is more echogenic than normal pancreatic tissue
  - CT: preferred modality for diagnosis/staging
- ductal dilation secondary to stone/tumour
  - MRCP: imaging of ductal system using MRI cholangiography
  - ERCP: endoscope to inject dye into the biliary tree and X-ray imaging to assess pancreatic and biliary ducts; therapeutic potential (stent placement, stone retrieval); acute pancreatitis is a complication in 5% of diagnostic procedures and 10% of therapeutic procedures
- pancreatitis and/or its complications: pseudocyst, abscess, necrosis, splenic artery aneurysm (see “itis” Imaging below)

“itis” Imaging

Acute Cholecystitis
- pathogenesis: inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or, in the case of acalculous cholecystitis, due to gallbladder ischemia or cholestasis (see General Surgery, GS46)
- best imaging modality: U/S (best sensitivity and specificity), nuclear medicine (HIDA scan) can help diagnose cases of acalculous or chronic cholecystitis
- findings: thick wall, pericholecystic fluid, gallstones, dilated gallbladder, positive sonographic Murphy’s sign
- management: cholecystectomy

Acute Appendicitis
- pathogenesis: luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess or peritonitis (see General Surgery, GS28)
- best imaging modality: U/S or CT
- findings:
  - U/S: thick-walled appendix, appendicolith, dilated fluid-filled appendix, non-compressible
  - U/S may also demonstrate other causes of RLQ pain (e.g. ovarian abscess, IBD, ectopic pregnancy)
  - CT: enlargement of appendix (>6 mm in outer diameter), enhancement of appendiceal wall, adjacent inflammatory stranding, appendicolith; also facilitates percutaneous abscess drainage
- management: appendectomy

Acute Diverticulitis
- pathogenesis: erosion of the intestinal wall (most commonly rectosigmoid) by increased intraluminal pressure or inspissated food particles → inflammation and focal necrosis → micro or macroscopic perforation (see General Surgery, GS31)
- best imaging modality: CT is modality of choice, although U/S is sometimes used
- contrast: oral and rectal contrast given before CT to opacify bowel
- findings:
  - cardinal signs: thickened wall, mesenteric infiltration, gas-filled diverticula, abscess
  - CT can be used for percutaneous abscess drainage before or in lieu of surgical intervention
  - sometimes difficult to distinguish from perforated cancer (therefore send abscess fluid for cytology and follow up with colonoscopy)
  - if chronic, may see fistula (most common to bladder) or sinus tract (linear or branching structures)
- management: appendectomy
draining...
Chronic Pancreatitis
- pathogenesis: (see Gastroenterology, G46)
- best imaging modality: MRCP
- findings: U/S, CT scan and MRI may show calcifications, ductal dilatation, enlargement of the pancreas and fluid collections (e.g. pseudocysts) adjacent to the gland. However, magnetic resonance cholangiopancreatography (MRCP) is becoming the diagnostic test of choice since it can show calcification and pancreatic duct obstruction.

Angiography of GI Tract
- anatomy of the GI tract arterial blood supply branches
  - celiac artery: hepatic, splenic, gastroduodenal, left/right gastric
  - superior mesenteric artery (SMA): jejunal, ileal, ileo-colic, right colic, middle colic
  - inferior mesenteric artery (IMA): left colic, superior rectal
- imaging modalities
  - conventional angiogram: invasive (usual approach via femoral puncture), catheter used
  - flush aortography: catheter injection into abdominal aorta, followed by selective arteriography of individual vessels
  - CT angiogram: non-invasive using IV contrast (no catheterization required)

Genitourinary System and Adrenal

Urological Imaging
KUB (kidneys, ureters, bladder)
- a frontal supine radiograph of the abdomen
- indication: useful in evaluation of radio-opaque renal stones (all stones but uric acid and indinavir), as well as indwelling ureteric stents or catheters
- findings: addition of intravenous contrast excreted by the kidney (intravenous urogram) allows greater visualization of the urinary tract, but has been largely replaced by CT urography

Abdominal CT
Renal Masses
- Bozniak classification for cystic renal masses
  - classes I-II are benign and can be disregarded
  - class IIF should be followed
  - classes III-IV are suspicious for malignancy, requiring additional workup

Table 13. Bozniak Classification for Cystic Renal Masses

<table>
<thead>
<tr>
<th>Classes</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple renal cysts</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>Fluid-attenuating well-defined lesion, no septation, no calcification, no solid components, hair thin wall</td>
</tr>
<tr>
<td>Class II</td>
<td>Same as class I + fine calcification or moderately thickened calcification in septae or walls; also includes hyperdense cysts (&lt;3 cm) that do not enhance with contrast</td>
</tr>
<tr>
<td>Complex renal cysts</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>Thick irregular walls, ± calcifications, ± septated, enhancing walls or septa with contrast</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>Same as class III + soft tissue enhancement with contrast (defined as &gt;10 Hounsfield unit increase, characterizing vascularity) with de-enhancement in venous phase ± areas of necrosis</td>
</tr>
</tbody>
</table>

- plain CT
  - indications: general imaging of renal anatomy, although specific study types have supplanted plain CT for many indications, including CT urography (upper tract uroepithelial malignancies and renal calculi) and triphasic CT (renal masses)
- CT urography
  - indications: excretory phase imaging allows detailed assessment of urinary tracts, high sensitivity (95%) for uroepithelial malignancies of the upper urinary tracts, useful for assessment of renal calculi
- triphasic CT
  - indications: standard imaging for renal masses, allows accurate assessment of renal arteries and veins and better characterization of suspicious renal masses, with particular utility in differentiating renal cell carcinoma from more benign masses
  - phases: unenhanced, nephrographic, and excretory

Imaging Modality Based on Presentation
- Acute testicular pain = Doppler, U/S
- Amenorrhea = U/S, MRI (brain)
- Bloating = U/S, CT
- Flank pain = U/S, CT
- Hematuria = U/S, Cystoscopy, CT
- Infertility = Hysterosalpingogram, MRI
- Lower abdominal mass = U/S, CT
- Lower abdominal pain = U/S, CT
- Renal colic = U/S, KUB, CT
- Testicular mass = U/S
- Urethral stricture = Urethrogram

Figure 18. Triphasic CT of an angiomyolipoma: showing fat density with non-contrast scan, mildly enhancing with contrast

Figure 19. Triphasic CT of a renal cell carcinoma: showing arterial enhancing right renal lesion with venous washout (shunting)
U/S
- indications: initial study for evaluation of kidney size and nature of renal masses (solid vs. cystic renal masses vs. complicated cysts); technique of choice for screening patients with suspected hydronephrosis (no intravenous contrast injection, no radiation to patient, and can be used in patients with renal failure); transrectal U/S (TRUS) useful to evaluate prostate gland and guide biopsies; doppler U/S to assess renal vasculature
- findings: solid renal masses are echogenic (bright on U/S), cystic renal masses have smooth well-defined walls with anechoic interior (dark on U/S), and complicated cysts have internal echoes within a thickened, irregular-wall

Retrograde Pyelography
- indications: visualize the urinary collecting system via a cystoscope, ureteral catheterization, and retrograde injection of contrast medium, ordered when the intrarenal collecting system and ureters cannot be opacified using intravenous techniques (patient with impaired renal function, high grade obstruction)
- findings: only yields information about the collecting systems (renal pelvis and associated structures)
  - no information regarding the parenchyma of the kidney

Voiding Cystourethrogram (VCUG)
- bladder filled with contrast to the point where voiding is triggered
- fluoroscopy (continuous, real-time) to visualize bladder
- indications: children with recurrent UTIs, hydronephrosis, hydroureter, suspected lower urinary tract obstruction or vesicoureteral reflux
- findings: contractility and evidence of vesicoureteric reflux

Retrograde Urethrogram
- a small Foley catheter placed into penile urethral opening
- indications: used mainly to study strictures or trauma to the male urethra (Figure 20)

MRI
- advantages: high spatial and tissue resolution, lack of exposure to ionizing radiation and nephrotoxic contrast agents
- indications: indicated over CT for depiction of renal masses in patients with previous nephron sparing surgery, patients requiring serial follow-ups (less radiation dosage), patients with reduced renal function, and patients with solitary kidneys

Renal Nuclear Scan

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Uses</th>
<th>Radionuclide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renogram</td>
<td>To assess renal function and collecting system: evaluation of renal failure, workup of urinary tract obstruction and hypertension, investigation of renal transplant</td>
<td>$^{99m}$Tc-pentetate (DTPA) or mertiatide (MAA3), and imaged at 1-3 s intervals with a gamma camera over the first 60 s to assess perfusion</td>
</tr>
<tr>
<td>Morphological</td>
<td>Assess renal anatomy: investigation of pyelonephritis and cortical scars</td>
<td>$^{99m}$Tc-DMSA, $^{99m}$Tc-glucicollidate</td>
</tr>
</tbody>
</table>

Gynecological Imaging

U/S
- transabdominal and transvaginal are the primary modalities, and are indicated for different scenarios
- transabdominal requires a full bladder to push out air containing loops of bowel
  - indication: good initial investigation for suspected pelvic pathology
- transvaginal approach provides enhanced detail of deeper/smaller structures by allowing use of higher frequency sound waves at reduced distances
  - indication: improved assessment of ovaries, first trimester development, and ectopic pregnancies

Hysterosalpingogram
- indications: useful for assessing pathology of the uterine cavity and fallopian tubes, evaluating uterine abnormalities (e.g. bicornuate uterus), or evaluation of fertility (absence of flow from tubes to peritoneal cavity indicates obstruction)
- performed by x-ray images of the pelvis after cannulation of the cervix and subsequent injection of opacifying agent

CT/MRI
- indications: evaluating pelvic structures, especially those adjacent to the adnexa and uterus
- invaluable for staging gynecological malignancies

Pregnancy should always be ruled out by β-HCG before CT of a female pelvis (or any organ system) is performed.
Sonohysterogram
- saline infusion sonohysterogram involves instilling fluid into the uterine cavity transcervically to provide enhanced endometrial visualization during transvaginal ultrasound examination.
- indications: abnormal uterine bleeding, uterine cavity abnormalities that are suspected or noted on transvaginal sonography (i.e. leiomyomas, polyps, synechiae), congenital abnormalities of the uterine cavity, infertility, recurrent pregnancy loss
- contraindications: pregnancy, pelvic infection

<table>
<thead>
<tr>
<th>Finding</th>
<th>Typical</th>
<th>Atypical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyps</td>
<td>A well-defined, homogeneous, polypoid lesion isoechoic to the endometrium with preservation of the endometrial-myometrial interface</td>
<td>cystic components, multiple polyps, broad base, hypoechoicity or heterogeneity</td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>Well-defined, broad-based, hypoechoic, solid masses with shadowing. Overlying layer of endometrium is echogenic and distorts the endometrial-myometrial interface</td>
<td>Pedunculated or multilobulated surface</td>
</tr>
<tr>
<td>Hyperplasia and Cancer</td>
<td>Diffuse echogenic endometrial thickening without focal abnormality, although focal lesions can occur. Endometrial cancer is typically a diffuse process, but early cases can be focal and appear as a polyloid mass</td>
<td></td>
</tr>
<tr>
<td>Adhesions</td>
<td>Mobile, thin, echogenic bands that cut across the endometrial cavity</td>
<td>Thick, broad-based bands that can completely obliterate the endometrial cavity, as in Asherman’s syndrome</td>
</tr>
</tbody>
</table>

### Adrenal Mass
- imaging modality: most often identified on CT scan, can use MR to distinguish benign from malignant masses

<table>
<thead>
<tr>
<th>Factors</th>
<th>Adrenocortical Adenoma</th>
<th>Adrenocortical Carcinoma</th>
<th>Pheochromocytoma</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (CT)</td>
<td>Usually ≤3 cm</td>
<td>Usually ≥4 cm</td>
<td>Usually &gt;3 cm</td>
<td>Variable around &lt;3 cm</td>
</tr>
<tr>
<td>Shape (CT)</td>
<td>Smooth margins and round/oval</td>
<td>Irregular with unclear margins</td>
<td>Round/oval with clear margins</td>
<td>Ovoid/irregular with unclear margins</td>
</tr>
<tr>
<td>Texture (CT)</td>
<td>Homogenous</td>
<td>Heterogeneous with mixed densities</td>
<td>Heterogeneous with cystic areas</td>
<td>Heterogeneous with mixed densities</td>
</tr>
<tr>
<td>Vascularity (CT)</td>
<td>Not highly vascular</td>
<td>Usually vascular</td>
<td>Usually vascular</td>
<td>Usually Vascular</td>
</tr>
<tr>
<td>Washout of Contrast Medium on CT</td>
<td>≥50% at 10 min</td>
<td>&lt;50% at 10 min</td>
<td>&lt;50% at 10 min</td>
<td>&lt;50% at 10 min</td>
</tr>
<tr>
<td>Growth</td>
<td>Stable or very slow (&lt;1 cm/yr)</td>
<td>Usually rapid (&gt;2 cm/yr)</td>
<td>Slow (0.5-1 cm/yr)</td>
<td>Variable</td>
</tr>
<tr>
<td>Other Findings</td>
<td>None</td>
<td>Necrosis, calcifications, and hemorrhage</td>
<td>Hemorrhage</td>
<td>Occasionally hemorrhage</td>
</tr>
<tr>
<td>MRI on T2 weighted imaging</td>
<td>Isointense in relation to liver</td>
<td>Hyperintense in relation to liver</td>
<td>Markedly hyperintense in relation to liver</td>
<td>Hyperintense in relation to liver</td>
</tr>
</tbody>
</table>

### Neuroradiology

**Modalities**
- CT is the modality of choice for most neuropathology; even under circumstances when MRI is preferred, CT is frequently the initial study because of its speed, availability and lower cost
- CT is preferred for
  - acute head trauma: CT is best for visualizing “bone and blood”; MRI is used in this setting only when CT fails to detect an abnormality in the presence of strong clinical suspicion
  - acute stroke: MRI ideal, CT most frequently used
  - suspected subarachnoid or intracranial hemorrhage
  - meningitis: rule out mass effect (e.g. cerebral herniation, shift) prior to lumbar puncture
  - tinnitus and vertigo: CT and MRI are used in combination to detect bony abnormalities and CN VIII tumours, respectively

**DDx for Ring Enhancing Lesion on CT with Contrast**
- MAGICAL DR
  - Metastases
  - Abscess
  - Glioblastoma (high grade astrocytoma)
  - Infarct
  - Contusion
  - AIDs
  - Lymphoma
  - Demyelination
  - Resolving hematoma

[*the 3 most common Dx’s*]
Skull Films
- rarely performed as CT is the modality of choice
- indications: include screening for destructive bony lesions (e.g. metastases), metabolic disease, skull anomalies, post-operative changes and confirmation of hardware placement, skeletal surveys
- generally not indicated for non-penetrating head trauma

CT
- excellent study for evaluation of bony abnormalities
- often done first without and then with intravenous contrast to show vascular structures or anomalies
- vascular structures and areas of blood-brain barrier impairment are opaque (e.g. hyperattenuating or white/show enhancement) with contrast injection
  - when in doubt, look for circle of Willis or confluence of sinuses to determine presence of contrast enhancement
- posterior fossa can be obscured by extensive bony artifact
- rule out skull fracture, epidural hematoma (lenticular shape), subdural hematoma (crescentic shape), subarachnoid hemorrhage, space occupying lesion, hydrocephalus, and cerebral edema
- multiplanar imaging can be performed with newer generation of multidetector CT scanners

Myelography
- introduction of water-soluble, low-osmotic-contrast media into subarachnoid space using lumbar puncture followed by x-ray or CT scan
- indications: excellent study for disc herniations, traumatic nerve root avulsions, patients with contraindication to MRI

MRI
- indications: shows brain and spinal soft tissue anatomy in fine detail, clearly distinguishes white from grey matter (especially T1-weighted series), multiplanar reconstruction helpful in pre-op assessment

Cerebral Angiography/CT Angiography/MR Angiography
- indications: evaluation of vascular lesions such as atherosclerotic disease, aneurysms, vascular malformations, arterial dissection
- conventional digital subtraction angiography (DSA) remains the gold standard for the assessment of neck and intracranial vessels; however, it is an invasive procedure requiring arterial (femoral) puncture; catheter manipulation has risk of vessel injury (e.g. dissection, occlusion, vasospasm, emboli)
- MR angiography (MRA) methods (phase contrast, time of flight, gadolinium-enhanced) and CT angiography (CTA) are much less invasive without actual risk to intracranial or neck vessels
- MRA and CTA are often used first as ‘screening tests’ for the assessment of subarachnoid hemorrhage, vasospasm, aneurysms

Table 17. Two Types of Hydrocephalus

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communicating/extra-ventricular</td>
<td>Obstruction distal to the ventricles e.g. at the level of the arachnoid granulations; imaging shows all ventricles dilated</td>
</tr>
<tr>
<td>Non-communicating</td>
<td>Obstruction within the ventricular system e.g. mass obstructing the aqueduct or foramen of Monro; imaging shows dilatation of ventricles proximal to the lesion</td>
</tr>
</tbody>
</table>

Nuclear Medicine
- SPECT using $^{99m}$Tc-exametazime (HMPAO) and $^{99m}$Tc-bicisate (ECD) imaging assesses cerebral blood flow by diffusing rapidly across the blood brain barrier and becoming trapped within cells
- $^{18}$FDG PET imaging assesses cerebral metabolic activity
Approach to CT Head

- think anatomically, work from superficial to deep
- scan: confirm that the imaging is of the correct patient, whether contrast was used, if the patient is aligned properly, if there is artifact present
- skin/soft tissue: examine the soft-tissue superficial to the skull, looking for thickening suggestive of hematoma or edema; also investigate: ear, orbital contents (globe, fat, muscles), parotid, muscles of mastication (masseter, temporalis, pterygoids), visualized pharynx
- bone and airspace (use the bone window): check calvarium, visualized mandible, visualized C-spine (usually C1 and maybe part of C2) for fractures, absent bone, lytic/sclerotic lesions; inspect sinuses and mastoid air cells for opacity that may suggest fluid, pus, blood, tumour, or fracture
- dura and subdural space: look for crescent-shaped hyperdensity in the subdural space as evidence of subdural hematoma; look for a lentiform hyperdensity in epidural space as evidence of epidural hematoma; check symmetry of dural thickness, where increased thickness may suggest the presence of blood
- parenchyma: look for symmetry of the parenchyma for evidence of midline shift; look for poor contrast between grey and white matter as evidence of possible infarction, tumour, edema, infection, or contusion; look for hyperdensities in the parenchyma suggestive of enhancing lesions, intracerebral hemorrhage, or calcification; central grey matter nuclei should be visible, including globus pallidus, putamen, and internal capsule, otherwise suspect infarct, tumour, or infection
- ventricles/sulci/cisterns: examine position of ventricles for evidence of midline compression/shift; look for hyperdensities in the ventricles indicative of ventricular/subdural hemorrhage; look at ventricular size for evidence of hydrocephalus; obliteration of sulci may suggest presence of edema causing effacement, possible blood filling in the sulci, or tumour; cistern hyperdensities may suggest blood
- dura/subdural hemosiderin: check for hyperdensity in the subdural space as evidence of subdural hematoma
- C-spine (usually C1 and maybe part of C2) for fractures, absent bone, lytic/sclerotic lesions; bone and airspace (use the bone window): check calvarium, visualized mandible, visualized C-spine (usually C1 and maybe part of C2) for fractures, absent bone, lytic/sclerotic lesions; inspect sinuses and mastoid air cells for opacity that may suggest fluid, pus, blood, tumour, or fracture

Selected Pathology

- see Neurosurgery, NS4-23 for intracranial mass lesions
- see Neurosurgery, NS30-35 and Plastic Surgery, PL28 for head trauma
- see Emergency Medicine, ER7 for vertebral trauma
- see Neurosurgery, NS24-29 and Orthopedics, OR21 for degenerative spinal abnormalities

Cerebrovascular Disease (see Neurology, N43-46 and Neurosurgery, NS18-23)

- pathogenesis of stroke: see Neurology, N43
- best imaging modality ischemic strokes usually cause infarcts which can be detected by both CT and MR
- findings of infarction:
  - early changes
    - CT
      - usually normal within 6 h of infarction
      - edema (loss of grey-white matter differentiation – “insular ribbon” sign, effacement of sulci, mass effect)
      - within 24 h, development of low-density, wedge-shaped area of infarction extending to periphery (correlating to vascular territory distal to affected artery)
      - refer to Functional Neuroanatomy software online (www.torontonotes.ca)
      - in case of ischemic stroke, may see hyperattenuating (bright) artery (hyperdense MCA sign) representing intravascular thrombus or embolus
      - in case of hemorrhagic stroke or transformation (common in basal ganglia and cortex), may see bright acute blood surrounded by edema
    - MRI
      - edema with high signal on T2-weighted images and FLAIR image (loss of grey-white matter differentiation, effacement of sulci, mass effect)
      - diffusion-weighted image (DWI) shows acute high signal changes demonstrating restricted movement of water indicative of cytotoxic edema. DWI usually indicates stroke damage before CT
      - apparent diffusion coefficient (ADC) image shows low signal intensity in acute ischemia (nadir 3-5 d, returns to baseline 1-4 wk)
  - subacute changes on CT and MRI
    - edema and mass effect more prominent
    - gyral enhancement with contrast indicative of blood-brain barrier breakdown
  - chronic changes on CT and MRI
    - encephalomalacia (parenchymal volume loss) with dilatation of adjacent ventricles

Diffusion-weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC) imaging

- diffusion-weighted imaging (DWI) shows acute high signal changes demonstrating restricted movement of water indicative of cytotoxic edema. DWI usually indicates stroke damage before CT
- apparent diffusion coefficient (ADC) image shows low signal intensity in acute ischemia (nadir 3-5 d, returns to baseline 1-4 wk)

Neural Imaging

- Symptom of stroke
  - Non-contrast CT
    - Hemorrhage absent
  - To detect infarct, MR scan with diffusion-weighted sequence OR a CTA

Early Signs of Brain Infarction at CT: Observer Reliability and Outcome after Thrombolytic Treatment – Systematic Review

Radiology 2005;235:444-453

Study: Systematic review of 15 studies between 1980-2001 that investigated inter-observer agreement of early CT signs of acute ischemic stroke, and prognostic value of early CT signs in patient outcome. There was a median of 30 CTs and 6 raters per study.

Patients: 3468 adult patients who underwent CT within 6 h of stroke.

Main Outcome: Degree of inter-observer agreement between stroke signs on CT, and risk of death or dependency (using validated stroke scales) based on CT signs used after 1-3 mo.

Results: Prevalence of all early infarction signs was 61%, and interobserver agreement was 0.14-0.78 (k statistic) for any early infarct sign.

Average sensitivity of detecting early ischemic stroke was 66% (range 20%-87%) and average specificity was 87% (range 56%-100%). Experience improved detection, but knowledge of patient history did not. An increased risk of poor outcome (death or dependency) was associated with any early infarction sign, with an odds ratio of 3.11 (95%CI, 2.71-4.48).

Conclusion: Further work is required to determine which signs are most reliably detected and whether any early infarction sign should influence decisions concerning thrombolysis.

Figure 29. CT images of early infarct: (A) absence of left insular ribbon (B) hyperdense artery
• carotid artery disease
  ▪ best imaging modality: Duplex Doppler U/S
  ▪ other modalities: MR angiography or CT angiography if carotid angioplasty or endarterectomy is under consideration (conventional angiography reserved for inadequate MRA or CTA)

Multiple Sclerosis (MS) (refer to Neurology, N46)
• best imaging modality: MRI has high sensitivity in diagnosing MS (>90%) but low specificity (71-74%)
• findings:
  ▪ characteristic lesion on MRI is cerebral or spinal plaque
  ▪ plaques typically found in periventricular region, corpus callosum (arranged at right angles to the corpus callosum), centrum semiovale, and to a lesser extent in deep white matter structures and basal ganglia
  ▪ “Dawson's fingers” refers to perivenular regions of demyelination that are seen to radiate outwards into the deep periventricular region
  ▪ plaques usually have ovoid appearance, hyperintense on T2 and hypointense on T1
  ▪ conventional T2 may underestimate plaque size and overall plaque burden – advanced techniques (diffusion tensor imaging and magnetic resonance spectroscopy) can be of use
  ▪ perivascular and interstitial edema may be prominent
• acute vs. chronic
  ▪ acute lesions: larger, ill-defined margins and become smaller with sharper margins with resolution of edema and inflammation present at time of acute plaque formation
  ▪ gadolinium enhancing lesions on T1-weighted MRI: accumulation of gadolinium in plaques is associated with new or newly active plaques and with pathologically confirmed acute inflammation in MS; gadolinium enhancement is transient and can persist up to 8 wk in acute plaques (persistence of enhancement should caution against diagnosis of MS)
  ▪ enhancement patterns: concentric ring-enhancing lesions with central contrast pallor arise in previously damaged areas or areas of accelerated local inflammation; ring-enhancing lesions weakly predict the development of persisting hypointense lesions on T1 MRI and are thought to be related to accelerated disease activity and extensive tissue damage, marking inflammation associated with aggressive disease
  ▪ most MS lesions are isointense to white matter on T1-weighted MRI, some are hypointense or “black holes” (especially in the supratentorial region). Nearly half of black holes revert to normal in a few months, presumably due to remyelination and resolution of edema. Persistent black holes may be markers of severe demyelination and axonal loss
  ▪ spinal cord lesions typical of MS:
    ▪ little or no cord swelling
    ▪ unequivocal hyperintensity on T2-weighted sequences
    ▪ size at least 3 mm but less than 2 vertebral segments in length
    ▪ occupy only part of the cord in cross-section
    ▪ focal (i.e. clearly delineated and circumscribed on T2-weighted sequences)

CNS Infections
• leptomeningitis
  ▪ pathogenesis: inflammation of the pia or arachnoid mater, most often secondary to hematogenous spread from infection or via organisms gaining access across areas not protected by the blood brain barrier (choroid plexus or circumventricular organs)
  ▪ pathogens include: S. pneumoniae, H. influenza, N. meningitidis, L. monocytogenes
  ▪ best imaging modality: best visualized with MRI (T2-weighted/FLAIR) over CT
  ▪ findings:
    ▪ meningeal enhancement (following the gyri/sulci, and/or basal cisterns), hydrocephalus (communicating), cerebral swelling, subdural effusion
    ▪ a normal MRI does not rule out leptomeningitis

• herpes simplex encephalitis (see Infectious Diseases, ID20)
  ▪ pathogenesis: inflammation of the brain parenchyma secondary to HSV infection, asymmetrically affects the limbic regions of the brain – temporal lobes, orbitofrontal region, insula, and cingulate gyrus
  ▪ best imaging modality: best imaged with MRI (T1- and T2-weighted imaging)
  ▪ findings:
    ▪ acute (within 4-5 d): high intensity lesions on T2 MRI in temporal and inferior frontal lobes, asymmetric
    ▪ strongly suggestive of HSV encephalitis
    ▪ DDx: infarct, tumour, status epilepticus, limbic encephalitis
    ▪ CT may show low density in temporal lobe and insula; rarely basal ganglia involvement
    ▪ long term may show parenchymal loss to affected areas
cerebritis/cerebral abscess
- Pathogenesis: an infection of the brain parenchyma (cerebritis) which can progress to a collection of pus (abscess), most frequently due to hematogenous spread of infectious organisms, commonly located in the distribution of the middle cerebral artery
- Pathogens include: S. aureus (often in IVDU, nosocomial), GN bacteria, Streptococcus, Bacteroides
- Best imaging modality: MRI including diffusion (DWI) imaging series – an abscess will be DWI positive; CT is still used as a viable alternative but overall MRI > CT
- Findings according to one of four stages of abscess formation:
  - Early cerebritis (1-3 d): inflammatory infiltrate with necrotic centre, low intensity on T1, high intensity on T2
  - Late cerebritis (4-9 d): ring enhancement may be present
  - Early capsule (10-13 d): ring enhancement
  - Late capsule (14 d or greater): well demarcated ring-enhancing lesion, low intensity core, with mass effect; considerable edema around the lesion, seen as hyperdensity on T2

Musculoskeletal System (MSK)

Modalities

Plain Film/X-Ray
- Usually initial study used in evaluation of bone and joint disorders
- Indications: fractures and dislocations, arthritis, assessment of malalignment, assessment of orthopedic hardware, initial assessment of bone tumors
- Minimum of two films orthogonal to each other (usually AP and lateral) to rule out a fracture
- Image proximal and distal joints (particularly important with paired bones, e.g. radius/ulna)
- Not very effective in evaluating soft tissue injury
- Advantages: fast, inexpensive, readily available, reproducible

CT
- Evaluation of fine bony detail
- Indications: assessment of complex, comminuted, intra-articular or occult fractures including distal radius, scaphoid, skull, spine, acetabulum, calcaneus, and sacrum
- Evaluation of soft tissue calcification/ossification
- Advantages: fast, reproducible, excellent bone evaluation, and spatial resolution
- Disadvantages: radiation dose, relatively poor soft tissue characterization in comparison with U/S and MRI

MRI
- Indications: evaluation of internal derangement of joints (ligaments, joint capsule, menisci, labrum, cartilage), assessment of tendons and muscle injuries, characterization and staging of soft tissue and bony masses
- Advantages: excellent soft tissue contrast, multiplanar imaging, no radiation
- Disadvantages: long imaging times, expensive, claustrophobia, contraindications (e.g. pacemakers, orbital metallic bodies), artifact around metal hardware

Ultrasound
- Indications: tendon injury (e.g. rotator cuff, Achilles tendon), detection of soft tissue masses and to determine whether cystic or solid, detection of foreign bodies, ultrasound guided biopsy and injections
- Doppler determines vascularity of structures
- Advantages: good soft tissue evaluation, easy contralateral comparison, dynamic imaging
- Disadvantages: operator dependent, poor for bone evaluation

Nuclear Medicine (Bone Scintigraphy)
- Determine the location and extent of bony lesions
- 99mTc-methylene diphosphonate (MDP) localize to areas of increased bone turnover or calcification – growth plate in children, tumours, infections, fractures, metabolic bone disease (e.g. Paget’s), sites of reactive bone formation, and periostitis
- Very sensitive, not specific (trauma, infection, inflammation look similar)

Approach to interpretation of bone X-Rays
- Identification: name, MRN, age of patient, type of study, region of investigation
- Soft tissues: swelling, calcification/ossification
- Joints: alignment, joint space, presence of effusion, osteophytes, erosions, bone density, overall pattern, and symmetry of affected joint
- Bone: periosteum, cortex, medulla, trabeculae, density, articular surfaces, bone destruction, bone production, appearance of the edges or borders of any lesions (Figure 34)
Trauma

Fracture/Dislocation
- description of fractures
- site of fracture (bone, region of bone, intra-articular vs. extra-articular)
- pattern of fracture line (simple vs. comminuted)
- displacement (distal fragment with reference to the proximal fragment)
- soft tissue involvement (calcification, gas, foreign bodies)
- type of fracture (stress vs. pathologic)
- for specific fracture descriptions and characteristics of fractures, see Orthopedics, OR5

Arthritis

Radiographic Hallmarks of OA
- joint space narrowing – typically non-uniform
- subchondral sclerosis
- subchondral cyst formation
- osteophytes

Radiographic Hallmarks of RA
- joint space narrowing – typically uniform
- soft tissue swelling
- erosions
- periarticular osteopenia

Bone Tumour

Approach
- metastatic tumours to bone are much more common than primary bone tumours, particularly if age >40 yr
- diagnosis usually requires a biopsy if primary not located
- few benign tumours/lesions have potential for malignant transformation
- MRI is good for tissue delineation and preoperative assessment of surrounding soft tissues, neurovascular structures, and medullary/marrow involvement
- plain film is less sensitive than other modalities but useful for assessing aggressiveness and constructing differential diagnosis

Considerations and Tumour Characteristics
- age – most common tumours by age group
  - <1 yr of age: metastatic neuroblastoma
  - 1-20 yr of age: Ewing's tumour in tubular bones
  - 10-30 yr of age: osteosarcoma and Ewing's tumour in flat bones
  - >40 yr of age: metastases, multiple myeloma, and chondrosarcoma
- multiplicity: metastases, myeloma, lymphoma, fibrous dysplasia, enchondromatosis
- location within bone
  - epiphysis: giant cell tumour, chondroblastoma, geode, eosinophilic granuloma, infection
  - metaphysis: simple bone cyst, aneurysmal bone cyst, enchondroma, chondromyxoid fibroma, nonossifying fibroma, osteosarcoma, chondrosarcoma
  - diaphysis: fibrous dysplasia, aneurysmal bone cyst, brown tumours, eosinophilic granuloma, Ewing's sarcoma
- expansile
  - aneurysmal bone cyst, giant cell tumour, enchondromas, brown tumours, metastases (especially renal and thyroid), plasmacytoma
- matrix mineralization
  - chondroid (popcorn calcification) or osseous
- margin/zone of transition: area between lesion and normal bone
- cortex: intact, disturbed
- periosteal reaction
- soft tissue mass
- see Figure 34 and Table 18

Types of Fractures
- Transverse
- Oblique
- Spiral

Types of Displacements
- Translation
- Angulation
- Rotation

Figure 33. X-ray of first carpometacarpal joint: normal image (left side) and osteoarthritis (right side) with joint space narrowing and subchondral sclerosis

Benign Lesions which may have Aggressive Features
- Osteomyelitis
- Osteoblastoma
- Aneurysmal bone cyst
- Langerhans cell histiocytosis
- Myositis ossificans

Periosteal Reaction
- "Onion skinning" = Ewing's sarcoma
- "Sunburst", "hair on end" = osteosarcoma
- "Codman's triangle" = osteosarcoma, Ewing's sarcoma, subperiosteal abscess

Lytic = decreased density
Sclerotic = increased density

Margination of lesions
- Punch out
- Thin rim of sclerosis
- Thick rim of sclerosis

Patterns of cortical disturbance
- Expansile
- Endosteal scalloping
- Invisible margin
- Saucerization

Patterns of medullary destruction
- Permeative
- Moth-eaten
- Solid undulating

Periosteal new bone formation
- Onion-skin layered
- Codman's Triangle
- Hair-on-end spiculated
- Sunburst divergent
- Solid undulating

Figure 34. Radiographic appearance of bone remodelling and destruction processes
### Metabolic Bone Disease

#### Osteoporosis
- Reduction in amount of normal bone mass; fewer and thinner trabeculae; diffuse process affecting all bones
- Dual energy x-ray absorptiometry (DEXA): gold standard for measuring bone mineral density
  - T-score: the number of standard deviations from the young adult mean, most clinically valuable
    - Osteopenia: \(-2.5 < \text{T-score} < -1\)
    - Osteoporosis: \(\text{T-score} \leq -2.5\)
  - Z-score: the number of standard deviations from the age-matched mean
  - Risk of fracture: related to bone mineral density, age, history of previous fractures, steroid therapy

#### Infection

**Osteomyelitis**
- MRI is the imaging modality of choice for demonstrating bone, bone marrow, and soft tissue abnormalities
- \(^{99}\text{Tc}\), followed by \(^{111}\text{In}\) labeled white cell scan or gallium radioisotope scan
- Plain film
  - Visible 8-10 d after process has begun
  - Osteomyelitic changes on plain film
    - Soft tissue swelling
    - Local periosteal reaction
    - Pockets of air (from anaerobes) may be seen in the tissues, may also suggest necrotizing fasciitis
    - Mottled and nonhomogeneous with a classic “moth-eaten” appearance
    - Cortical destruction

**Bone Abscess**
- Overlying cortex has periosteal new bone formation
- Sharply outlined radiolucent area with variable thickness in zone of transition
- Variable thickness periosteal sclerosis
- Sequestrum: a piece of dead bone within a Brodie's abscess
- A sinus tract or cloaca may communicate between the abscess through the cortex to the surface of the bone

#### Metastatic Bone Tumours
- All malignancies have potential to metastasize to bone
- Metastases are 20-30x more common than primary bone tumours
- Metastasis can cause a lytic or a sclerotic reaction when seeding to bone
- When a primary malignancy is first detected, a bone scan is often part of the initial work-up
- May present with pathological fractures or pain
- Biopsy or determination of primary is the only way to confirm the diagnosis
- Most common metastatic bone tumours: breast, prostate, lung, see Orthopedics, OR45

#### Table 18. Characteristics of Benign and Malignant Bone Lesions

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin sclerotic margin/sharp delineation of lesion</td>
<td>Poor delineation of lesion – wide zone of transition</td>
</tr>
<tr>
<td>Overlying cortex intact</td>
<td>Loss of overlying cortex/bony destruction</td>
</tr>
<tr>
<td>No or simple periosteal reaction</td>
<td>Periosteal reaction</td>
</tr>
<tr>
<td>No soft tissue mass</td>
<td>Soft tissue mass</td>
</tr>
<tr>
<td>Note: for specific bone tumours see Orthopedics, OR42</td>
<td></td>
</tr>
</tbody>
</table>

#### Table 19. Characteristic Bone Metastases of Common Cancers

<table>
<thead>
<tr>
<th>Lytic</th>
<th>Sclerotic</th>
<th>Expansile</th>
<th>Peripheral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Prostate</td>
<td>Thyroid</td>
<td>Kidney</td>
</tr>
<tr>
<td>Lung</td>
<td>Breast</td>
<td>Renal</td>
<td>Lung</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Lymphoma</td>
<td></td>
<td>Melanoma</td>
</tr>
<tr>
<td>Kidney</td>
<td>Lung</td>
<td></td>
<td>(KLM: flies to the periphery)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Bowel</td>
<td>Medulloblastoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treated tumours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Metabolic Bone Disease

**Osteoporosis**
- Reduction in amount of normal bone mass; fewer and thinner trabeculae; diffuse process affecting all bones
- Dual energy x-ray absorptiometry (DEXA): gold standard for measuring bone mineral density
  - T-score: the number of standard deviations from the young adult mean, most clinically valuable
    - Osteopenia: \(-2.5 < \text{T-score} < -1\)
    - Osteoporosis: \(\text{T-score} \leq -2.5\)
  - Z-score: the number of standard deviations from the age-matched mean
  - Risk of fracture: related to bone mineral density, age, history of previous fractures, steroid therapy

**Diagnostic sensitivity of DEXA highest when BMD measured at lumbar spine and proximal femur.**
• appearance on plain film
  ▪ osteopenia: reduced bone density on plain films
  ▪ may also be seen with osteomalacia, hyperparathyroidism, and disuse
  ▪ compression of vertebral bodies
  ▪ biconcave vertebral bodies ("codfish" vertebrae)
  ▪ long bones have appearance of thinned cortex and increased medullary cavity
  ▪ look for complications of osteoporosis
    ▪ e.g. insufficiency fractures: hip, vertebrae, sacrum, pubic rami
• see **Endocrinology, E42**

**Osteomalacia/Rickets**
• reduction in bone mineral density, usually due to vitamin D deficiency, resulting in softening and bowing of long bones
• similar to osteoporosis, initial radiological appearance of osteopenia (coarse and poorly defined bone texture)
• “fuzzy”, ill-defined trabeculae
• Looser’s zones (pseudofracture)
  ▪ characteristic radiologic feature
  ▪ fissures or clefts at right angles to long bones and extending through cortex
• DDx: osteomalacia, chronic renal disease, fibrous dysplasia, hyperthyroidism, Paget’s, osteodystrophy, X-linked hypophosphatemia

**Hyperparathyroidism**
• most common cause is renal failure (secondary hyperparathyroidism)
• chondrocalcinosis
  ▪ calcium crystal deposition in hyaline cartilage or fibrocartilage (including arteries and periarticular soft tissue)
  ▪ resorption of bone typically in hands (subperiosteal and at tufts), SI joints (subchondral), skull (“salt and pepper” appearance), osteoclastoma (brown tumours)
  ▪ “rugger jersey spine”: band-like osteosclerosis at superior/inferior margins of vertebral bodies
• see **Endocrinology, E38**

**Paget’s Disease**
• abnormal remodeling involving single or multiple bones – especially skull, spine, pelvis
• 3 phases: 1st phase = lytic, 2nd phase = mixed (lytic/sclerotic), 3rd phase = sclerotic
• features
  ▪ coarsening of the trabeculae with bone expansion
  ▪ bone softening/bowing
  ▪ bone scan will reveal high activity, especially at bone ends
  ▪ thickened cortex
• see **Endocrinology, E46**
Nuclear Medicine

Brain

- $^{99m}$Tc-exametazime (HMPAO) and $^{99m}$Tc-bicisate (ECD) imaging to assess cerebral blood flow, taken up in cortical and subcortical grey matter; used for dementia, traumatic brain injury and to a lesser extent vasculitis, neuropsychiatric disorders and stroke
- PET imaging assesses metabolic activity by using $^{18}$FDG
- CSF imaging, intrathecal administration of $^{111}$In-DTPA to evaluate CSF leak or to differentiate normal pressure hydrocephalus from other causes of hydrocephalus
- ventricular shunt evaluation for obstruction (most commonly ventricular peritoneal) with $^{99m}$Tc or $^{111}$In-DTPA

Thyroid

Radioactive Iodine Uptake (see Endocrinology, E22)

- index of thyroid function (trapping and organification of iodine)
- radioactive $^{131}$I or $^{123}$I given PO to fasting patient
- measure percentage of administered iodine taken up by thyroid
- increased RAU: toxic multinodular goiter, toxic adenoma, Graves’ disease
- decreased RAU: subacute thyroiditis, late Hashimoto’s disease, hormone suppression
- falsely decreased in patient with recent radiographic contrast studies, high dietary iodine (e.g. seaweed)

Thyroid Imaging (Scintiscan)

- $^{99m}$Tc pertechnetate IV or radioactive iodine ($^{123}$I)
- provides functional anatomic detail
- hot (hyperfunctioning) lesions
  - adenoma, toxic multinodular goiter
  - usually benign, cancer very unlikely (less than 1%)
- cold (hypofunctioning) lesions
  - cancer must be considered until biopsy negative even though only 6-10% are cancerous
- iso/intense lesions
  - cancer must be considered as an iso/intense lesion may represent cold nodules superimposed on normal tissue
  - if cyst suspected, correlate with U/S
- serum thyroglobulin to detect recurrent thyroid cancer post-treatment

Radioiodine Ablation

- $^{123}$I for Graves’ disease, multinodular goiter, thyroid cancer

Respiratory

V/Q Scan

- examine areas of lung in which ventilation and perfusion do not match
- ventilation scan
  - patient breathes radioactive gas ($^{99m}$Tc-DTPA, $^{133}$Xe, Technegas) through a closed system, filling alveoli proportionally to ventilation
  - ventilation scan defects indicate: airway obstruction, chronic lung disease, bronchospasm, tumour mass obstruction
- perfusion scan
  - radiotracer injected IV ($^{99m}$Tc-MAA) trapped in pulmonary capillaries (1 in 1500 arterioles occluded) according to blood flow
  - gives a map of pulmonary circulation
  - relatively contraindicated in severe pulmonary HTN and right-to-left shunt
  - with PE
    - areas of lung are well ventilated but not perfused (unmatched defect)
    - defects are wedge-shaped, extend to periphery, usually bilateral and multiple
    - reported as high probability, intermediate, low very low, or normal
    - V/Q scans for PE have been largely replaced by CT scan with contrast (see Respirology, R18)
  - not valid for assessment of PE when patients have intrinsic lung diseases and ventilatory problems
Cardiac

Myocardial Perfusion Scanning
- for investigation of angina, atypical chest pain, coronary artery disease, and follow-up post-bypass
- thallium-201 (a radioactive analogue of potassium), \(^{99m}\text{Tc}\) sestamibi (MIBI), or \(^{99m}\text{Tc}\) tetrofosmin
- injected at peak exercise (physical stress) or after persantine challenge (vasodilator) and again later at rest
- persistent defect (at rest and stress) suggests infarction; reversible defect (only during stress) suggests ischemia
- used to discriminate between reversible (ischemia) vs. irreversible (infarction) changes when other investigations are equivocal
- see Cardiology and Cardiovascular Surgery, C10 for more details

Radionuclide Ventriculography
- \(^{99m}\text{Tc}\) tagged to red blood cells
- first pass through right ventricle → pulmonary circulation → left ventricle; provides information about RV function
- cardiac MUGA scan (MUltiple GAted acquisition scan) sums multiple cardiac cycles
  - evaluation of LV function
  - images are obtained by gating (synchronizing) the count acquisitions to the ECG signal
  - MUGA scan can be used to study the function of the heart at a particular stage of contraction
- provides information on ejection fraction (normal = 50-65%), ventricular volume, and wall motion

Abdomen and Genitourinary System

HIDA (Hepatobiliary IminoDiacetic Acid) Scan
- IV injection of \(^{99m}\text{Tc}\)-disofenin (DISIDA) or \(^{99m}\text{Tc}\)-mebrofenin (BRIDA) which is bound to protein, taken up, and excreted by hepatocytes into biliary system
- can be performed in non-fasting state but prefer NPO after midnight
- gallbladder visualized when cystic duct is patent, usually seen by 30 min to 1 h
- if gallbladder is not visualized, suspect obstructed cystic duct (acute or chronic cholecystitis)
- acute cholecystitis: no visualization of gallbladder at 4 h or after administration of morphine at 30 min
- chronic cholecystitis: no visualization of gallbladder at 1 h but seen at 4 h or after morphine administration
- differential diagnosis of obstructed cystic duct: acute cholecystitis, decreased hepatobiliary function (commonly due to alcoholism), bile duct obstruction, parenteral nutrition, fasting less than 4 h or more than 24 h
- filling of gallbladder rules out cholecystitis (<1% probability)
- assess bile leaks post-operatively

RBC Scan
- IV injection of radiotracer with sequential images of the abdomen (\(^{99m}\text{Tc}\ RBCs)
- GI bleed
  - if bleeding acutely at <0.5 mL/min, the focus of activity in the images generally indicates the site of the acute bleed, look for a change in shape and location on sequential image
  - if bleeding acutely at >0.5 mL/min, use angiography (more specific)
- RBC scan is more sensitive for lower GI bleed
- liver lesion evaluation
  - hemangioma has characteristic appearance: cold early, fills in later

Renal Scan
- see Genitourinary System, MI16

Scrotal Scintigraphy
- scrotal scintigraphy has now been replaced by Doppler U/S
Bone

Bone Scan
- isotopes
  - ⁹⁹ᵐTc-diphosphonate
    - triphasic bone scan: flow → blood pool → delayed bone images
    - uptake can distinguish bone vs. soft tissue infection and septic arthritis vs. osteomyelitis vs. peripheral cellulitis
    - acute osteomyelitis: increased activity in flow, blood pool, and delayed bone images; usually does not cross joint
    - septic arthritis and cellulitis: increased activity in blood pool and normal or slightly increased activity in delayed images; may cross joint
  - ¹¹¹In WBC: tracks the active migration of the WBC, more specific for infection
  - ⁶⁷Ga citrate: may see uptake in some tumours, also more specific for infection
- radioactive tracer binds to hydroxyapatite of bone matrix
- increased binding when increased blood supply to bone and/or high bone turnover (active osteoblasts)
- indications:
  - bone pain of unknown origin
  - AVN
  - suspected malignancy
  - staging malignancy (cancer of breast, prostate, kidney or lung)
  - follow up after treatment
  - detection and follow up of primary bone disease
  - assessment of skeletal trauma
  - detection of soft tissue calcification
  - renal failure
- differential diagnosis of positive bone scan:
  - bone metastases from breast, prostate, lung, thyroid
  - primary bone tumour
  - arthritis
  - fracture
  - infection
  - anemia
  - Paget's disease
- multiple myeloma: typically normal or cold (false negative); need a skeletal survey
- "superscan": increased bone uptake and poor renal uptake due to diffuse metastases or metabolic causes (renal osteodystrophy)

Interventional Radiology

Vascular Procedures

Angiography
- injection of contrast material through a catheter placed directly into an artery or vein to delineate vascular anatomy
- catheter can be placed into a large vessel (e.g. aorta, vena cava) for a "flush" or selectively placed into a branch vessel for more detailed examination of smaller vessels and specific organs
- indications: diagnosis of primary occlusive or stenotic vascular disease, aneurysms, coronary, carotid and cerebral vascular disease, PE, trauma, bleeding (GI, hemoptysis, hematuria), vascular malformations, as part of endovascular procedures (EVAR, thrombolysis, stenting and angioplasties)
- complications: puncture site hematoma, infection, pseudoaneurysm, AV fistula, dissection, thrombosis, embolic occlusion of a distal vessel
- significant complications occur in <5% of patients
- due to improved technology, non-invasive evaluation of vascular structures is being performed more frequently (colour Doppler U/S, CT angiography and MR angiography)
- see Neuroradiology, MI18

Percutaneous Transluminal Angioplasty (PTA) and Stents
- introduction and inflation of a balloon into a stenosed vessel to restore distal blood supply
- common alternative to surgical bypass grafting with five year patency rates similar to surgery, depending on site
- renal, iliac, femoral, mesenteric, subclavian, coronary and carotid artery stenoses are amenable to treatment

Thrombolytic Therapy for Pulmonary Embolism
Cochrane DB Syst Rev 2009;3:CD004437
Study: Systematic review of randomized controlled trials comparing thrombolytic therapy with placebo, heparin, or surgical intervention.
Patients: 679 patients with acute PE
Intervention: Thrombolytics vs. heparin or placebo.
Outcome: Death rate, recurrence of PE, major and minor hemorrhagic events.
Results: Non-significant difference between thrombolytics and heparin or placebo in all measured outcomes. RT-PA and heparin together reduced need for treatment for in-hospital events. Thrombolitics improved hemodynamic outcome, lung VQ scans, pulmonary angio assessment and echocardiograms greater than heparin. Need for further double-blinded RCTs.
Conclusion: We cannot conclude whether thrombolytic therapy is better than heparin for pulmonary embolism based on limited evidence found.
• vascular stents may help improve long term results by keeping the vessel wall patent after PTA
• stents are also used for angioplasty failure or complications
• stent grafts (metal mesh covered with durable fabric) may provide an alternative treatment option for aneurysms and AV fistulas
• complications: similar to angiography, but also includes vessel rupture

**Thrombolytic Therapy**
• may be systemic (IV) or catheter directed
• infusion of a fibrinolytic agent (urokinase, streptokinase, TNK, tPA – used most commonly) via a catheter inserted directly into a thrombus
• can restore blood flow in a vessel obstructed with a thrombus or embolus
• indications: treatment of ischemic limb (most common indication), early treatment of MI or stroke to reduce organ damage, treatment of venous thrombosis (DVT or PE)
• complications: bleeding, stroke, distal embolus, reperfusion injury with myoglobinuria and renal failure if advanced ischemia present

**Embolization**
• injection of occluding material into vessels
• permanent agents: amplatzer plugs, coils, glue and onyx
• temporary: gel foam, autologous blood clots
• indications: management of hemorrhage (epistaxis, trauma, GI bleed, GU bleed), treatment of AVM, pre-operative treatment of vascular tumours (bone metastases, renal cell carcinoma), varicocele embolization for infertility, symptomatic uterine fibroids
• complications:
  • post embolization syndrome (pain, fever, leukocytosis)
  • unintentional embolization of a non-target organ with resultant ischemia

**Inferior Vena Cava Filter**
• insertion of metallic “umbrellas” to mechanically trap emboli and prevent PE
• may be temporary (retrievable) or permanent
• inserted via femoral vein, jugular vein, or antecubital vein
• usually placed infrarenally to avoid renal vein thrombosis
• indications: contraindication to anticoagulation, failure of adequate anticoagulation (e.g. recurrent PE despite therapeutic anticoagulant levels), complication of anticoagulation

**Central Venous Access**
• variety of devices available
• peripherally inserted central catheter (PICC), external tunneled catheter (Hickman or dialysis catheters), subcutaneous port (Portacath*)
• indications: chemotherapy, TPN, long-term antibiotics, administration of fluids and blood products, blood sampling
• complications: venous thrombosis and central venous stenosis, infection including sepsis, pneumothorax

**Nonvascular Interventions**

**Percutaneous Biopsy**
• replaces open surgical procedure
• many sites are amenable to biopsy using U/S, fluoroscopy or CT guidance
• complications:
  • false negative biopsies due to sampling error or tissue necrosis
  • pneumothorax in 30% of lung biopsies, chest tube required in approximately 5%
  • pancreatic biopsies are associated with risk of inducing acute pancreatitis
  • transjugular liver biopsies can be performed to minimize bleeding complications in patients with uncorrectable coagulopathies or ascites

**Abscess Drainage**
• placement of a drainage catheter into an infected fluid collection
• administer broad spectrum IV antibiotics prior to procedure
• routes: percutaneous (most common), transgluteal, transvaginal, transrectal
• complications:
  • hemorrhage
  • injury to intervening structures (e.g. bowel)
  • bacteremia, sepsis

Advanced ischemia patients should receive surgery rather than thrombolysis.

Chemoembolization delivers chemotherapy directly into the tumour through its feeding blood supply and traps the drug in place by embolization.

**Indications for Central Venous Access**
- FAT CAB
- Fluids
- Antibiotics
- TPN
- Chemotherapy
- Administration of blood
- Blood sampling

**Figure 36. Retrievable IVC filter**

**Figure 37. Femoral arteriogram:**
distal occlusion of superficial femoral artery

ERCP is the primary modality for distal common bile duct obstructions.
Percutaneous Biliary Drainage (PBD)/Cholecystostomy
- placement of drainage catheter ± metallic stent into obstructed biliary system (PBD) or gallbladder (cholecystostomy) for relief of jaundice or infection
- percutaneous gallbladder access can be used to crush or remove stones
- indications:
  - cholecystostomy: acute cholecystitis
  - percutaneous biliary drainage: biliary obstruction secondary to stone or tumour, cholangitis
- complications:
  - acute: sepsis, hemorrhage
  - long-term: tumour overgrowth and stent occlusion

Percutaneous Nephrostomy
- placement of catheter into renal collecting system
- indications: hydronephrosis (urinary obstruction as a result of a stone or tumour), pyonephrosis, ureteric injury with or without urinary peritonitis (traumatic or iatrogenic)
- complications: bacteria and septic shock, hematuria due to pseudoaneurysm or AV fistulas, injury to adjacent organs

Gastrostomy/Gastrojejunostomy
- percutaneous placement of catheter directly into either stomach (gastrostomy) or through stomach into small bowel (transgastric jejunostomy)
- indications:
  - feeding: inability to eat (most commonly CNS lesion, e.g. stroke) or esophageal obstruction
  - decompression: gastric outlet obstruction
- complications: gastroesophageal reflux with aspiration, peritonitis, hemorrhage, bowel or solid organ injury

Radiofrequency (RF) Ablation
- U/S or CT guided probe is inserted into tumour, RF energy delivered through probe causes heat deposition and tissue destruction
- indications: hepatic tumours (HCC and metastases), renal tumours
- complications: destruction of neighbouring tissues and structures, bleeding

Breast Imaging

Modalities

Mammography
Description
- x-ray imaging of the breasts for screening in asymptomatic patients, or diagnosis of clinically-detected or screening-detected abnormalities (see General Surgery, GS54)

Indications
- screening
  - begin screening from age 50 q1-2 yr
  - if over the age of 70, continue screening mammography if in good general health
  - not routinely recommended if under the age of 50 unless strong family history
  - if positive family Hx, begin screening 5-10 yr younger than the first degree relative who developed breast cancer
- diagnostic
  - signs and symptoms suggestive of breast cancer include a lump or thickening, localized nodularity, dimpling or contour deformity, a persistent focal area of pain, and spontaneous serous or sanguinous nipple discharge from a single duct
  - women with abnormal screening mammograms
  - follow-up of women with previous breast cancer
  - suspected complications of breast implants
Table 20. Breast Imaging Reporting and Data System (BI-RADS®) Mammography Categories

<table>
<thead>
<tr>
<th>Assessment Categories</th>
<th>Imaging Findings</th>
<th>Follow-up Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI-RADS 0</td>
<td>Incomplete</td>
<td>Additional imaging</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comparison to prior films</td>
</tr>
<tr>
<td>BI-RADS 1</td>
<td>Negative</td>
<td>Routine screening</td>
</tr>
<tr>
<td>BI-RADS 2</td>
<td>Benign</td>
<td>Routine screening</td>
</tr>
<tr>
<td>BI-RADS 3</td>
<td>Probably benign</td>
<td>Unilateral mammogram at 6 mo</td>
</tr>
<tr>
<td></td>
<td>Likelihood of malignancy is &lt;2%</td>
<td></td>
</tr>
<tr>
<td>BI-RADS 4</td>
<td>Suspicious abnormality</td>
<td>Biopsy</td>
</tr>
<tr>
<td>BI-RADS 5</td>
<td>Highly suspicious of malignancy</td>
<td>Biopsy</td>
</tr>
<tr>
<td></td>
<td>Likelihood of malignancy is 95%</td>
<td></td>
</tr>
<tr>
<td>BI-RADS 6</td>
<td>Malignancy confirmed by biopsy</td>
<td>Definitive therapy</td>
</tr>
</tbody>
</table>

Breast MRI

Description
- breast MRI should be used only after mammography and ultrasound investigation
- sensitive for detecting invasive breast cancer (95-100%) but specificity variable (37-97%)
- use as a screening modality has been limited to high risk patients

Indications
- evaluation of previously diagnosed breast cancer: positive margins, recurrence, response to chemotherapy
- post-surgical resection of breast cancer
- known BRCA1 or BRCA2 mutation, or other gene predisposing to breast cancer
- untested first-degree relative of a carrier of such a gene mutation
- family history consistent with a hereditary breast cancer syndrome and estimated personal lifetime cancer risk >25%
- high-risk marker on prior biopsy (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ)
- radiation therapy to chest (before age 30)
- NOTE: MRI should not be used to screen the general population or to differentiate between benign and malignant lesions

Ultrasound

Definition
- ultrasound can determine if a mass is cystic or solid and is commonly used during biopsy

Indications
- identification and characterization of palpable abnormalities
- evaluation of ambiguous mammographic findings in the determination of cystic versus solid characteristics
- evaluation of patients with suspected silicone implant rupture and problems associated with breast implants
- guidance for interventional procedures
- breast sonography is the initial imaging technique to evaluate palpable masses in women under 30 and in lactating and pregnant women

Breast Interventional Procedures

Description
- breast interventional procedures include fine needle aspirate biopsy, core needle biopsy, abscess drainage, and cyst aspiration (see General Surgery, GS56)

Indications
- cystic mass: complex cyst, symptomatic, suspected abscess
- solid mass: confirm diagnosis of a lesion suspicious for malignancy (BI-RADS® Category 4 or 5) or confirm diagnosis of a probable benign mass (BI-RADS® Category 3)
- initial percutaneous biopsy procedure that was insufficient or discordant with imaging
- presurgical ultrasound-guided localization of a lesion
Breast Findings

Breast Masses

- **definition:** a space occupying lesion seen in two different projections; if seen in only a single projection it should be called a "density" until its three-dimensionality is confirmed

| Table 21. Mammographic Features of Benign and Malignant Breast Masses |
|---|---|---|
| **Shape** | Benign | Malignant |
| | Oval, round, lobular | Irregular |
| **Margin** | Circumscribed, well-defined | Indistinct, microlobulated, speculated |
| **Density** | Radiolucent (oil cyst, lipoma, fibrolipoma, galdactocele, hamartoma) | Radiodense |
| **Calcifications (± mass)** | Popcorn (hyalinizing fibroadenoma), lucent centred (oil cyst/fat necrosis), layering (milk of calcium), vascular, round, scattered | Pleomorphic (vary in size and shape), amorphous (indistinct), fine linear, coarse heterogenous, regional, segmental, clustered |

Other Findings

- tubular density/dilated duct: branching tubular structures usually represent enlarged ducts (milk ducts); if they are clearly identified as such, these densities are of little concern
- intramammary lymph node: typical lymph nodes are circumscribed, reniform and often have a fatty notch and centre; usually less than 1 cm, and usually seen in the outer, often upper part of the breast; when these characteristics (particularly fatty centre or notch) are well seen, the lesion is almost always benign and insignificant
- focal asymmetric density: area of breast density with similar shape on two views, but completely lacking borders and conspicuity of a true mass; must be carefully evaluated with focal compression to exclude findings of a true mass or architectural distortion
  - if focal compression shows mass-like character, or if the area can be palpated, biopsy must be considered

References


Canadian Association of Radiologists (CAR) standard for breast Imaging. Ottawa: Canadian Association of Radiologists, 1998.


Goldstein S. Saline infusion sonohysterogram. Up to Date, 2012.


Acronyms ................................. 2

Basic Anatomy Review ................. 2
Anatomy of the Kidney
Renal Structure and Function
Renal Hemodynamics

Assessment of Renal Function ........ 4
Measurement of Renal Function
Urinalysis
Urine Microscopy
Urine Electrolytes

Electrolyte Disorders .................. 7
Sodium Homeostasis
Hyponatremia
Hypernatremia
Potassium Homeostasis
Hypokalemia
Hyperkalemia

Acid-Base Disorders .................... 14
Metabolic Acidosis
Metabolic Alkalosis

Vascular Diseases of the Kidney ........ 17
Large Vessel Disease
Small Vessel Disease

Glomerular Disease .................... 19
Histological Terms for Glomerular Changes
Clinical Presentation of Glomerular Disease
Glomerular Syndromes
Investigations for Glomerular Disease
Secondary Causes of Glomerular Disease

Tubulointerstitial Disease ............ 25
Tubulointerstitial Nephritis (TIN)
Acute Tubular Necrosis (ATN)
Analgesic Nephropathies

Systemic Disease with Renal Manifestation .............. 28
Diabetes
Scleroderma
Multiple Myeloma
Malignancy

Hypertension (HTN) .................... 30
Hypertensive Nephrosclerosis
Renovascular Hypertension
Renal Parenchymal Hypertension

Cystic Diseases of the Kidney .......... 31
Adult Polycystic Kidney Disease
Medullary Sponge Kidney
Autosomal Recessive Polycystic Kidney Disease

Acute Kidney Injury (AKI) ............ 33
Approach to AKI

Chronic Kidney Disease (CKD) ......... 34
Management of Chronic Kidney Disease

Renal Failure .......................... 35
Presentation of Renal Failure

Renal Replacement Therapy .......... 36
Dialysis
Renal Transplantation

Common Medications .................. 38

Landmark Nephrology Trials .......... 39

References ............................ 40
The Nephron

- basic structural and functional unit of the kidney, approximately 1 million per kidney
- direction of blood flow: afferent arteriole → glomerular capillaries → efferent arteriole → vasa recta (the capillaries surrounding the tubules) → renal venules

The Glomerulus

- site where blood constituents are filtered through to the kidney tubules for excretion or reabsorption
- consists of following cell types:
  - Mesangial cells: structural cells that support the vascular tree. They are also contractile and produce vasoactive substances to help control blood flow
  - Capillary endothelial cells: one of the cells of the glomerular filtration barrier and help form the plasma filtration apparatus due to their sinusoidal nature and glyocalyx. Contribute to the production of the glomerular basement membrane (GBM)
  - Visceral epithelium (podocytes): one of the cells of the glomerular filtration barrier and help form the plasma filtration apparatus due to their interdigitated foot process that form slit diaphragms. Contribute to the production of the glomerular basement membrane (GBM)

4. Parietal epithelium

- lines the interior of Bowman's capsule and contains a podocyte progenitor population
- filtration occurs across the glomerular filtration barrier (endothelium, GBM, podocytes) into Bowman's space (Figure 1)
- particles are selectively filtered by size (<60 kDa) and change (negative charge repelled)
The Renal Tubules

- reabsorption and secretion occur between the renal tubules and vasa recta forming urine for excretion
- each segment of the nephron selectively transports various solutes and water and is targeted by specific diuretics

![Renal Hemodynamic Parameters](image)

RBF = 20% of CO — 1 L/min
RPF = RBF*(1-Hct)
GFR = ~120 mL/min in healthy adult
(98% of this volume is reabsorbed)
FF = GFR/RPF
(normally 20%)

![Figure 1. The glomerulus](image)

**Figure 1. The glomerulus**

**The Renal Tubules**

- reabsorption and secretion occur between the renal tubules and vasa recta forming urine for excretion
- each segment of the nephron selectively transports various solutes and water and is targeted by specific diuretics

![Figure 2. Tubular segments of the nephron](image)

**Figure 2. Tubular segments of the nephron**
Renal Hemodynamics

- Glomerular Filtration Rate (GFR)
  - the rate of fluid transfer between glomerular capillaries and Bowman’s space
  - 180 L/d, of which 99% is reabsorbed, giving a daily urine output of 1.0-1.5 L
  - normal urine output is >0.5 ml/kg/h in adults
  - GFR is highest in early adulthood, decreasing thereafter
- renal autoregulation maintains constant GFR over mean arterial pressures of 70-180 mmHg
- 2 mechanisms of autoregulation:
  - myogenic mechanism: release of vasoactive factors in response to changes in perfusion pressure (e.g. ↑ perfusion pressure → afferent arteriolar constriction → ↓ GFR)
  - tubuloglomerular feedback: changes in [Na+] delivery to macula densa lead to afferent arteriolar tone (e.g. increased delivery causes afferent constriction)
- Filtration Fraction (FF)
  - percentage of RPF filtered across the glomeruli
  - expressed as a ratio: FF = GFR/RPF; normal = 0.2 or 20%
  - angiotensin II (AII) constricts renal efferent arterioles which increases FF thereby maintaining GFR
- renin is released from juxtaglomerular apparatus in response to decreased RPF

Assessment of Renal Function
Measurement of Renal Function

- glomerular filtration rate (GFR) = rate of filtration of plasma by the glomeruli
- most renal functions decline in parallel with a decrease in GFR
- inulin clearance is the gold standard for measuring GFR, but very rarely used clinically
- clinically, GFR is estimated using serum creatinine concentrations [Cr]
- creatinine (Cr) is a metabolite of creatine (intermediate in muscle energy metabolism)
- Cr is freely filtered at the glomerulus with no tubular reabsorption
- tubular secretion varies based on level of renal function (10% to >50%)
- rate of production determined by muscle mass
- Cr filtered = Cr excreted (at steady state)

Ways to Estimate GFR Using Serum Creatinine Concentration
1. Calculate creatinine clearance (CrCl)
   - calculation provides reasonable estimate of GFR
   - measure plasma [Cr], 24-h urine volume and urine [Cr]
     - GFR/d = (urine [Cr] x urine volume/d)/(plasma [Cr])
     - must use same units for urine [Cr] and plasma [Cr]
2. Cockcroft-Gault formula
   - serum Cr used along with age, gender and weight (kg) to estimate GFR (see sidebar)
   - normal range is >90 mL/min (>1.5 mL/s)
3. MDRD (Modification of Diet in Renal Disease) formula
   - most common way in which GFR is estimated (MDRD 7 equation)
   - complex formula incorporating age, gender, serum Cr, African descent, but does not include weight
   - GFR is reported as mL/min/1.73 m² body surface area

4. CKD-EPI equation
   - the best current equation
   - calculated using serum Cr, age, sex and race

Limitations of Using Serum Cr Measurements
1. must be in steady state
   - constant GFR and rate of production of Cr from muscles
   - sudden injury may reduce GFR substantially, but it takes time for Cr to accumulate and then re-establish steady state
   - clinical correlation: in acute kidney injury, the rise in creatinine is often delayed
2. GFR must fall substantially before plasma [Cr] rises above normal laboratory range
   - with progressive renal failure, remaining nephrons compensate with hyperfiltration
   - GFR is relatively preserved despite significant structural damage
3. plasma [Cr] is influenced by the rate of Cr production
   - lower production with smaller muscle mass (i.e. female, elderly, low weight)
   - e.g. consider plasma [Cr] of 100 µmol/L (1.13 mg/dL) in both of these patients
     - 20 yr-old man who weighs 100 kg, GFR = 144 mL/min
     - 80 yr-old woman who weighs 50 kg, GFR = 30.6 mL/min
   - clinical correlation: GFR decreases with age but would not be reflected as a rise in serum creatinine due to the age-associated decline in muscle mass
4. tubular secretion of creatinine increases as GFR decreases
   - serum creatinine and CrCl overestimate low GFR
   - certain drugs (cimetidine, trimethoprim) can interfere with Cr secretion
5. errors in Cr measurement
   - very high bilirubin level causes [Cr] to be falsely low
   - acetooacetic acid (a ketone body) and certain drugs (cefoxitin) can cause falsely high [Cr]

Measurement of Urea Concentration
- urea is the major end product of protein metabolism
- plasma urea concentration reflects renal function but should not be used alone as it is modified by a variety of other factors
- urea production reflects dietary intake of protein and catabolic rate; increased protein intake or catabolism (sepsis, trauma, GI bleed) cause urea level to rise
- ECF volume depletion causes a rise in urea independent of GFR or plasma [Cr]
- in addition to filtration, a significant amount of urea is reabsorbed along the tubule
- reabsorption is increased in sodium-avid states such as ECF volume depletion
- typical ratio of urea to [Cr] in serum is 1:12 in SI units (using mmol/L for urea and µmol/L for Cr), and 14:1 in MKS units (urea expressed as BUN in mg/dL and Cr in mg/dL)

Urinalysis
- use dipstick in freshly voided urine specimen to assess the following:

1. Specific Gravity
   - ratio of the mass of equal volumes of urine/H₂O
   - range is 1.001 to 1.030
   - values <1.010 reflect dilute urine, values >1.020 reflect concentrated urine
   - value usually 1.010 in end stage renal disease (isosthenuria)

2. pH
   - urine pH is normally between 4.5-7.0; if persistently alkaline, consider:
     - renal tubular acidosis
     - UTI with urease-producing bacteria (e.g. Proteus)

3. Glucose
   - freely filtered at glomerulus and reabsorbed in proximal tubule
   - causes of glycosuria include
     1. hyperglycemia >9-11 mmol/L (>160-200 mg/dL) leads to filtration that exceeds tubular resorption capacity
     2. increased GFR (e.g. pregnancy)
     3. proximal tubule dysfunction (e.g. Fanconi’s syndrome)

4. Protein
   - dipstick only detects albumin; other proteins (e.g. Bence-Jones, Ig, Tamm-Horsfall) may be missed
   - microalbuminuria (defined as ≥2.0 mg/mmol creatinine in males and ≥2.8 mg/mmol creatinine in females) is not detected by standard dipstick (see Diabetes and the Kidney, NP28)
   - sulfosalicylic acid detects all protein in urine by precipitation
   - gold standard: 24-h timed urine collection for total protein

Clinical Settings in which Urea Level is Affected Independent of Renal Function
Disproportionate Increase in Urea
- Volume depletion (prerenal azotemia)
- GI hemorrhage
- High protein diet
- Sepsis
- Catabolic state with tissue breakdown
- Corticosteroid or cytotoxic agents

Disproportionate Decrease in Urea
- Low protein diet
- Liver disease

Estimating Urine Osmolality
Last 2 digits of the specific gravity x 30 = urine osmolality approximately
  e.g. specific gravity of 1.020 = 600 mOsm

24 h Urine Collection
- Discard first morning specimen
- Collect all subsequent urine for the next 24 h
- Refrigerate between voids
- Collect second morning specimen

Clarity: Cloudiness may indicate infection
Colour: usually pale yellow or amber, but may be colourless (diabetes insipidus, excess water intake), bright yellow (due to riboflavin ingestion or vitamin tablets), or dark yellow (concentrated urine in intravascular volume depletion)

Assessment of Renal Function  
Toronto Notes 2014
5. Leukocyte Esterase
- enzyme found in WBC and detected by dipstick
- presence of WBCs indicates infection (e.g. UTI) or inflammation (e.g. AIN)

6. Nitrites
- nitrates in urine are converted by bacteria to nitrites
- high specificity, low sensitivity for UTI

7. Ketones
- positive in alcoholic/diabetic ketoacidosis, prolonged starvation, fasting

8. Hemoglobin
- positive in hemoglobinuria (hemolysis), myoglobinuria (rhabdomyolysis) and true hematuria (RBCs seen on microscopy)

### Urine Microscopy
- centrifuge urine specimen for 3-5 min, discard supernatant, resuspend sediment and plate on slide
- shaking tube vigorously may disrupt casts

#### Table 2. Comparison of Urinary Sediment Findings

<table>
<thead>
<tr>
<th>Active Sediment</th>
<th>Bland Sediment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any one or more of the following seen on microscopy</strong></td>
<td></td>
</tr>
<tr>
<td>Red cell casts</td>
<td>Only hyaline casts</td>
</tr>
<tr>
<td>White cell casts</td>
<td>&lt; 2 red cells per HPF</td>
</tr>
<tr>
<td>Muddy-brown granular or epithelial cell casts</td>
<td>&lt; 4 white cells per HPF</td>
</tr>
<tr>
<td>&gt; 2 red cells per high power field (HPF)</td>
<td>Small quantities of crystals</td>
</tr>
<tr>
<td>&gt; 4 white cells per HPF</td>
<td>Small amount of bacteria</td>
</tr>
<tr>
<td><strong>Significance</strong></td>
<td><strong>Significance</strong></td>
</tr>
<tr>
<td>Highly suggestive of significant pathology, casts specifically suggest renal pathology</td>
<td>Reduced likelihood of significant pathology, but not ruled out</td>
</tr>
</tbody>
</table>

#### Table 3. Interpretation of Casts

<table>
<thead>
<tr>
<th>Cast Type</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaline casts</td>
<td>Physiologic (concentrated urine, fever, exercise)</td>
</tr>
<tr>
<td>Red blood cell casts</td>
<td>Glomerular bleeding (glomerulonephritis, vasculitis)</td>
</tr>
<tr>
<td>White blood cell casts</td>
<td>Infection (pyelonephritis)</td>
</tr>
<tr>
<td>Pigmented granular casts (heme granular casts, muddy brown)</td>
<td>Acute tubular necrosis</td>
</tr>
<tr>
<td>Fatty casts</td>
<td>Heavy proteinuria (&gt; 3.5 g/d)</td>
</tr>
<tr>
<td>Pigmented granular casts</td>
<td>Acute glomerulonephritis</td>
</tr>
<tr>
<td>Hyaline casts</td>
<td>Physiologic (concentrated urine, fever, exercise)</td>
</tr>
<tr>
<td>Red blood cell casts</td>
<td>Glomerular bleeding (glomerulonephritis, vasculitis)</td>
</tr>
<tr>
<td>White blood cell casts</td>
<td>Infection (pyelonephritis)</td>
</tr>
<tr>
<td>Pigmented granular casts (heme granular casts, muddy brown)</td>
<td>Acute tubular necrosis</td>
</tr>
<tr>
<td>Fatty casts</td>
<td>Heavy proteinuria (&gt; 3.5 g/d)</td>
</tr>
</tbody>
</table>
3. CRYSTALS
- uric acid: consider acid urine, hyperuricosuria
- calcium phosphate: alkaline urine
- calcium oxalate: consider hyperoxaluria, ethylene glycol poisoning
- sulfur: sulfa-containing antibiotics

Urine Electrolytes
- commonly measure: Na⁺, K⁺, Cl⁻, osmolality and pH
- no ‘normal’ values; electrolyte excretion depends on intake and current physiological state
- results must be interpreted in the context of a patient’s current state, e.g.:
  1. ECF volume depletion: expect low urine [Na⁺] (kidneys should be retaining Na⁺)
     - urine [Na⁺] >40 mmol/L suggests a renal problem or the action of a diuretic
     - urine [Na⁺] <20 mmol/L suggests the patient is pre-renal
  2. daily urinary potassium excretion rate should be decreased (<20 mmol/d) in hypokalemia
     - if higher than 20 mmol/d, suggests renal contribution to hypokalemia
- osmolality is useful to estimate the kidney’s concentrating ability
- FENa refers to the fractional excretion of Na⁺
  \[ \text{FE}_{\text{Na}} = \frac{\text{Urine} \ [\text{Na}^+] \times \text{Plasma} \ [\text{Cr}] }{\text{Plasma} \ [\text{Na}^+] \times \text{Urine} \ [\text{Cr}]} \]
  \[ \text{FE}_{\text{Na}} < 1\% \text{ suggests the pathology is pre-renal} \]

Examples of Common Urine Electrolyte Abnormalities
- high urine [Na⁺] (>40 mmol/L) in the setting of acute renal failure: indicates renal disease
- high urine [Na⁺] (>40 mmol/L) in the setting of hyponatremia: generally from causes such as diuretics, tubular disease (e.g. Bartter’s syndrome), SIADH
- additionally, urine pH is useful to grossly assess renal acidification
  - “low” pH (<5.5) in the presence of low serum pH is an appropriate renal response
  - a high pH in this setting might indicate a renal acidification defect (e.g. RTA)

Electrolyte Disorders
Sodium Homeostasis
- hyponatremia and hypernatremia are disorders of water balance
  - hyponatremia usually suggests too much water in the extracellular fluid relative to Na⁺
  - hypernatremia usually suggests too little water in the extracellular fluid relative to Na⁺
- solutes (such as Na⁺, K⁺, glucose) that cannot freely traverse the plasma membrane contribute to effective osmolality and induce transcellular shifts of water
  - water moves out of cells in response to increased ECF osmolality
  - water moves into cells in response to decreased ECF osmolality
- ECF volume is determined by Na⁺ content rather than concentration
  - Na⁺ deficiency leads to ECF volume contraction
  - Na⁺ excess leads to ECF volume expansion
- clinical signs and symptoms of hyponatremia and hypernatremia are secondary to cells (especially in the brain) shrinking (hypermotremia) or swelling (hyponatremia)

<table>
<thead>
<tr>
<th>Fluid Compartment</th>
<th>Hypovolemic</th>
<th>Hypervolemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JVP (Jugular Venous Pressure)</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthostatic drop</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Auscultation of heart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Auscultation of lungs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Normal to increased</td>
<td>Inspiratory crackles</td>
</tr>
<tr>
<td>Interstitial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin turgor</td>
<td>Decreased</td>
<td>Normal/increased</td>
</tr>
<tr>
<td>Edema (dependent)</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output</td>
<td>Decreased*</td>
<td>Variable</td>
</tr>
<tr>
<td>Body weight</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Hct, serum protein</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

*If there is a renal abnormality (e.g. osmotic diuresis), the urine output may be increased despite the presence of hypovolemia
Hyponatremia

- hyponatremia: serum $[Na^+] < 136$ mmol/L
- can be associated with hypo-osmolality (most common), iso-osmolality, or hyperosmolality

![Diagram of Approach to Hyponatremia]

### Signs and Symptoms
- depend on degree of hyponatremia and more importantly, velocity of progression from onset
- acute hyponatremia ($< 24-48$ h) more likely to be symptomatic
- chronic hyponatremia ($> 24-48$ h) less likely to be symptomatic due to adaptation
  - adaptation: normalization of brain volume through loss of cellular electrolytes (within hours) and organic osmolytes (within days)
  - adaptation is responsible for the risks associated with overly rapid correction
- neurologic symptoms predominate (secondary to cerebral edema): headache, nausea, malaise, lethargy, weakness, muscle cramps, anorexia, somnolence, disorientation, personality changes, depressed reflexes, decreased level of consciousness (LOC)

### Complications
- seizures, coma, respiratory arrest, permanent brain damage, brainstem herniation, death
- risk of brain cell shrinkage with rapid correction of hyponatremia
  - can develop osmotic demyelination of pontine and extrapontine neurons; may be irreversible (e.g. central pontine myelinolysis: cranial nerve palsies, quadriplegia, decreased LOC)

### Risk Factors for Osmotic Demyelination
- rise in serum $[Na^+]$ with correction $> 8$ mmol/L/d if chronic hyponatremia
- associated hypokalemia and/or malnutrition (i.e. low muscle mass)
- if patient with hyponatremia and hypovolemia is given large volume of isotonic fluid (ADH is stimulated by hypovolemia; when hypovolemia is corrected, the ADH level falls suddenly causing sudden brisk water diuresis, and therefore rapid rise in serum $Na^+$ level)
- patient with psychogenic polydipsia, deprived of water

### Investigations
- ECF volume status assessment
- serum electrolytes, glucose, Cr
- serum osmolality, urine osmolality
- urine $Na^+$ (urine $Na^+$ $< 10-20$ mmol/L suggests volume depletion as the cause of hyponatremia)
- assess for causes of SIADH (see Table 6)
- TSH, free T4, and cortisol levels
- consider CXR and possibly CT chest if suspect pulmonary cause of SIADH (e.g. small cell lung Ca)
- consider CT head if suspect CNS cause
Treatment of Hyponatremia

- general measures for all patients
  - water restriction to <1 L/d (unless hypovolemic give normal saline)
  - treat underlying cause
  - monitor serum Na+ frequently to ensure correction is not occurring too rapidly
  - monitor urine output frequently: high output of dilute urine is the first sign of dangerously rapid correction of hyponatremia

Table 5. Treatment of Acute and Chronic Hypoosmolar Hyponatremia

<table>
<thead>
<tr>
<th>Onset</th>
<th>Symptomatic</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (&lt;48 h)</td>
<td>Yes</td>
<td>Rapid correction (Hypertonic 3% saline)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Rapid correction only if marked drop in Na+</td>
</tr>
<tr>
<td>Chronic (&gt;48 h)</td>
<td>Yes</td>
<td>Slow correction (Hypertonic 3% saline)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Water restriction, NS, NaCl tablet</td>
</tr>
</tbody>
</table>

A. Definitely Acute (known to have developed over <24-48 h)

- commonly occurs in hospital (dilute IV fluid, post-operative increased ADH)
- less risk from rapid correction since adaptation has not fully occurred
- if symptomatic
  - correct rapidly with 3% NaCl 1-2 cc/kg/h up to serum [Na+] = 125-130 mmol/L
  - may need furosemide to address volume overload
- if asymptomatic, treatment depends on severity
  - if marked fall in plasma [Na+], treat as symptomatic

B. Chronic or Unknown

1. if severe symptoms (seizures or decreased LOC)
   - must partially correct acutely
   - aim for increase of Na+ by 1-2 mmol/L/h for 4-6 h
   - limit total rise to 8 mmol/L in 24 h
   - IV 3% NaCl at 1-2 cc/kg/h
   - may need furosemide
2. if asymptomatic
   - water restrict to <1 L/d fluid intake
   - consider IV 0.9% normal saline (NS) + furosemide (reduces urine osmolality, augments excretion of H₂O)
   - consider NaCl tablet or Oxocubes® as a source of Na+
3. refractory
   - furosemide and IV NS
   - demeclocyline 300-600 mg PO bid (antagonizes effect of ADH on collecting duct; avoid if cirrhosis or congestive heart failure as nephrotoxic in these settings)
   - extra osmoles – give oral urea (increases loss of water without Na+, 30-60 g/d)
   - slow rate of IV 3% NaCl (e.g. 10 cc/h = 120 mmol/d of sodium which will increase serum [Na+] by about 3 mmol/L/d)
4. always pay attention to patient's ECF volume status – if already volume-expanded, unlikely to give NaCl; if already volume-depleted, almost never appropriate to give furosemide

C. Options if overly rapid correction occurs

- give water (IV D5W)
- give ADH to stop water diuresis (DDAVP 1-2 µg IV)

Impact of IV Solution on Plasma Na+

- formula to estimate the change in serum Na+ caused by retention of 1 L of any infusate
  \[
  \text{TBW} = (\text{for men}) 0.6 \times \text{wt(kg)}; (\text{for women}) 0.5 \times \text{wt(kg)}
  \]
  \[
  \text{change in serum [Na+] = } \frac{\text{infusate [Na+] - serum [Na+]}}{\text{TBW} + 1 \text{ L}}
  \]
  \[
  \text{formula assumes there are no losses of water or electrolytes}
  \]

SYNDROME OF INAPPROPRIATE ANTI DIURETIC HORMONE SECRETION (SIADH)

1. urine that is inappropriately concentrated for the serum osmolality
2. high urine sodium (>20-40 mmol/L)
3. high FEₙₙₙ

Beware of Rapid Correction of Hyponatremia

- Inadvertent rapid correction of hyponatremia can easily occur
- e.g. patient with hyponatremia due to SIADH from nausea
- Anti-emetic given for relief of hyponatremia-induced nausea
- ADH quickly turned off in the absence of nausea, the kidneys rapidly excrete the excess free water, and the serum [Na+] rises rapidly
- Patient at risk of osmotic demyelination
- High output dilute urine (>100 cc/h, <100 mOsm/L) in the setting of hyponatremia is usually the first sign of dangerously rapid correction of serum sodium

Correction of Na+ in hyponatremia should not exceed 8 mmol/L/24 h unless definitely known to be <24-48 h duration. Frequent monitoring of serum Na+ and urine output is essential.

Concentration of Na+ in Common Infusates

- Na+ in 0.45% NaCl = 77 mmol/L
- Na+ in 0.9% NaCl = 154 mmol/L
- Na+ in 3% NaCl = 513 mmol/L
- Na+ in 5% NaCl = 855 mmol/L
- Na+ in Ringer's lactate = 130 mmol/L
- Na+ in D5W = 0
Table 6. Disorders Associated with SIADH

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Polymony</th>
<th>CNS</th>
<th>Drugs</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour</td>
<td>Pneumonia</td>
<td>Mass lesion</td>
<td>Antidepressants</td>
<td>Post-op state</td>
</tr>
<tr>
<td>Small cell Ca</td>
<td>Lungs</td>
<td>Enccephalitis</td>
<td>TCAs</td>
<td>Pain</td>
</tr>
<tr>
<td>Bronchogenic Ca</td>
<td>Acute respiratory failure</td>
<td>Subarachnoid hemorrhage</td>
<td>SSRIs</td>
<td>Severe nausea</td>
</tr>
<tr>
<td>Pancreatic AdenoCa</td>
<td>Positive pressure ventilation</td>
<td>Stroke</td>
<td>Antineoplastics</td>
<td>HIV</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td></td>
<td>Head trauma</td>
<td>Vincristine</td>
<td></td>
</tr>
<tr>
<td>Thymoma</td>
<td></td>
<td>Acute psychosis</td>
<td>Cytoxophosphamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute intermittent par Nyria</td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DDAVP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oxytocin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nicotine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Barbiturates</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chlorpropamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACE inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hyponatremia

- serum [Na⁺] < 135 mmol/L
- too little water relative to total body Na⁺; always a hyposmolar state
- usually due to net water loss, rarely due to hypertonic Na⁺ gain
- results from problems with water intake (access, thirst) and/or site of increased water loss (renal or extrarenal)
- less common than hyponatremia because patients are protected against hyponatremia by thirst and release of ADH

Signs and Symptoms
- with acute hyponatremia no time for adaptation, therefore more likely to be symptomatic
- adaptive response: cells import and generate new osmotically active particles to normalize size
- due to brain cell shrinkage: altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, seizures, coma, death
- ± polyuria, thirst, signs of hypovolemia

Complications
- increased risk of vascular rupture resulting in intracranial hemorrhage
- rapid correction may lead to cerebral edema due to ongoing brain hyposmolarity

Table 7. Treatment Hypovolemic and Hypervolemic Hyponatremia

<table>
<thead>
<tr>
<th>Volume Status</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>Give free water OR by NG tube</td>
</tr>
<tr>
<td></td>
<td>Give IV D5W, 0.45%NS, or 3.3% dextrose with 0.3% NaCl (“2/3 and 1/3”)</td>
</tr>
<tr>
<td>Hypervolemic</td>
<td>Diuresis or dialysis (D5W once fluid deficit)</td>
</tr>
</tbody>
</table>

Treatment of Hypovolemic Hyponatremia
- general measures for all patients
  - give free water (oral or IV)
  - treat underlying cause
  - monitor serum Na⁺ frequently to ensure correction is not occurring too rapidly
  - if evidence of hemodynamic instability, must first correct volume depletion with NS bolus
  - loss of water is often accompanied by loss of Na⁺ but a proportionately larger water loss
  - in patients with presumed normal total body Na⁺ content, use formula to calculate H₂O deficit
  (see sidebar)
  - replace free water deficit
  - encourage patient to drink pure water, as oral route is preferred for fluid administration
  - if unable to replace PO or NG, correct H₂O deficit with hypotonic IV solution
  - use formula (see Hyponatremia, NP9) to estimate expected change in serum Na⁺ with 1L infusate
  - aim to lower [Na⁺] by no more than 12 mmol/L in 24 h (0.5 mmol/L/h)
  - must also provide maintenance fluids and replace ongoing losses
  - rule of thumb: give 2 cc/kg/h of free water to correct serum [Na⁺] by about 0.5 mmol/L/h or 12 mmol/L/d

Correction of serum [Na⁺] in hyponatremia should not exceed 12 mmol/L/24 h.

Table 7. Treatment Hypovolemic and Hypervolemic Hyponatremia

<table>
<thead>
<tr>
<th>Volume Status</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>Give free water OR by NG tube</td>
</tr>
<tr>
<td></td>
<td>Give IV D5W, 0.45%NS, or 3.3% dextrose with 0.3% NaCl (“2/3 and 1/3”)</td>
</tr>
<tr>
<td>Hypervolemic</td>
<td>Diuresis or dialysis (D5W once fluid deficit)</td>
</tr>
</tbody>
</table>

Treatment of Hypervolemic Hyponatremia
- general measures as above
- hypervolemic hyponatremia: remove excess total body Na⁺ with diuresis or dialysis (if renal failure present), then replace water deficit using D5W

Correction of serum [Na⁺] in hyponatremia should not exceed 12 mmol/L/24 h.

1 L D5W approximately equals 1 L of free water
1 L 0.45% NS approximately equals 500 mL of free water
DIABETES INSIPIDUS (DI)
• collecting tubule is impermeable to water due to absence of ADH or impaired response to ADH
• central defect in release of ADH (central DI) or renal response to ADH (nephrogenic DI)

Etiology
• central DI: neurosurgery, granulomatous diseases, trauma, vascular events, and malignancy
• nephrogenic DI: lithium (most common), hypokalemia, hypercalcemia, and congenital

Diagnosis
• urine osmolality inappropriately low in patient with hypernatremia ($U_{\text{osm}} < 300 \text{ mOsm/kg}$)
• serum vasopressin concentration may be absent or low (central), or elevated (nephrogenic)
• dehydration test: $\text{H}_2\text{O}$ deprivation until loss of 3% of body weight or until urine osmolarity rises above plasma osmolarity; if fails to concentrate urine, most likely DI
• administer DDAVP (exogenous ADH) (10 µg intranasally or 2 µg SC or IV):
  • central DI: diagnosed if there is rise in urine osmolality, fall in urine volume
  • nephrogenic DI: exogenous ADH fails to concentrate urine as kidneys do not respond
  • treat with water (IV D5W or PO water), thiazides may help as well (reduced ECF volume stimulates proximal tubular reabsorption of sodium and water, leading to less delivery of glomerular filtrate to ADH sensitive parts of renal tubule, and therefore lower urine volume results)

Potassium Homeostasis
• approximately 98% of total body $K^+$ stores are intracellular
• normal serum $K^+$ ranges from 3.5-5.0 mEq/L
• in response to $K^+$ load, rapid removal from ECF is necessary to prevent life-threatening hyperkalemia
• insulin, catecholamines, and acid-base status influence $K^+$ movement into cells
• aldosterone has a minor effect
• potassium excretion is regulated at the distal nephron
  • $K^+$ excretion = urine flow rate $\times$ urine $[K^+]$

Factors which Increase Renal $K^+$ Loss
• hyperkalemia
• increased distal tubular urine flow rate and Na$^+$ delivery (thiazides and loop diuretics)
• increased aldosterone activates epithelial sodium channel (eNaC) in cortical collecting duct, causing Na$^+$ reabsorption and $K^+$ excretion
• metabolic alkalosis
• hypomagnesemia
• increased non-reabsorbable anions in tubule lumen: $\text{HCO}_3^-$, penicillin, salicylate

Hypokalemia
• serum $[K^+] < 3.5 \text{ mEq/L}$

Signs and Symptoms
• usually asymptomatic, particularly when mild (3.0-3.5 mmol/L)
• nausea, vomiting, fatigue, generalized weakness, myalgia, muscle cramps, and constipation
• if severe: arrhythmias, muscle necrosis, and rarely paralysis with eventual respiratory impairment
• arrhythmias occur at variable levels of $K^+$; more likely if digoxin use, hypomagnesemia, or CAD
• ECG changes are more predictive of clinical picture than serum $[K^+]$
  • U waves most important (low amplitude wave following a T wave)
  • flattened or inverted T waves
  • depressed ST segment
  • prolongation of Q-T interval
  • with severe hypokalemia: P-R prolongation, wide QRS, arrhythmias; increases risk of digitalis toxicity

Figure 5. ECG changes in hypokalemia
Approach to Hypokalemia
1. emergency measures: obtain ECG; if potentially life threatening, begin treatment immediately
2. rule out transcellular shifts of K⁺ as cause of hypokalemia
3. assess contribution of dietary K⁺ intake
4. spot urine K:Cr, should be less than 1 in setting of hypokalemia
   - if <1 consider GI loss
   - if >1 consider renal loss
5. consider 24-h K⁺ excretion
6. if renal K⁺ loss, check BP and acid-base status
7. may also assess plasma renin and aldosterone levels, serum [Mg²⁺]

Hyperkalemia
- serum [K⁺] > 5.0 mEq/L

Signs and Symptoms
- usually asymptomatic but may develop nausea, palpitations, muscle weakness, muscle stiffness, paresthesias, areflexia, ascending paralysis, and hypoventilation
- impaired renal ammoniagenesis and metabolic acidosis
- ECG changes and cardiotoxicity (do not correlate well with serum $[K^+]$)
  - peaked and narrow T waves
  - decreased amplitude and eventual loss of P waves
  - prolonged PR interval
  - widening of QRS and eventual merging with T wave (sine-wave pattern)
  - AV block
  - ventricular fibrillation, asystole

Figure 7. ECG changes in hyperkalemia

Table 8. Causes of Hyperkalemia

<table>
<thead>
<tr>
<th>Facetious</th>
<th>Increased Intake</th>
<th>Cellular Release</th>
<th>Decreased Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample hemolysis*</td>
<td>Diet</td>
<td>Intravascular hemolysis</td>
<td>Decreased GFR</td>
</tr>
<tr>
<td>Sample taken from vein where IV KCl is running</td>
<td>KCl tabs</td>
<td>Rhabdomyolysis</td>
<td>• Renal failure</td>
</tr>
<tr>
<td>Prolonged use of tourniquet</td>
<td>IV KCl</td>
<td>Insulin deficiency</td>
<td>• Low effective circulating volume</td>
</tr>
<tr>
<td>Leukocytosis (extreme)</td>
<td>Salt substitute</td>
<td>Hyperosmolar states (e.g. hyperglycemia)</td>
<td>• NSAIDs in renal insufficiency</td>
</tr>
<tr>
<td>Thrombocytosis (extreme)</td>
<td></td>
<td>Metabolic acidosis [except for keto-and lactic acidosis]</td>
<td>Normal GFR but hypoadosteronism (see Table 9)</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td>Tumour lysis syndrome Drugs</td>
<td></td>
</tr>
<tr>
<td>KCl tabs</td>
<td></td>
<td>• β-blockers</td>
<td></td>
</tr>
<tr>
<td>IV KCl</td>
<td></td>
<td>• Digitalis overdose [blocks Na+/K+ ATPase]</td>
<td></td>
</tr>
<tr>
<td>Salt substitute</td>
<td></td>
<td>• Succinylcholine</td>
<td></td>
</tr>
</tbody>
</table>

*Most common

Table 9. Causes of Hyperkalemia with Normal GFR

<table>
<thead>
<tr>
<th>Decreased Aldosterone Stimulus (low renin, low aldosterone)</th>
<th>Decreased Aldosterone Production (normal renin, low aldosterone)</th>
<th>Aldosterone Resistance (decreased tubular response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyporeninemic, hypoadosteronism</td>
<td>• Adrenal insufficiency of any cause (e.g. Addison’s disease, AIDS, metastatic cancer)</td>
<td>$K^+$-sparing diuretics</td>
</tr>
<tr>
<td>• Associated with DM2, NSAIDs, chronic interstitial nephritis, HIV</td>
<td>• ACE inhibitors</td>
<td>• Spironolactone</td>
</tr>
<tr>
<td>• Cyclosporine, tacrolimus</td>
<td>• Angiotensin II receptor blockers</td>
<td>• Amiloride</td>
</tr>
<tr>
<td>• Heparin</td>
<td>• Heparin</td>
<td>• Triamterene</td>
</tr>
<tr>
<td>• Congenital adrenal hyperplasia with 21-hydroxylase deficiency</td>
<td>• Tumour lysis syndrome Drugs</td>
<td>• Renal tubular disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other $K^+$-sparing drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pentamidine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Trimethoprim</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cyclosporine, tacrolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudohypoaldosteronism (rare inherited tubular disorders)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>K+-sparing diuretics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Spironolactone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Amiloride</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Triamterene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Renal tubular disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other $K^+$-sparing drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pentamidine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Trimethoprim</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cyclosporine, tacrolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudohypoaldosteronism (rare inherited tubular disorders)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$K^+$-sparing diuretics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Spironolactone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Amiloride</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Triamterene</td>
</tr>
</tbody>
</table>

Approach to Hyperkalemia
1. emergency measures: obtain ECG, if life threatening begin treatment immediately
2. rule out factitious hyperkalemia; repeat blood test
3. hold exogenous $K^+$ (PO and IV), and any $K^+$ retaining medications
4. assess potential causes of transcellular shift
5. estimate GFR (calculate CrCl using Cockcroft-Gault)

Treatment
- acute therapy is warranted if ECG changes are present, or if patient is symptomatic
- tailor therapy to severity of increase in $[K^+]$ and ECG changes
  - $[K^+] < 6.5$ and normal ECG
    - treat underlying cause, stop $K^+$ intake, increase the loss of $K^+$ via urine and/or GI tract (see below)
  - $[K^+]$ between 6.5 and 7.0, no ECG changes: add insulin to above regimen
  - $[K^+] > 7.0$ and/or ECG changes: first priority is to protect the heart, add calcium gluconate to above

1. Protect the Heart
- calcium gluconate 1-2 amps (10 mL of 10% solution) IV
- antagonizes cardiac toxicity of hyperkalemia, protects cardiac conduction system, no effect on serum $[K^+]$
- onset within minutes, lasts 30-60 min (N.B. May require repeat doses during treatment course of hyperkalemia)
2. Shift K⁺ into Cells
- regular insulin (Insulin R) 10-20 units IV, with 1-2 amp D50W (give D50W before insulin)
  - onset of action 15-30 min, lasts 1-2 h
  - monitor capillary blood glucose q1h because of risk of hypoglycemia
  - can repeat every 4-6 h
  - caution giving D50W before insulin if hyperkalemia is severe as it can cause a serious arrhythmia
- NaHCO₃ 1-3 ampules (given as 3 ampules of 7.5% or 8.4% NaHCO₃ in 1L D5W)
  - onset of action 15-30 min, transient effect, drives K⁺ into cells in exchange for H⁺
  - more effective if patient has metabolic acidosis
- β₂-agonist (Ventolin®) in nebulized form (dose = 2 cc or 10 mg inhaled) or 0.5 mg IV
  - onset of action 30-90 min, stimulates Na⁺/K⁺ ATPase
  - caution if patient has heart disease as tachycardia may result from this high dose of β₂-agonist

3. Enhance K⁺ Removal from Body
- via urine (preferred approach)
  - furosemide (≥40 mg IV), may need IV NS to avoid hypovolemia
  - fludrocortisone (synthetic mineralocorticoid) if suspect aldosterone deficiency
- via gastrointestinal tract
  - cation-exchange resins: calcium resonium or sodium polystyrene sulfonate (Kayexalate®)
    (increasingly falling out of favor due to risk of colonic necrosis; works by binding Na⁺ in exchange for K⁺, and controversial how much K⁺ is actually removed – main benefit may be the diarrhea it causes) plus lactulose PO to avoid constipation (must ensure that patient has a bowel movement after resin is administered)
  - Kayexalate® enemas with tap water (and definitely not with sorbitol as rectal sorbitol can cause colonic necrosis)
- dialysis (renal failure, life threatening hyperkalemia unresponsive to therapy)

---

**Acid-Base Disorders**

- acid-base homeostasis influences protein function and can critically affect tissue and organ function with consequences to cardiovascular, respiratory, metabolic and CNS function
- see Respirology R5 for more information on respiratory acidosis/alkalosis
- normal concentration of HCO₃⁻ = 24 mEq/L (range: 22-30)
- normal pCO₂ = 40 mmHg (range: 36-44)
- each acid base disorder has an appropriate compensation
  - inadequate compensation or overcompensation can indicate the presence of a second acid-base disorder
  - e.g. in metabolic acidosis, inadequate compensation means there is also respiratory acidosis; overcompensation means there is also respiratory alkalosis

---

**Figure 8. Approach to acid-base disorders**
Approach

1. Identify the primary disturbance (Figure 8)
   - respiratory acidosis, metabolic acidosis, respiratory alkalosis, metabolic alkalosis

2. Evaluate compensation. If compensation is not appropriate, a second acid-base disorder is likely present
   - compensation occurs in the same direction as the primary disturbance
     - metabolic acidosis: for every 1 mmol/L decrease in HCO₃⁻, pCO₂ should decrease by 1 mmHg
     - metabolic alkalosis: for every 10 mmol/L increase in HCO₃⁻, pCO₂ should increases by 5-7 mmHg
     - respiratory acidosis: for every 10 mmHg increase in pCO₂, HCO₃⁻ should increase by 1 (acute) or 3 (chronic) mmol/L
     - respiratory alkalosis: for every 10 mmHg decrease in pCO₂, HCO₃⁻ should decrease by 2 (acute) or 5 (chronic) mmol/L

3. Calculate Plasma Anion Gap (AG)
   - AG = [Na⁺] – ([HCO₃⁻] + [Cl⁻])
   - baseline = 12, range 10-14
   - AG can be altered by plasma albumin level: for each 10 g/L fall in albumin, lower baseline AG by 3 (e.g. if plasma [albumin]= 20 g/L, expect AG = 6)

4. If AG elevated, compare increase in AG with decrease in HCO₃⁻
   - if increase in AG < decrease in HCO₃⁻, there is a coexisting non-AG metabolic acidosis
   - if increase in AG > decrease HCO₃⁻, there is a coexisting metabolic alkalosis

5. Calculate Osmolar Gap
   - osmolar gap = measured osmolality – calculated osmolality
     - calculated osmolality = (2 x [Na⁺]) + [urea] + [glucose] (all units are in mmol/L)
     - normal osmolar gap <10
     - if AG >10, consider: methanol poisoning, ethylene glycol poisoning, OR another cause of acidosis plus ethanol ingestion

Metabolic Acidosis

Etiology and Pathophysiology

1. Increased Metabolic Acidosis (4 types)
   1. L-lactic acid
      - Type A: due to tissue hypoperfusion (any cause of shock), ischemic bowel, profound hypoxemia
      - Type B: non-hypoxic – multiple causes. The most common is failure to metabolize normally produced lactic acid in the liver due to severe liver disease. Other causes include: excessive alcohol intake, thiamine deficiency, metformin accumulation (metformin interferes with electron transport chain), certain antiretrovirals, large tumours, mitochondrial myopathies
      - D-lactic acid: rare syndrome characterized by episodes of encephalopathy and metabolic acidosis
        - occurs in the setting of carbohydrate malabsorption (e.g. short bowel syndrome), colonic bacteria that produce D-lactic acid, a carbohydrate load, diminished colonic motility and impaired D-lactate metabolism
   2. Ketoacidosis
      - diabetic
      - starvation
      - alcoholic (decreased carbohydrate intake and vomiting)
   3. Toxins
      - methanol (toxic to brain and retina, can cause blindness and brain death): metabolized to formic acid
      - ethylene glycol (toxic to brain and kidneys): metabolized to oxalic acid (envelope shaped crystals in urine) and multiple other acids
      - salicylate (e.g. ASA) overdose, causes acidosis due to salicylic acid, and also accumulation of lactic acid (salicylate at toxic levels impairs electron transport chain) and ketoacid (salicylate activates fat breakdown)
   4. Advanced renal failure (i.e. serum Cr increased at least 5x above baseline – a very low GFR causes anion retention, and renal disease leads to impaired bicarbonate production)
2. Normal AG Metabolic Acidosis (Hyperchloremic Acidosis)

- diarrhea (HCO3⁻ loss from GI tract)
- RTA (renal tubular acidosis)
  - type I RTA (distal): inability to secrete H⁺ in collecting duct, leading to impaired excretion of ammonium into urine
  - type II RTA (proximal): impaired HCO3⁻ reabsorption
  - type IV RTA: defective ammoniagenesis due to decreased aldosterone, hyporesponsiveness or hyperkalemia

- to help distinguish renal causes from non-renal causes, use Urine Anion Gap = (Na⁺ + K⁺) – Cl⁻

  - if <0, suggests adequate NH4⁺ in urine (likely nonrenal cause: diarrhea)
  - if >0, suggests problem is lack of NH4⁺ in urine (e.g. distal RTA)

Treatment of Metabolic Acidosis

- treat underlying cause
  - insulin for DKA
  - ethanol + dialysis for methanol or ethylene glycol poisoning
  - alkaline diuresis ± dialysis if ASA overdose
- correct coexisting disorders of K⁺ (see Hyperkalemia, NP12)
- consider treatment with exogenous alkali (e.g. NaHCO3) if:
  - severe reduction in [HCO3⁻] e.g. <8 mmol/L, especially with very low pH (<7)
  - no metabolizable anion (e.g. salicylate, formate, oxalate, sulphate, since these cannot be further metabolized)

- note: lactate and ketoacid anions can be metabolized to HCO3⁻
- risks of sodium bicarbonate therapy
  - hypokalemia: causes K⁺ to shift into cells (correct K⁺ deficit first)
  - ECF volume overload: Na⁺ load given with NaHCO3 can exacerbate pulmonary edema
  - overshoot alkalosis: abrupt, poorly tolerated transition from overly aggressive alkali loading, partial conversion of accumulated organic anions to HCO3⁻ and persisting hyperventilation

Metabolic Alkalosis

Pathophysiology

- requires initiating event and maintenance factors
- precipitating factors
  - GI (vomiting, NG tube) or renal loss of H⁺
  - exogenous alkali (oral or parenteral administration), milk alkali syndrome
  - diuretics (contraction alkalosis): decreased excretion of HCO3⁻, decreased ECF volume, therefore increased [HCO3⁻]
  - post-hypercapnia: renal compensation for respiratory acidosis is HCO3⁻ retention, rapid correction of respiratory disorder results in transient excess of HCO3⁻
- maintenance factors
  - volume depletion: increased proximal reabsorption of NaHCO3 and increased aldosterone
  - hyperaldosteronism (1º or 2º; distal Na⁺ reabsorption in exchange for K⁺ and H⁺ excretion leads to HCO3⁻ generation; aldosterone also promotes hypokalemia
  - hypokalemia: transtubular K⁺/H⁺ exchange, stimulus for ammoniagenesis and HCO3⁻ generation

Figure 9. Approach to metabolic alkalosis
Evaluate Compensation (identify co-existing respiratory acid-base disorders)
- hypoventilation (an upper limit to compensation exists – breathing cannot be stopped; see Figure 9)

Treatment
- treat underlying cause
- correct underlying disease, replenish K⁺ and Mg²⁺ deficits, and possibly K⁺-sparing diuretic
- saline sensitive metabolic alkalosis (most common)
  - treatment: volume repletion
  - ± carbonic anhydrase inhibitor (e.g. acetazolamide) to facilitate loss of HCO₃⁻ in urine
- saline resistant metabolic alkalosis
  - ECF volume normal or high
  - usually aldosterone or glucocorticoid excess
  - remove source of aldosterone or glucocorticoid ± spironolactone

Vascular Diseases of the Kidney

Large Vessel Disease

Table 10. Summary of Vascular Diseases

<table>
<thead>
<tr>
<th>Large Vessel Disease</th>
<th>Small Vessel Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute renal artery occlusion (infarct)</td>
<td>Hypertensive nephrosclerosis</td>
</tr>
<tr>
<td>Renal artery stenosis (ischemia)</td>
<td>Atheroembolic renal disease</td>
</tr>
<tr>
<td>Renal vein thrombosis</td>
<td>Thrombotic microangiopathy</td>
</tr>
<tr>
<td></td>
<td>Scleroderma</td>
</tr>
<tr>
<td></td>
<td>Calcineurin inhibitor nephropathy</td>
</tr>
</tbody>
</table>

1. RENAL INFARCTION (ACUTE RENAL ARTERY OCCLUSION)
- important, potentially reversible cause of renal failure

Etiology
- abdominal trauma, surgery, embolism, vasculitis, extra-renal compression, hypercoagulable state, aortic dissection
- kidney transplant more vulnerable

Signs and Symptoms (depend on presence of collateral circulation)
- fever, nausea, vomiting, flank pain
- leukocytosis, elevated AST, ALP
- marked elevated LDH (LDH >4 times upper limit of normal with minimal elevations in AST/ALT strongly suggestive)
- acute onset hypertension (activation of RAAS) or sudden worsening of long-standing hypertension
- renal dysfunction, i.e. elevated Cr (if bilateral, or solitary functioning kidney)

Investigations
- renal arteriography (more reliable but risk of atheroembolic renal disease)
- contrast-enhanced CT or magnetic resonance angiography, duplex Doppler studies (operator dependent)

Treatment
- prompt localization of occlusion and restoration of blood flow
- anticoagulation, thrombolysis, percutaneous angioplasty or clot extraction, surgical thrombectomy
- medical therapy in the long-term to reduce risk (e.g. antihypertensives)

2. ISCHEMIC RENAL DISEASE (RENAL ARTERY STENOSIS)
- chronic renal impairment secondary to hemodynamically significant renal artery stenosis or microvascular disease
- significant cause of ESRD: 15% in patients over 50 yr old (higher prevalence if significant vascular disease)
- usually associated with large vessel disease elsewhere
- causes of renal artery stenosis:
  - atherosclerotic plaques (90%): proximal 1/3 renal artery, usually males >55 yr, smokers
  - electrolytes, osmolality (gently rehydrate when needed, i.e. CHF)
  - fibromuscular dysplasia (10%): distal 2/3 renal artery or segmental branches, usually young females (typical onset <30 yr) (gently rehydrate when needed, i.e. CHF)
- when there is decreased renal blood flow (RBF), GFR is dependent on angiotensin II-induced efferent arteriolar constriction which raises the filtration fraction (GFR/RBF)
most common cause of secondary hypertension ("renovascular hypertension"), 1-2% of all hypertensive patients

- etiology
  - decreased renal perfusion of one or both kidneys leads to increased renin release and subsequent angiotensin production
  - increased angiotensin raises blood pressure in two ways
    1. causes generalized arteriolar constriction
    2. release of aldosterone increases Na⁺ and water retention
  - elevated blood pressure can in turn lead to further damage of kidneys and worsening HTN

Risk Factors
- >50 yr old
- smoking
- other atherosclerotic disease (dyslipidemia, diabetes, diffuse atherosclerosis)

Signs and Symptoms
- severe/refractory HTN and/or hypertensive crises, with negative family history of HTN
- asymmetric renal size
- epigastric or flank bruits
- spontaneous hypokalemia (renin activation in under-perfused kidney)
- increasing Cr with ACEI/ARB
- flash pulmonary edema with normal LV function

Investigations
- must establish presence of renal artery stenosis and prove it is responsible for renal dysfunction
- duplex Doppler U/S (kidney size, blood flow): good screening test (operator dependent)
- digital subtraction angiography (risk of contrast nephropathy)
- CT or MR angiography (effective noninvasive tests to establish presence of stenosis, for MR avoid gadolinium contrast if eGFR <30 mL/min because of risk of systemic dermal fibrosis)
- ACEI renography (i.e. captopril renal scan)
- renal arteriography (gold standard)

Treatment
- surgical: percutaneous angioplasty ± stent, surgical revascularization, occasionally surgical bypass
- medical: BP lowering medications (ACEI is drug of choice if unilateral renal artery disease but contraindicated if bilateral renal artery disease)
- little or no benefit if therapy is late i.e. kidney is already shrunken (however, therapy can be considered to save the opposite kidney if normal)

3. RENAL VEIN THROMBOSIS

Etiology
- hypercoagulable states (e.g. nephrotic syndrome, especially membranous), ECF volume depletion, extrinsic compression of renal vein, significant trauma, malignancy (e.g. RCC), sickle cell disease
- clinical presentation determined by rapidity of occlusion and formation of collateral circulation

Signs and Symptoms
- acute: nausea/vomiting, flank pain, hematuria, elevated plasma LDH, ± rise in Cr, sudden rise in proteinuria
- chronic: PE (typical first presenting symptom), increasing proteinuria and/or tubule dysfunction

Investigations
- renal venography (gold standard), CT or MR angiography, duplex Doppler U/S

Treatment
- thrombolytic therapy ± percutaneous thrombectomy for acute RVT
- anticoagulation with heparin then warfarin (1 yr or indefinitely, depending on risk factors)

Small Vessel Disease

1. HYPERTENSIVE NEPHROSCLEROSIS
- see Hypertension, NP30

2. ATHEROEMBOLIC RENAL DISEASE
- progressive renal insufficiency due to embolic obstruction of small and medium-sized renal vessels by atheromatous emboli
- spontaneous or after renal artery manipulation (surgery, angiography, percutaneous angioplasty)
anticoagulants and thrombolytics interfere with ulcerated plaque healing and can worsen disease

investigations:
- eosinophilia, eosinophiluria and hypocomplementia
- renal biopsy: needle-shaped cholesterol clefs (due to tissue-processing artifacts) with surrounding tissue reaction in small/medium-sized vessels

- treatment:
  - no effective treatment; avoid angiographic and surgical procedures in patients with diffuse atherosclerosis, medical therapy for concomitant cardiovascular disease
- prognosis: poor overall, at least a third will develop ESRD

3. THROMBOTIC MICROANGIOPATHY
- etiologies include the spectrum of TTP-HUS, DIC, severe preeclampsia
- renal involvement more common in HUS than TTP
- renal involvement characterized by fibrin thrombi in glomerular capillary loops ± arterioles
- treatment:
  - depends on cause
  - supportive therapy
  - TTP-HUS: plasma exchange, corticosteroids (splenectomy and rituximab if refractory)

- avoid platelet transfusions and ASA

4. CALCINEURIN INHIBITOR NEPHROPATHY
- cyclosporine and tacrolimus
- causes both acute reversible and chronic, largely irreversible nephrotoxicity
- major cause of kidney failure in other solid organ transplant (e.g. heart)
- acute: due to afferent and efferent glomerular capillary constriction leading to decreased GFR (tubular vacuolization)
- pre-renal azotemia
- treatment: calcium channel blockers or prostaglandin analogs, reduce dose of cyclosporine or switch to another immunosuppressive drug
- chronic: result of obliterative arteriolopathy causing interstitial nephritis and CRF ( striped fibrosis), less frequent now due to lower doses of calcineurin inhibitors

Glomerular Disease

Histological Terms of Glomerular Changes

Extent of Changes
- terms used to describe histologically the number of glomeruli affected in a given condition:
  - diffuse: majority of glomeruli abnormal (>50%)
  - focal: some glomeruli affected
- terms used to describe histologically the extent to which individual glomeruli are affected in a given condition:
  - global: entire glomerulus abnormal
  - segmental: only part of the glomerulus abnormal

Types of Changes
- proliferation: hyperplasia of one of the glomerular cell types (mesangial, endothelial, parietal epithelial), with or without inflammatory cell infiltration
- membranous changes: capillary wall thickening due to immune deposits or alterations in basement membrane
- crescent formation: parietal epithelial cell proliferation and mononuclear cell infiltration form crescent-shape in Bowman's space

Clinical Presentation of Glomerular Disease

Important Points to Remember
- glomerular disease has diverse clinical presentations including hematuria, proteinuria, hypertension, edema and decreased GFR
- each glomerulopathy presents as one of four major glomerular syndromes (these are NOT diagnoses):
  - acute nephritis
  - rapidly progressive glomerulonephritis
  - nephrotic
  - asymptomatic urinary abnormalities

Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation (ELITE-Symphony Trial) NEJM 2007;357:2562-2575

Study: Multicentre, randomized controlled trial with 12 mo follow-up.

Patients: 1645 patients scheduled to receive a single organ kidney transplant.

Intervention: Mycophenolate mofetil, corticosteroids and either: 1) standard dose cyclosporine; 2) low dose cyclosporine with daclizumab induction; 3) low dose tacrolimus with daclizumab induction; 4) low dose sirolimus with daclizumab induction.

Primary Outcome: Estimated Cockcroft-Gault GFR 12 mo after transplantation.

Results: the Tacrolimus arm showed significantly higher eGFR at 12 mo compared to all other arms (65.4 mL/min vs. 57.1, 59.4, 56.7 for arms 1, 2, 4 respectively; p<0.001). The Tacrolimus arm also showed decreased rates of acute rejection at 6 mo and 12 mo vs. all arms (p<0.001); improved allograft survival against standard dose cyclosporine and sirolimus; and decreased treatment failure against all other arms. There was no difference in overall patient survival between groups. Sirolimus has the highest incidence of lymphoedema, delayed wound healing, and serious adverse events; tacrolimus has significantly higher rates of new-onset diabetes; and cyclosporine regimes had the lowest incidence of diarrhea but highest opportunistic infection rates.

Conclusion: Immunosuppression regiments using low dose tacrolimus and daclizumab induction decrease nephrotoxicity while maintaining therapeutic immunosuppression in renal transplant patients.
glomerulopathies can be caused by a primary disease OR can occur secondary to a systemic disease
some glomerulopathy can present as more than one syndrome at different times

The Nephritic-Nephrotic Spectrum
glomerular pathology can present with a clinical picture anywhere on a spectrum with pure nephritic and pure nephrotic syndromes at the extremes (see Figure 10)

PROTEINURIA
hallmark of nephrotic syndromes
24-h urine protein: gold standard to assess degree of proteinuria
urea albumin-to-creatinine ratio (ACR): used to screen for diabetic nephropathy
microalbuminuria
defined as ACR ≥2.8 mg/mmol (female) or ≥2.0 mg/mmol (male)
marker of vascular endothelial function
an important prognostic marker for kidney disease in diabetes and hypertension (see Diabetes, NP28)
an elevated ACR ≥2.0 or 2.8 mg/mmol is the earliest sign of diabetic nephropathy
composition of normal total urine protein
upper limit of normal daily excretion of total protein is 150 mg/d
upper limit of normal daily excretion of albumin is 30 mg/d
the other normally excreted proteins are either filtered low molecular weight proteins (such as immunoglobulin, light chains or β-2 microglobulin) or proteins secreted by the tubular epithelial cells (e.g. Tamm-Horsfall mucoprotein)

PATHOLOGIC PROTEINURIA
Tubulointerstitial
Normally low molecular weight (LMW) proteins (<60 kD) pass through glomerular filtration barrier and are reabsorbed in proximal tubule
Proximal tubule dysfunction causes impaired reabsorption and increased excretion of LMW proteins
Albumin (>60 kD) is NOT affected. Thus, edema is partly secondary to salt and water retention
Glomerular
Normally, the filtration barrier is selectively permeable to SIZE (<60 kD) and CHARGE (repels negative particles). Thus, albumin is filtered to a very limited extent through a normal glomerulus
Damage to any component of the glomerular filtration barrier results in loss of albumin and other high MW proteins. Thus, edema is secondary to hypoalbuminemia (low oncotic pressure), but also due to enhanced renal tubular reabsorption of filtered sodium and water (possibly due to filtered proteins stimulating the action of cortical collecting duct epithelial sodium channel)
Overflow
Increased production of LMW proteins which exceeds the reabsorptive capacity of the proximal tubule
Plasma cell dyscrasias: produce light chain Ig (multiple myeloma, Waldenstrom’s macroglobulinemia, monoclonal gammopathy of undetermined significance)

Figure 10. Spectrum of glomerular pathology

Figure 11. Classification of proteinuria
Table 11. Daily Excretion of Protein

<table>
<thead>
<tr>
<th>Daily Excretion</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150 mg total protein (and &lt;30 mg albumin)</td>
<td>Normal</td>
</tr>
<tr>
<td>30-300 mg albumin</td>
<td>Microalbuminuria</td>
</tr>
<tr>
<td>&gt;3500 mg total protein /1.73m² BSA</td>
<td>Nephrotic range proteinuria</td>
</tr>
<tr>
<td>Variable amount of proteinuria</td>
<td>Can be seen with glomerular disease; i.e. mild glomerular disease can lead to a</td>
</tr>
<tr>
<td></td>
<td>mild degree of proteinuria, proliferative lesions may also be associated with some degree of proteinuria</td>
</tr>
<tr>
<td>Up to 2000 mg per d</td>
<td>Possible tubular disease because of failure to reabsorb filtered proteins</td>
</tr>
</tbody>
</table>

Investigations
- urine R&M, C&S, urea, Cr
- further workup (if degree of proteinuria >0.5 g/d, casts and/or hematuria)
  - CBC, glucose, electrolytes, 24-h urine protein and Cr
  - urine and serum immunoelectrophoresis, abdominal/pelvic ultrasound
  - serology: ANA, RF, p-ANCA (MPO), c-ANCA, (PR3) Hep B, Hep C, HIV, Anti-steptolysin-O (ASOT)
- indications for nephrology referral
  - generally, if there is ‘heavy’ proteinuria, should refer to nephrologist
  - heavy proteinuria is ACR >30 mg/mmol
- definitely if there is nephrotic syndrome: marked proteinuria >3.5 g/1.73m²/d with hypoalbuminemia (<35 g/L)

HEMURATURIA
- hallmark of nephritic syndromes
- presence of blood or RBCs in urine
  - gross hematuria: pink, red, or tea-coloured urine
    - in gross hematuria, the urine should be centrifuged:
      - if the sediment is red, true hematuria.
      - if the supernatant is red, test for heme with a dipstick
        - if supernatant +ve for heme: myoglobinuria or hemoglobinuria
        - if –ve for heme: pseudohematuria. Consider medications (e.g. rifampin), food dyes (e.g. beets) or metabolites (e.g. porphyria)
  - microscopic hematuria: normal coloured urine, >2-3 RBCs/HPF on microscopy

Red Urine/Hematuria

- –ve dipstick, no RBCs
  - Pseudohematuria
  - Food (beets), dyes, medication (rifampin)
- +ve dipstick, +ve RBCs (true hematuria)
  - Hemoglobin (hemolysis)
- +ve dipstick, no RBCs (malignant)
  - Myoglobin (rhabdomyolysis)
- Hematological
  - Coagulopathy, sickle cell
- Renal
  - Nephrolithiasis, trauma, tumour, prostatitis, urethritis
  - Dysuria or flank pain common
  - Isomorphic RBCs, no casts
  - Blood at beginning (urethritis) or end (prostate, bladder) of stream
- Primary
  - Membrane-proliferative GN
  - Post-streptococcal GN
  - Rapidly-progressive GN
  - Interstitial nephritis (acute and chronic)
  - Papillary necrosis
  - IgA nephropathy
- Secondary
  - Connective tissue diseases (CTD)
    - Wegener’s, Goodpasture’s, SLE, Chung-Strauss, HSP
  - Infection
    - Pyelonephritis
  - Hereditary
    - Alport’s, polycystic kidney disease (PCKD)

Investigations for Hematuria
- Hx and Px: family history of nephrolithiasis, hearing loss (Alport’s), cerebral aneurysm (PCKD), diet, recent URTI, irritative and obstructive urinary symptoms (UTI)
- urine R&M, C&S, urea, Cr
- renal ultrasound
- 24-h urine stone workup if there is a history of stone formation or if there is a stone noted on imaging: calcium, oxalate, citrate, magnesium, uric acid, cysteine
Glomerular Syndromes

1. Acute NEPHRITIC SYNDROME
   • a subset of nephritic syndrome in which the clinical course proceeds over days

Etiology
   • etiology can be divided into low and normal complement levels (Figure 13)
   • frequently immune-mediated, with Ig and C3 deposits found in GBM
   • outcome dependent on etiology

Clinical/Lab Features
   • proteinuria (but <3.5 g/1.73 m²/d), abrupt onset hematuria (microscopic or macroscopic, azotemia (increased Cr and urea), RBC casts and/or dysmorphic RBCs in urine, oliguria, HTN (due to salt and water retention), peripheral edema/puffy eyes, smoky urine (see sidebar)

2. RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (Rpgn)/CREASENTIC GLOMERULONEPHRITIS
   • a subset of nephritic syndrome in which the clinical course proceeds over weeks to months
   • clinical diagnosis, not histopathological
   • any cause of glomerulonephritis can present as RPGN (except minimal change disease)
   • additional etiologies seen only as RPGN: Goodpasture’s syndrome and granulomatosis with polyangiitis (previously called Wegener’s granulomatosis)

Clinical/Lab Features
   • fibrous crescents typically present on renal histopathology
   • RBC casts and/or dysmorphic RBCs in urine
   • classified by immunofluorescence staining (see Figure 13)
   • Type I: Anti-GBM mediated (15% of cases)
   • Type II: Immune Complex Mediated (24% of cases)
   • Type III: Non-Immune Mediated (60% of cases)
   • Type IV: Double Antibody Positive Disease (RPGN Type IV)
     • Has features of Type I and Type III
     • Double antibody positive

3. NEPHROTIC SYNDROME

Clinical/Lab Features
   • heavy proteinuria (>3.5 g/1.73 m²/d)
   • hypoalbuminemia
   • edema
• hyperlipidemia (elevated LDL cholesterol, lipuria (fatty casts and oval fat bodies on microscopy)
• hypercoagulable state (due to antithrombin III, Protein C and Protein S urinary losses)
• patient may report frothy urine
• glomerular pathology on renal biopsy:
  • minimal change disease (or minimal lesion disease or nil disease) – i.e. glomeruli appear normal on light microscopy
  • membranous glomerulopathy
  • focal segmental glomerulosclerosis (FSGS)
  • membranoproliferative glomerulonephritis
  • nodular glomerulosclerosis
• each can be idiopathic or secondary to a systemic disease or drug (sirolimus can cause proteinuria without obvious glomerular pathology)

Table 12. Nephrotic Syndrome

<table>
<thead>
<tr>
<th>Secondary Causes</th>
<th>Minimal Change</th>
<th>Membranous Glomerulopathy</th>
<th>Focal Segmental Glomerulosclerosis</th>
<th>Membranoproliferative Glomerulonephritis</th>
<th>Nodular Glomerulosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin's lymphoma</td>
<td>HBV, SLE, solid tumours (lung, breast, GI)</td>
<td>Reflux nephropathy, HIV, HBV, obesity</td>
<td>HCV, malaria, SLE, leukemia, lymphoma, infected shunt</td>
<td>Diabetes mellitus, amyloidosis</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Gold, pericillamine</td>
<td>Heroin</td>
<td>Steroids, ACEI/ARB for proteinuria</td>
<td>Steroids, ACEI/ARB for proteinuria</td>
<td></td>
</tr>
<tr>
<td>Therapy</td>
<td>Steroids</td>
<td>Reduce BP, ACEI, steroids</td>
<td>Aspirin®, ACEI, dipyridamole (Persantine®) – controversial</td>
<td>Treat underlying cause</td>
<td></td>
</tr>
</tbody>
</table>

4. ASYMPTOMATIC URINARY ABNORMALITIES

Clinical/Lab Features
• proteinuria (usually <2 g/d) and/or microscopic or macroscopic hematuria
  • isolated proteinuria
  • can be postural
  • occasionally can signal beginning of more serious GN (e.g. FSGS, IgA nephropathy, amyloid, diabetic nephropathy)
• hematuria with or without proteinuria
  • IgA nephropathy (Berger's disease): most common type of primary glomerular disease worldwide, usually presents after viral URTI
  • hereditary nephritis (Alport's disease): X-linked nephritis often associated with sensorineural hearing loss; proteinuria <2 g/d
  • thin basement membrane disease: usually autosomal dominant, without proteinuria; benign
  • benign recurrent hematuria: hematuria associated with febrile illness, exercise or immunization; a diagnosis of exclusion after other possibilities are ruled out

Investigations for Glomerular Disease

• blood work
  • first presentation: electrolytes, Cr, urea, albumin, fasting lipids
  • determining etiology: CBC, ESR, serum immunoelectrophoresis, anti-GBM, C3, C4, ANA, p-ANCA, c-ANCA, cryoglobulins, HBV and HCV serology, ASOT (anti-streptolysin titres), VDRL, HIV
• urinalysis: RBCs, WBCs, casts, protein
• 24-h urine for protein and CrCl
• radiology
  • CXR (infiltrates, CHF, pleural effusion)
  • renal ultrasound
• renal biopsy (percutaneous or open) if heavy proteinuria or renal insufficiency, and cause not obviously diabetic nephropathy
• urine immunoelectrophoresis
  • for Bence-Jones protein if proteinuria present

Secondary Causes of Glomerular Disease

Amyloidosis
• nodular deposits of amyloid in mesangium, usually related to amyloid light chain (AL)
• presents as nephrotic range proteinuria with progressive renal insufficiency
• can be primary or secondary
• secondary causes: multiple myeloma, TB, rheumatoid arthritis, malignancy
Systemic Lupus Erythematosus (SLE)
- lupus nephritis can present as any of the glomerular syndromes
- nephrotic syndrome with an active sediment is most common presentation
- glomerulonephritis caused by immune complex deposition in capillary loops and mesangium with resulting renal injury
- serum complement levels are usually low during periods of active renal disease
- children and males with SLE are more likely to develop nephritis

Henoch-Schönlein Purpura (HSP)
- seen more commonly in children
- purpura on buttocks and legs, abdominal pain, arthralgia and fever
- glomeruli show varying degrees of mesangial hypercellularity
- IgA and C3 staining of mesangium
- usually benign, self-limiting course, 10% progress to CKD

Goodpasture’s Disease
- antibodies against type IV collagen present in lungs and GBM
- more common in 3rd and 6th decades of life, men slightly more affected than females
- present with RPGN type I and hemoptysis/dyspnea
- pulmonary hemorrhage more common in smokers and males
- treat with plasma exchange, cyclophosphamide, prednisone

ANCA Associated Vasculitis [i.e. Granulomatosis with Polyangiitis and Microscopic Polyangiitis (formerly Wegener’s Granulomatosis)]
- pr3-ANCA (c-ANCA) most commonly associated with the clinical picture of granulomatosis with polyangiitis (previously called Wegener’s granulomatosis)
- mpo-ANCA (p-ANCA) most commonly associated with the clinical picture of microscopic polyangiitis
- renal involvement very common
- focal segmental necrotizing RPGN with no immune staining
- may be indolent or fulminant in progression
- vasculitis and granulomas rarely seen on renal biopsy
- treating typically involves cyclophosphamide and prednisone

Cryoglobulinemia
- cryoglobulins: monoclonal IgM and polyclonal IgG
- presents as purpura, fever, Raynaud’s phenomenon and arthralgias
- at least 50% of patients have hepatitis C
- renal disease seen in 40% of patients (isolated proteinuria/hematuria progressing to nephritic syndrome)
- most patients have decreased serum complement (C4 initially)
- treat hepatitis C, plasmapheresis
- overall prognosis: 75% renal recovery

Shunt Nephritis
- immune-complex mediated nephritis associated with chronically infected ventriculoatrial shunts inserted for treatment of hydrocephalus
- presents as acute nephritic syndrome with decreased serum complement
- nephrotic range proteinuria in 25% of patients

EULAR Recommendations for the Management of Systemic Lupus Erythematosus (SLE)  
Ann Rheum Dis 2008;67:195-205

Lupus Nephritis Recommendations

Monitoring: Renal biopsy, urine sediment analysis, proteinuria, and kidney function may have independent predictive ability for clinical outcome in therapy of lupus nephritis but need to be interpreted in conjunction. Changes in immunological tests (anti-dsDNA, serum C3) have only limited ability to predict the response to treatment and may be used only as supplemental information.

Treatment: In patients with proliferative lupus nephritis, glucocorticoids in combination with immunosuppressive agents are effective against progression to end-stage renal disease. Long-term efficacy has been demonstrated only for cyclophosphamide-based regimens, which are however associated with considerable adverse effects. In short- and medium-term trials, mycophenolate mofetil has demonstrated at least similar efficacy compared with pulse cyclophosphamide and a more favourable toxicity profile: failure to respond by 6 mo should evoke discussions for intensification of therapy. Flares following remission are not uncommon and require diligent follow-up.

End-stage renal disease: Dialysis and transplantation in SLE have long-term patient and graft-survival rates comparable with those observed in non-diabetic non-SLE patients, with transplantation being the method of choice.
HIV-Associated Renal Disease
1. direct nephrotoxic effect of HIV infection, antiretroviral drugs (e.g. tenofovir, indinavir) and other drugs used to treat HIV-associated infections
2. HIV-associated nephropathy (HIVAN)
   - histology: focal and segmental glomerular collapse with mesangial sclerosis, "collapsing FSGS"
   - tubular cystic dilatation and tubulo-reticular inclusions
   - clinical features: predominant in black men, heavy proteinuria, progressive renal insufficiency
   - prognosis: kidney failure within 1 yr without treatment
   - therapy: short-term, high dose steroids, ACEI, HAART

Infective Endocarditis
- manifests as mild form of acute nephritic syndrome with decreased serum complement
- S. aureus is most common infecting agent
- treatment with appropriate antibiotics usually resolves GN

Hepatitis B
- can result in membranous nephropathy, polycystic nodosa, membranoproliferative GN

Hepatitis C
- can result in membranoproliferative GN, cryoglobulinemia and membranous nephropathy

Syphilis
- can result in membranous GN

Tubulointerstitial Disease

Tubulointerstitial Nephritis (TIN)

Definition
- cellular infiltrates affecting primarily the renal interstitium and tubular cells
- functional tubule defects are disproportionately greater than the decrease in GFR
- classified as acute or chronic

Signs and Symptoms
- manifestation of disease depends on site of tubule affected
  1. proximal tubule (e.g. multiple myeloma, heavy metals)
     - Fanconi syndrome: decreased reabsorption in proximal tubule causing glycosuria, aminoaciduria, phosphaturia, hypouricemia
     - proximal RTA (decreased bicarbonate absorption): Type II RTA
  2. distal tubule (e.g. amyloidosis, obstruction)
     - distal RTA (Type I RTA), usually hypokalemic
     - Na+ -wasting nephropathy
     - ± hyperkalemia leading to type IV RTA (where reduced renal bicarbonate production is caused by hyperkalemia)
  3. collecting duct (e.g. sickle cell anemia, analgesics, PCKD)
     - urinary concentrating defect leading to mild nephrogenic DI
     - polyuria

1. ACUTE TUBULOINTERSTITIAL NEPHRITIS (TIN)

Definition
- rapid (days to weeks) decline in renal function
- 10-20% of all acute kidney injury

Etiology
- hypersensitivity
  1. antibiotics: β-lactams, sulfonamides, rifampin, quinolones, cephalosporins
  2. other: NSAIDs, allopurinol, furosemide, thiazides, triamterene, PPIs, acyclovir, phenytoin, cimetidine
- infections
  - bacterial pyelonephritis, Streptococcus, brucellosis, Legionella, CMV, EBV, toxoplasmosis, leptospirosis
- immune
  - SLE, acute allograft rejection, Sjögren's syndrome, sarcoidosis, mixed essential cryoglobulinemia
  - idiopathic

Pathophysiology
- acute inflammatory cell infiltrates into renal interstitium
Signs and Symptoms
- AKI
- if hypersensitivity reaction: may see fever, skin rash, arthralgia, serum sickness-like syndrome (particularly rifampin)
- if pyelonephritis: flank pain and costo-vertebral angle (CVA) tenderness
- other signs and symptoms based on underlying etiology
- hypertension and edema are uncommon

Investigations
- mild, non-nephrotic range proteinuria and microscopic hematuria
- urine
  - sterile pyuria, WBC casts, mild proteinuria, hematuria
  - eosinophils if allergic interstitial nephritis
- blood
  - increased Cr and urea
  - eosinophilia if drug reaction
  - normal AG metabolic acidosis (RTA)
  - hypophosphatemia, hyperkalemia, hyponatremia
- gallium scan often shows intense signal due to inflammatory infiltrate
- renal biopsy definitive

Treatment
- treat underlying cause (e.g. stop offending medications, antibiotics if pyelonephritis)
- corticosteroids (may be indicated in allergic or immune disease)

Prognosis
- recovery within 2 wk if underlying insult can be eliminated
- the longer the patient is in renal failure, the less likely full renal recovery becomes

2. CHRONIC TUBULOINTERSTITIAL NEPHRITIS

Definition
- characterized by slowly progressive renal failure, moderate proteinuria and signs of abnormal tubule function

Etiology
- persistence or progression of acute TIN
- urinary tract obstruction: most important cause of chronic TIN (tumours, stones, bladder outlet obstruction, vesicoureteral reflux)
- chronic pyelonephritis due to vesicoureteral reflex or UTI with obstruction
- nephrotoxins
  - exogenous
    - analgesics: NSAIDs (common), acetaminophen
    - cisplatin, lithium, cyclosporine, tacrolimus
    - heavy metals (lead, cadmium, copper), lithium, mercury, arsenic
    - radiation
    - chinese herbs
  - endogenous
    - hypercalcemia, hypokalemia, oxalate, uric acid nephropathy
- vascular disease: ischemic nephrosclerosis, atheroembolic disease
- malignancies: multiple myeloma, lymphoma
- granulomatous: TB, sarcoidosis, granulomatosis with polyangiitis
- immune: SLE, Sjögren’s, cryoglobulinemia, Goodpasture’s, amyloidosis, renal graft rejection, vasculitis
- hereditary: cystic diseases of the kidney, sickle cell disease
- others: radiation, Balkan (endemic) nephropathy

Pathophysiology
- fibrosis of interstitium with atrophy of tubules, mononuclear cell inflammation

Signs and Symptoms
- tubular dysfunction (e.g. acidosis, electrolyte disturbances)
- progressive renal failure with azotemia and uremia
- dependent on underlying etiology

Treatment
- stop offending agent or treat underlying disease
- supportive measures: correct metabolic disorders (Ca²⁺, PO₄³⁻) and anemia
Findings which Suggest Chronic Tubulointerstitial Nephritis
• normal AG metabolic acidosis
• hyperkalemia (out of proportion to degree of renal insufficiency)
• polyuria, nocturia
• partial or complete Fanconi’s syndrome
• urine: mild proteinuria, few RBCs and WBCs, no RBC casts
• ultrasound: shrunken kidneys with irregular contours

Acute Tubular Necrosis (ATN)

Definition
• abrupt and sustained decline in GFR within minutes to days after ischemic/nephrotoxic insult
• GFR reduced (this serves the purpose of avoiding life-threatening urinary loss of fluid and electrolytes from non-functioning tubules)

Etiology

Clinical Presentation
• typically presents as an abrupt rise in urea and Cr after a hypotensive episode, sepsis, rhabdomyolysis, or administration of nephrotoxic drug
• urine: high FE\textsubscript{Na}, pigmented-granular casts

Complications
• hyperkalemia: can occur rapidly and cause serious arrhythmias
• metabolic acidosis, decreased Ca\textsuperscript{2+}, increased PO\textsubscript{4}\textsuperscript{3-}, hypoalbuminemia

Investigations
• blood: CBC, electrolytes, Cr, urea, Ca\textsuperscript{2+}, PO\textsubscript{4}\textsuperscript{3-}, blood gases
• urine: R&M, electrolytes, osmolality, microscopic urinalysis searching for pigmented granular casts
• ECG
• abdominal ultrasound
• rule out other causes of pre-renal/post-renal azotemia and intrinsic AKI (GN, AIN, vasculitis)

Therapy
• largely supportive once underlying problem is corrected
• loop diuretics may help manage volume overload and reduce tubular metabolic requirements to allow for recovery (controversial)
• consider early dialysis in severe/rapidly progressing cases to prevent uremic syndrome

Prevention
• correct fluid balance before surgical procedures
• for patients with chronic renal disease requiring radiographic contrast:
  • give N-acetylcysteine 600-1200 mg PO bid day before and day of procedure, give intravenous isotonic fluid (either NaCl or NaHCO\textsubscript{3})
  • isotonic NaHCO\textsubscript{3} at 3 mL/kg over 1h before procedure and 1 mL/kg/h for 6 h post-procedure if not contraindicated
  • avoid giving diuretics, ACEI, cyclosporine on morning of procedure if possible
• use renal-adjusted doses of nephrotoxic drugs in patients with renal insufficiency

Meta-analysis: Effectiveness of Drugs for Preventing Contrast-induced Nephropathy

Ann Intern Med 2006;144:284-294

Purpose: To determine the effectiveness of N-acetylcysteine, theophylline, fenoldopam, dopamine, iloprost, statin, furosemide, or mannitol on preventing nephropathy.

Study Selection: Only randomized, controlled trials that used these agents in patients receiving iodinated contrast.

Results: In the 41 RCTs included N-acetylcysteine (RR = 0.62 [0.44-0.88]) and Theophylline (RR = 0.49 [0.23-0.98]) reduced the risk of nephropathy more than saline alone. Furosemide increased the risk (RR = 3.27 [1.48-7.26]). Other agents did not affect risk of nephropathy.

Conclusion: N-acetylcysteine is more renoprotective than hydration alone.
Analgesic Nephropathies

1. Vasomotor Acute Kidney Injury (AKI)
   - normally prostaglandins vasodilate afferent renal arteriole to maintain blood flow
   - NSAIDs act by blocking cyclooxygenase enzyme, thereby preventing prostaglandin synthesis and causing renal ischemia
   - more common in elderly, underlying renal disease, hypovolemia (diuretics, CHF, cirrhosis, nephrotic syndrome)
   - clinically: develop prerenal azotemia within a few days of starting NSAID
   - treatment: discontinue NSAID, dialysis rarely needed

2. Acute Interstitial Nephritis (AIN)
   - fenoprofen (60%), ibuprofen, naproxen
   - may be associated with minimal change glomerulopathy and nephrotic range proteinuria
   - resolves eventually with discontinuation of NSAID, may require interval dialysis
   - short term high dose steroids (1 mg/kg/d of prednisone) may hasten recovery

3. Chronic Interstitial Nephritis
   - due to excessive consumption of antipyretics (phenacetin or acetaminophen) in combination with NSAIDs
   - seen in patients who also have emotional stress, psychiatric symptoms and GI disturbance
   - papillary necrosis
     - gross hematuria, flank pain, declining renal function
     - calyceal filling defect seen with IVP – “ring sign”
   - increased risk of transitional cell carcinoma of renal pelvis
   - good prognosis if discontinue analgesics

4. Acute Tubular Necrosis (ATN)
   - can be caused by acetaminophen
     - incidence of renal dysfunction is related to the severity of acetaminophen ingestion
   - vascular endothelial damage can also occur
   - both direct toxicity and ischemia contribute to the tubular damage
   - renal function spontaneously returns to baseline within 1-4 wk
   - dialysis may be required during the acute episode of ingestion

5. Other Effects of NSAIDs
   - sodium retention (2° to reduced GFR)
   - hyperkalemia, HTN (2° to hyporeninemic hypoaldosteronism)
   - excess water retention (due to elimination of ADH – antagonistic effect of prostaglandins)

Systemic Disease with Renal Manifestation

Diabetes

- diabetic nephropathy: presence of microalbuminuria or overt nephropathy (i.e. macroalbuminuria) in patients with DM who lack indicators of other renal diseases
- most common cause of end-stage renal failure in North America
- 35-50% of patients with Type 1 DM will develop nephropathy, unknown percentage of Type 2
- at diagnosis up to 30% of patients with Type 2 DM have albuminuria (75% microalbuminuria, 25% overt nephropathy)
- microalbuminuria is a risk factor for progression to overt nephropathy and cardiovascular disease
- once macroalbuminuria is established, renal function declines, 50% patients reach ESRD within 7-10 yr
- associated with HTN and diabetic retinopathy (especially Type 1 DM) and/or neuropathy (especially Type 2 DM)
- indication of possible nondiabetic cause of renal disease in patients with DM:
  - rising Cr with little/no proteinuria
  - lack of retinopathy or neuropathy (microvascular complications)
  - persistent hematuria (microscopic or macroscopic)
  - signs or symptoms of systemic disease
  - inappropriate time course; rapidly rising Cr, renal disease in a patient with short duration of DM
  - family history of nondiabetic renal disease (e.g. PCKD, Alport’s)

DM is one of the causes of ESRD that does not result in small kidneys at presentation of ESRD. The others are amyloidosis, HIV nephropathy, PCKD and multiple myeloma.

Abnormal Urine ACR Values from 2008 Canadian Diabetes Association CPG
>2.0 mg/mmol in males
>2.8 mg/mmol in females

ACEI can cause hyperkalemia. Therefore, be sure to watch serum K⁺, especially if patient has DM and renal insufficiency.
DIABETIC RENAL COMPLICATIONS

1. Progressive Glomerulosclerosis
   - classic diabetic glomerular lesion: Kimmelstiel-Wilson nodular glomerulosclerosis (15-20%)
   - more common lesion is diffuse glomerulosclerosis with a uniform increase in mesangial matrix

Table 13. Stages of Diabetic Progressive Glomerulosclerosis

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ GFR (120-150%) - compensatory hyperfiltration</td>
<td>Detectable microalbuminuria (0-300 mg/24 h)</td>
<td>Macroalbuminuria (&gt;300 mg/24 h)</td>
<td>↑ proteinuria (&gt;500 mg/24 h)</td>
</tr>
<tr>
<td>↓ slightly increased mesangial matrix</td>
<td>Albumin-Creatinine ratio (ACR) 2.0-20 mg/mmol in men (18-180 mg/dL)</td>
<td>ACR in men &gt;20 mg/mmol, (&gt;180 mg/dL)</td>
<td>↓ GFR</td>
</tr>
<tr>
<td></td>
<td>ACR in women &gt;28 mg/mmol (&gt;250 mg/dL)</td>
<td>Proteinuria (+ve urine dipstick)</td>
<td>&lt;20% glomerular filtration surface area present</td>
</tr>
<tr>
<td></td>
<td>↑ mesangial matrix</td>
<td>Normal GFR</td>
<td>Sclerosis glomeruli</td>
</tr>
</tbody>
</table>

2. Accelerated Atherosclerosis
   - common finding
   - decreased GFR
   - may increase Angiotensin II production resulting in increased BP
   - increased risk of ATN secondary to contrast media

3. Autonomic Neuropathy
   - affects bladder leading to functional obstruction and urinary retention
   - residual urine promotes infection
   - obstructive nephropathy

4. Papillary Necrosis
   - Type 1 DM susceptible to ischemic necrosis of medullary papilla
   - sloughed papillae may obstruct ureter
   - can present as renal colic or with obstructive features ± hydronephrosis

2013 Canadian Diabetics Association Clinical Practice Guidelines on Chronic Kidney Disease in Diabetest

- screen for microalbuminuria with a random urine test for albumin to Cr ratio (ACR) and eGFR with a serum creatinine (using MRDR equation)
  - Type 1 DM: annually In post-pubertal individuals after 5 yr of diagnosis
  - Type 2 DM: at diagnosis, then annually
  - If eGFR >60 mL/min or ACR <2.0 mg/mmol: there is no CKD, re-screen in 1 yr
  - If urine ACR >20.0 mg/mmol: diagnose CKD.
  - If ACR <20.0 mg/mmol but >2.0 mg/mmol: order serum Cr for eGFR in 3 mo and 2 repeats of random urine ACRs over the next 3 mo. At 3 mo: If eGFR <60 mL/min or if >2/3 ACRs are >2.0 mg/mmol, diagnose CKD
  - if CKD diagnosed, ordered urine R-M and dipstick, if negative then diagnose CKD in Diabetes
  - with CKD in Diabetes: urine ACR and serum Cr (for eGFR) every 6 mo
  - delay screening if transient cause of albuminuria or low eGFR
  - evaluate for other causes of proteinuria, rule out nondiabetic renal disease
  - avoid unnecessary potential nephrotoxins (NSAIDs, aminoglycosides, dye studies)

Priorities in the Management of Patients with DM

1. vascular protection for all patients with diabetes
   - ACEI, antiplatelet therapy (as indicated)
   - BP control, glycemic control, lifestyle modification, lipid control

2. optimization of BP in patients who are hypertensive
   - treat according to hypertension guidelines

3. renal protection for DM patients with nephropathy (even in absence of HTN)
   - Type 1 DM: ACEI
   - Type 2 DM: CrCl >60 mL/min: ACEI or ARB – CrCl <60 mL/min: ARB
   - 2nd line agents: nondihydropyridine calcium channel blockers (diltiazem, verapamil)
   - ACEI and ARB can be safely used together if needed for control of significant proteinuria (monitor for hyperkalemia and acute rise in Cr)
   - check serum Cr and K⁺ levels within 1 wk of initiating ACEI or ARB and at time of acute illness
   - serum Cr can safely be allowed to rise up to 30% with initiation of ACEI or ARB, usually stabilizes after 2-4 wk, monitor for significant worsening of renal function or hyperkalemia
   - if >30% rise in serum Cr or hyperkalemia, discontinue medication and consider 2nd line agent
   - consider holding ACEI, ARB and/or diuretic with acute illness and in women before becoming pregnant
   - consider referral to nephrologist if ACR >60 mg/mmol, eGFR <30 mL/min, progressive kidney function loss, unable to achieve BP targets or unable to stay on ACEI or ARB

Results: The number of outcome events was similar for telmisartan (n=1147) and ramipril (1150); HR 1.00, CI 0.92-1.09, but was increased with combination therapy (1233; HR 1.09, 1.01-1.18, p=0.037). The need for dialysis or doubling of serum Cr increased more slowly in the telmisartan group versus placebo or amlodipine. The difference in absolute mortality or secondary end point was not significant. Conclusion: Telmisartan conferred significant renoprotective benefits in patients with type 2 diabetes and nephropathy, independent of blood pressure lowering effects.
Scleroderma

- 50% of scleroderma patients have renal involvement (mild proteinuria, high Cr, HTN)
- histology: media thickened, "onion skin" hypertrophy of small renal arteries, fibrinoid necrosis of afferent arterioles and glomeruli
- 10-15% scleroderma patients have a "scleroderma renal crisis" (occurs in first few years of disease): malignant HTN, ARF, microangiopathy, volume overload, visual changes, HTN encephalopathy
- renal involvement usually occurs early in the course of illness
- treatment: BP control with ACEI slows progression of renal disease

Multiple Myeloma

- see Hematology, H47
- malignant proliferation of plasma cells in the bone marrow with the production of immunoglobulins
- patients may present with severe bone disease and renal failure
- light chains are filtered at the glomerulus and appear as Bence-Jones proteins in the urine (monoclonal light chains)
- kidney damage can occur by several mechanisms:
  - hypercalcemia
  - light chain cast nephropathy (LCCN, see below) or "myeloma kidney"
  - hyperuricemia
  - infection
  - secondary amyloidosis
  - monoclonal Ig deposition disease (MIDD)
  - diffuse tubular obstruction
- LCCN
  - large tubular casts in urine sediment (light chains + Tamm-Horsfall protein)
  - proteinuria and renal insufficiency, can progress rapidly to kidney failure
- MIDD
  - deposits of monoclonal Ig in kidney, liver, heart and other organs
  - mostly light chains (85-90%)
  - causes nodular glomerulosclerosis (similar to diabetic nephropathy)
- lab features: increased BUN, increased Cr, urine protein immunoelectrophoresis positive for Bence-Jones protein (not detected on urine dipstick)
- poor candidates for kidney transplantation

Malignancy

- cancer can have many different renal manifestations
- kidney transplantation cannot be performed unless malignancy is cured
  - solid tumours: mild proteinuria or membranous GN
  - lymphoma: minimal change GN (Hodgkin's) or membranous GN (non-Hodgkin's)
  - renal cell carcinoma
  - tumour lysis syndrome: hyperuricemia, diffuse tubular obstruction
  - chemotherapy (especially cisplatin): ATN or chronic TIN
  - pelvic tumours/mets: post-renal failure secondary to obstruction
  - 2a amyloidosis
  - radiotherapy (radiation nephritis)

Hypertension (HTN)

- HTN occurs in about 20% of population
- etiology classified as primary ("essential"); makes up 90% of cases) or secondary
- primary: hypertension due to other factors that cause renal disease (hypertensive nephrosclerosis) or worsen pre-existing renal disease
- secondary: diseases of renal parenchyma or renal vasculature that cause hypertension
### Hypertensive Nephrosclerosis

<table>
<thead>
<tr>
<th></th>
<th>Chronic Nephrosclerosis</th>
<th>Malignant Nephrosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td>Slow vascular sclerosis with ischemic changes affecting intralobular and afferent arterioles</td>
<td>Fibrinoid necrosis of arterioles, disruption of vascular endothelium</td>
</tr>
<tr>
<td><strong>Clinical Picture</strong></td>
<td>African American, underlying chronic kidney disease, chronic hypertensive disease</td>
<td>Acute elevation in BP (dBP &gt; 120 mmHg), HTN encephalopathy</td>
</tr>
<tr>
<td><strong>Urineysis</strong></td>
<td>Mild proteinuria, normal urine sediment</td>
<td>Proteinuria and hematuria (RBC casts)</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>Blood pressure control, (target &lt;140/90) with frequent follow-up</td>
<td>Lower dBP to 100-110 mmHg within 6-24 h</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Can progress to renal failure despite patient adherence</td>
<td>Lower survival if renal insufficiency develops</td>
</tr>
</tbody>
</table>

### Renovascular Hypertension

- see *Vascular Diseases of the Kidney, NP17*

### Renal Parenchymal Hypertension

- HTN secondary to GN, AIN, diabetic nephropathy, or any other chronic renal disease
- mechanism of HTN not fully understood but may include
  - excess RAAS activation due to inflammation and fibrosis in multiple small intra-renal vessels
  - production of unknown vasopressors, lack of production of unknown vasodilators, or lack of clearance of endogenous vasopressor
  - ineffective sodium excretion with fluid overload

**Investigations**

- as well as investigations for renovascular HTN, additional tests may include
  - 24-h urinary estimations of Cr clearance and protein excretion
  - imaging (U/S, CT)
  - serology for collagen-vascular disease
  - renal biopsy

**Treatment**

- most chronic renal disease is irreversible, but treatment of HTN can slow the progression of renal insufficiency
- control ECF volume: Na+ restriction (88 mmol/d intake), diuretic, dialysis with end-stage disease
- ACEI or ARB may provide added benefit (monitor K+ and Cr) if there is significant proteinuria (>300 mg/d)

### Cystic Diseases of the Kidney

- characterized by epithelium-lined cavities filled with fluid or semisolid debris within the kidneys
- includes: simple cysts (present in 50% of population over 50), medullary cystic kidney, medullary sponge kidney, polycystic kidney disease (autosomal dominant and recessive) and acquired cystic kidney disease (in chronic hemodialysis patients)

### Adult Polycystic Kidney Disease

- autosomal dominant; at least 2 genes: PKD1 (chr 16p) and PKD2 (chr 4q)
- PKD1 (1:400), PKD2 (1:1000) accounts for about 10% of cases of renal failure
- patients generally heterozygous for mutant polycystin gene but accumulate a series of second 'somatic hits' precipitating the condition
- PKD1 encodes a protein that is responsible for cell-cell and cell-matrix interaction and sensing fluid flow by associating with cilia
- PKD2 encodes a protein that is a Ca2+ permeable nonselective cation channel that associates with cilia and is thought to control intracellular Ca2+ in response to flow
- defect leads to abnormal proliferation and apoptosis of tubular epithelial cells leading to cyst growth
- extrarenal manifestations: most common; multiple asymptomatic hepatic cysts (33%), cerebral aneurysm (10%), diverticulosis and mitral valve prolapse (25%)?
- polycystic liver disease rarely causes liver failure
- less common: cysts in pancreas, spleen, thyroid, ovary, seminal vesicles, and aorta
Signs and Symptoms
- often asymptomatic; discovered incidentally on imaging or by screening those with FHx
- acute abdominal flank pain/dull lumbar back pain
- hematuria (microscopic frequently initial sign, gross)
- nocturia (urinary concentrating defect)
- rarely extra-renal presentation (e.g. ruptured berry aneurysm, diverticulitis)
- HTN (increased renin due to focal compression of intrarenal arteries by cysts) (60-75%)
- ± palpable kidneys

Common Complications
- urinary tract and cyst infections, HTN, CRF, nephrolithiasis (5-15%), flank and chronic back pain

Clinical Course
- polycystic changes are always bilateral and can present at any age
- clinical manifestations rare before age 20-25
- kidneys are normal at birth but may enlarge to 10 times normal size
- variable progression to renal functional impairment (ESRD in up to 50% by age 60)

Investigations
- radiographic diagnosis: best accomplished by renal U/S (enlarged kidneys, multiple cysts throughout renal parenchyma, increased cortical thickness, splaying of renal calyces)
- CT abdo with contrast (for equivocal cases, occasionally reveals more cystic involvement)
- gene linkage analysis for PKD1 for asymptomatic carriers
- Cr, BUN, urine R&M (to assess for hematuria)

Treatment
- goal: to preserve renal function by prevention and treatment of complications
- educate patient and family about disease, its manifestations and inheritance pattern
- genetic counselling: transmission rate 50% from affected parent
- prevention and early treatment of urinary tract and cyst infections (avoid instrumentation of GU tract)
- TMP/SMX, ciprofloxacin: able to penetrate cyst walls, achieve therapeutic levels
- adequate hydration to prevent stone formation
- avoid contact sports due to greater risk of injury to enlarged kidneys
- screen for cerebral aneurysms if family history of aneurysmal hemorrhages
- monitor blood pressure and treat hypertension with ACEI
- dialysis or transplant for ESRD (disease does not recur in transplanted kidney)
- may require nephrectomy to create room for renal transplant

Medullary Sponge Kidney
- common, autosomal dominant, usually diagnosed in 4th-5th decades
- multiple cystic dilatations in the collecting ducts of the medulla
- renal stones, hematuria and recurrent UTIs are common features
- an estimated 10% of patients who present with renal stones have medullary sponge kidney
- nephrocalcinosis on abdominal x-ray in 50% patients, often detect asymptomatic patients incidentally
- diagnosis: contrast filled medullary cysts on IVP, characteristic radial pattern (“bouquet of flowers”), “swiss cheese” appearance on morphology
- treat UTIs and stone formation as indicated
- does not result in renal failure

Autosomal Recessive Polycystic Kidney Disease
- 1:20,000 incidence
- prenatal diagnosis by enlarged kidneys
- perinatal death from respiratory failure
- patients who survive perinatal period develop CHF, HTN, chronic kidney disease
- treated with kidney and/or liver transplant
**Acute Kidney Injury (AKI)**

**Definition**
- abrupt decline in renal function leading to increased nitrogenous waste products normally excreted by the kidney
- formerly known as Acute Renal Failure (ARF)

**Clinical Features**
- azotemia (increased BUN, Cr)
- abnormal urine volume (anuria, oliguria, polyuria)

---

**Approach to AKI**

**Investigations**
- blood: CBC, electrolytes, Cr, urea (think prerenal if increase in urea is relatively greater than increase in Cr), Ca\(^{2+}\), PO\(_4\)^{3-}
- urine volume, C&S, R&M: sediment, casts, crystals
- urinary indices: electrolytes, osmolality
- Foley catheterization (rule out bladder outlet obstruction)
- fluid challenge (i.e. fluid bolus to rule out most prerenal causes)
- imaging: abdo U/S (assess kidney size, hydronephrosis, post-renal obstruction)
- indications for renal biopsy
  - diagnosis is not certain
  - prerenal azotemia or ATN is unlikely
  - oliguria persists >4 wk

**Treatment**
1. preliminary measures
   - pre-renal
     - correct prerenal factors: optimize volume status and cardiac performance using fluids that will stay in the plasma subcompartment (NS, albumin, blood/plasma), hold ACEI/ARB (gently rehydrate when needed, i.e. CHF)
   - renal
     - address reversible renal causes: d/c nephrotoxic drugs, treat infection, and optimize electrolytes
   - post-renal
     - consider obstruction: structural (stones, strictures) vs. functional (neuropathy)
     - treat with Foley catheter, indwelling bladder catheter, nephrostomy, stenting
2. treat complications
   - fluid overload
   - NaCl restriction
   - high dose loop diuretics
   - hyperkalemia (refer to Approach to Hyperkalemia, NP13)

---

**Figure 17. Approach to acute kidney injury**

**Table: Differentiating Pre-renal from ATN**

<table>
<thead>
<tr>
<th>Pre-renal</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Na(^+)</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Urine Na(^+)/Cr</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Fella</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

---

**Clues to Pre-Renal Etiology**
- Clinical: Decreased BP, increased HR, and orthostatic HR and BP changes
- Increased (urea) >> Increased (Cr)
- Urine Na\(^+\) <10-20 mmol/L
- Urine osmolality >500 mOsm/kg
- Fractional excretion of Na\(^+\) <1%

**Clues to Renal Etiology**
- Appropriate clinical context
- Urinalysis positive for casts: Pigmented granular – ATN, WBC – AIN, RBC – GN

**Clues to Post-Renal Etiology**
- Known solitary kidney
- Older man
- Recent retroperitoneal surgery
- Anuria
- Palpable bladder
- Ultrasound shows hydronephrosis

**Drugs Implicated in Pre-Renal Azotemia**
- Anti-hypertensives
- Diuretics
- NSAIDs
- ACEI/ARBs
**Chronic Kidney Disease (CKD)**

**Definition**
- progressive and irreversible loss of kidney function
- abnormal markers (Cr, urea)
  - GFR <60 mL/min for >3 mo or
  - kidney pathology seen on biopsy or
  - decreased renal size on U/S (kidneys <9 cm)
- clinical features of chronic kidney disease
  - volume overload and hypertension
  - electrolyte and acid-base balance disorders (e.g. metabolic acidosis)
  - uremia

**Table 15. Stages of Chronic Kidney Disease (KDIGO, 2013)**

<table>
<thead>
<tr>
<th>GFR categories (mL/min/1.73m²)</th>
<th>Persistent Albuminuria Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A1</td>
</tr>
<tr>
<td>G1 ≥90</td>
<td>1 if CKD</td>
</tr>
<tr>
<td>G2 60-89</td>
<td>1 if CKD</td>
</tr>
<tr>
<td>G3a 45-59</td>
<td>1</td>
</tr>
<tr>
<td>G3b 30-44</td>
<td>2</td>
</tr>
<tr>
<td>G4 15-29</td>
<td>3</td>
</tr>
<tr>
<td>G5 &lt;15 (kidney failure)</td>
<td>4+</td>
</tr>
</tbody>
</table>

**Prognosis**
- high morbidity and mortality in patients with sustained AKI and multi-organ failure

**Management of Chronic Kidney Disease**

- **diet**
  - protein restriction with adequate caloric intake limits endogenous protein catabolism
  - K⁺ restriction (40 mmol/d)
  - Na⁺ and water restriction
  - PO₄³⁻ restriction (1 g/d)
  - avoid extra-dietary Mg²⁺ (i.e. antacids)
- **medical**
  - treatment of secondary hyperparathyroidism
  - calcium supplements (e.g. TUMS®) treats hypocalcemia when given between meals and binds phosphate when given with meals
  - consider calcitriol (1,25-dihydroxy-vitamin D) if hypocalcemic
  - sevelamer (phosphate binder) if both hypercalcemic and hyperphosphatemic
  - vitamin D analogues are being introduced in the near future
  - cinacalcet for hyperparathyroidism (sensitizes parathyroid to Ca²⁺, decreasing PTH)
  - sodium bicarbonate for metabolic acidosis
  - erythropoietin injections (Hct <30%) for anemia; target Hct 33-36%
  - ACEI for hypertension (target 130/80 or less), loop diuretics when GFR <25 mL/min
  - statins for dyslipidemia
- adjust dosages for renally excreted medications (avoid nephrotoxic medications)
- dialysis (hemodialysis, peritoneal dialysis)
- renal transplantation

**Incidence of Etiologies of Chronic Kidney Disease (CKD)**

- Diabetes: 42.9%
- Hypertension: 26.4%
- Glomerulonephritis: 9.9%
- Other/Unknown: 7.7%
- Interstitial nephritis/Pyelonephritis: 4.0%
- Cystic/Hereditary/Congenital: 3.1%
- Secondary GN/Vasculitis: 2.4%

**Management of Complications of CKD**

- **NEPHRON**
  - N = Low-nitrogen diet
  - E = Electrolytes: monitor K⁺
  - P = pH: metabolic acidosis
  - H = Hypertension
  - R = RBCs: manage anemia with erythropoietin
  - O = Osteodystrophy: give calcium between meals (to increase Ca²⁺) and calcium with meals (to bind and decrease PO₄³⁻)
  - N = Nephrotoxins: avoid nephrotoxic drugs (ASA, gentamicin) and adjust doses of renally excreted medications

**Renin Angiotensin System Blockade and Cardiovascular Outcomes in Patients with Chronic Kidney Disease and Proteinuria: A Meta-analysis**

- Am Heart J 2008;155:791-805
- Purpose: To evaluate the role of renin angiotensin system (RAS) blockade in improving cardiovascular CV outcomes in patients with chronic kidney disease (CKD).
- Study Selection: Randomized controlled trials that analyzed CV outcomes in patients with CKD/proteinuria treated with RAS blockade (ACEI/ARB) compared to placebo and control (β-blockers, calcium-channel blockers and other antihypertensive-based therapy) therapy in the study.
- Results: Twenty-five trials (N = 45758) were included. Compared to placebo, RAS blockade reduced the risk of heart failure in patients with diabetic nephropathy. In patients with non-diabetic CKD, RAS blockade decreased CV outcome compared to control therapy.
- Conclusions: RAS blockade reduced CV outcomes in diabetic nephropathy as well as non-diabetic CKD.
Prevention of Progression
• as above
• control of hypertension, diabetes, cardiovascular risk factors (e.g. smoking cessation)
• avoid nephrotoxins
• address reversible causes of AKI

Renal Failure

Presentation of Renal Failure

1. Volume Overload
• due to increase in total body Na⁺ content
• signs: weight gain, HTN, pulmonary or peripheral edema

2. Electrolyte Abnormalities
• high
  • K⁺ (decreased renal excretion, increased tissue breakdown)
  • PO₄³⁻ (decreased renal excretion, increased tissue breakdown)
  • Ca²⁺ (rare; happens during recovery phase after rhabdomyolysis-induced acute kidney injury or in settings where hypercalcemia contributes to renal failure, such as in multiple myeloma or sarcoidosis)
  • uric acid
• low
  • Na⁺ (failure to excrete excessive water intake)
  • Ca²⁺ (decreased Vit D activation, hyperphosphatemia, hypoalbuminemia)
  • HCO₃⁻ (especially with sepsis or severe heart failure)

3. Uremic Syndrome
• manifestations result from retention of urea and other metabolites as well as hormone deficiencies

Signs and Symptoms of Renal Failure

Figure 18. Signs and symptoms of renal failure
Complications
- CNS: decreased LOC, stupor, seizure
- CVS: cardiomyopathy, CHF, arrhythmia, pericarditis, atherosclerosis
- GI: peptic ulcer disease, gastrroduodenitis, AVM
- hematologic: anemia, bleeding tendency (platelet dysfunction), infections
- endocrine:
  - decreased testosterone, estrogen, progesterone
  - increased FSH, LH
- metabolic:
  - renal osteodystrophy: secondary increased PTH due to decreased Ca\(^{2+}\), high PO\(_4\)\(^{3-}\) and low active vitamin D
  - osteitis fibrosa cystica
  - hypertriglyceridemia, accelerated atherogenesis
  - decreased insulin requirements, increased insulin resistance
- dermatologic: pruritus, ecchymosis, hematoma, calciphylaxis (vascular Ca\(^{2+}\) deposition)

Renal Replacement Therapy

Dialysis

Indications for Dialysis in Chronic Renal Failure

Table 16. Indications for Dialysis

<table>
<thead>
<tr>
<th>Absolute Indications</th>
<th>Relative Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume overload*</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Hyperkalemia*</td>
<td>Decreased cognitive functioning</td>
</tr>
<tr>
<td>Severe metabolic acidosis*</td>
<td>Profound fatigue and weakness</td>
</tr>
<tr>
<td>Neurologic signs or symptoms of uremia (encephalopathy, neuropathy, seizures)</td>
<td>Severe anemia unresponsive to erythropoietin</td>
</tr>
<tr>
<td>Uremic pericarditis</td>
<td>Persistent severe pruritus</td>
</tr>
<tr>
<td>Refractory accelerated hypertension</td>
<td>Restless leg syndrome</td>
</tr>
<tr>
<td>Clinically significant bleeding diathesis</td>
<td></td>
</tr>
<tr>
<td>Persistent severe nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td>Plasma Cr &gt; 1060 µmol/L (12 mg/dL) or Urea &gt; 36 mmol/L (100 mg/dL; clinical picture also important)</td>
<td></td>
</tr>
</tbody>
</table>

*Unresponsive to medications

- **h*emodialysis**: blood is filtered across a semipermeable membrane removing accumulated toxic waste products, solutes, excess fluid (ultrafiltration), and restoring buffering agents to the bloodstream
  - available as intermittent (e.g. three times per week), continuous (CVVHD) or sustained low efficiency (SLED)
  - can be delivered at home or in-centre, nocturnal
  - vascular access can be achieved through a central line, an artificial graft or an arterio-venous fistula
  - patients with chronic kidney disease should be referred for surgery to attempt construction of a primary AV fistula when their eGFR is <20 mL/min, the serum Cr level quoted as >350 µmol/L (>4.0 mg/dL), or within 1 yr of an anticipated need
- **peritoneal dialysis**: peritoneum acts as a semipermeable membrane similar to hemodialysis filter
  - advantages: independence, fewer stringent dietary restrictions, better rehabilitation rates
  - available as continuous ambulatory (CAPD; four exchanges per day) or cyclic (CCPD; machine carries out exchanges overnight)
  - refer patients with chronic renal disease to a nephrologist early on to facilitate treatment and plan in advance for renal replacement therapy (RRT)

How to Write Dialysis Orders
(MUST BE INDIVIDUALIZED)
- Filter Type (e.g. F800)
- Length (e.g. 4h 3 times/wk or 2h daily)
- Q Blood Flow (max 500 cc/min)
- Ultrafiltration (e.g. 2 L or to target dry weight)
- Na\(^+\) 140 (can be adjusted by starting at 155 and “ramping” down to minimize cramping)
- K\(^+\) [based on serum (K\(^+\))]
  - Serum K\(^+\) Dialysate
    - 4-6 1.5
    - 3.5-4 2.5
    - <3.5 3.5
  - Ca\(^{2+}\) 1.25
  - HCO\(_3\) 40
  - Heparin (none, tight (500 U/h) or full (1000 U/h))
  - IV fluid to support BP (e.g. N/S)
### Table 17. Peritoneal Dialysis vs. Hemodialysis

<table>
<thead>
<tr>
<th>Rate</th>
<th>Peritoneal Dialysis</th>
<th>Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Home</td>
<td>Hospital (usually)</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>Osmotic pressure via dextrose dialysate</td>
<td>Hydrostatic pressure</td>
</tr>
<tr>
<td>Solute Removal</td>
<td>Concentration gradient and convection</td>
<td>Concentration gradient and convection</td>
</tr>
<tr>
<td>Membrane</td>
<td>Peritoneum</td>
<td>Semi-permeable artificial membrane</td>
</tr>
<tr>
<td>Method</td>
<td>Indwelling catheter in peritoneal cavity</td>
<td>Line from vessel to artificial kidney</td>
</tr>
<tr>
<td>Complications</td>
<td>Infection at catheter site</td>
<td>Vascular access (clots, collapse)</td>
</tr>
<tr>
<td></td>
<td>Bacterial peritonitis</td>
<td>Bacteremia</td>
</tr>
<tr>
<td></td>
<td>Metabolic effects of glucose</td>
<td>Bleeding due to heparin</td>
</tr>
<tr>
<td></td>
<td>Difficult to achieve adequate clearance in patients with large body mass</td>
<td>Disequilibrium syndrome (headache, cerebral edema, hypotension, nausea, muscle cramps related to solute/water flux over short time)</td>
</tr>
</tbody>
</table>

### Renal Transplantation

- Preferred modality of RRT, best way to reverse uremic signs and symptoms
- Provides maximum replacement of GFR
- Only therapy shown to improve survival in patients with ESRD
- Native kidneys usually left in situ
- 2 types: deceased donor, living donor (related or unrelated)
- Kidney transplanted into iliac fossa, transplant renal artery anastomosed to external iliac artery of recipient
- 1 yr renal allograft survival rates ≥90%

**Complications**

- Leading causes of late allograft loss: interstitial fibrosis/tubular atrophy (IFTA) and death with functioning graft
- #1 cause of mortality in transplanted patients is cardiovascular disease
- Immunosuppressant drug therapy: side effects include infections, malignancy (skin, Kaposi’s sarcoma, post-transplant lymphoproliferative disorder)
- Acute rejection: graft site tenderness, rise in Cr, oliguria, ± fever, although symptoms are uncommon
- De novo glomerulonephritis (usually membranous)
- New-onset diabetes mellitus (often due to prednisone use)
- Cyclosporine or tacrolimus nephropathy (refer to Small Vessel Disease, NP18)
- Chronic allograft nephropathy
  - Early allograft damage caused by episodes of acute rejection and acute peritransplant injuries
  - Immunologic and nonimmunologic factors (HTN, hyperlipidemia, age of donor, quality of graft, new onset diabetes)
- Transplant glomerulopathy from antibody injury causes nephrotic proteinuria
- CMV (cytomegalovirus) infection and other opportunistic infections usually occur between 1 and 6 mo post-transplant
- BK virus (polyoma virus) nephropathy can result from over-immunosuppression and lead to graft loss

**When to Initiate Dialysis**

CrCl <20 mL/min
- Educate patient regarding dialysis; if not a candidate for peritoneal dialysis, make arrangements for AV fistula

CrCl <15 mL/min
- Weigh risk and benefits for initiating dialysis

CrCl <10 mL/min
- Dialysis should be initiated

**NOTE**
- Cockcroft-Gault equation (or Modification of Diet in Renal Disease equation) should be used to measure kidney function
- Monitor for uremic complications
- Significant benefits in quality of life can occur if dialysis started before CrCl <15 mL/min
- It is unclear whether patients who start dialysis early have increased survival
- A preemptive transplant can be considered if patient is stable, in order to avoid dialysis

**Commonly Used Immunosuppressive Drugs**

- Calcineurin inhibitors
- Calcitriol
- Antiproliferative medications
  - Mycophenolate Mofetil
  - Azathioprine
- Other agents
  - Sirolimus
  - Prednisone
- Anti-lymphocyte antibodies
  - Thymoglobulin
  - Basiliximab

**Survival Among Nocturnal Home Hemodialysis Patients Compared to Kidney Transplant Recipients**

**Recipients**

- Retrospective, matched cohort with 4-5 yr average follow up.
- Population: 117 nocturnal home dialysis (NHD) patients (mean age 46, 68% white) were matched to 533 deceased donor transplant (DTX) patients and 533 live donor (LTX) transplant patients (1:3:3 ratio).
- Intervention: Nocturnal home dialysis versus live or deceased donor transplant.
- Outcome: Primary outcome was all cause mortality
- Results: No significant difference in survival or hazard ratio between NHD and DTX. Significant survival benefit for patients undergoing LTX versus NHD. Significant mortality hazard ratio reduction with LTX (0.51) with no difference in hazard ratio for DTX versus NHD reference.
- Conclusion: NHD has comparable mortality to DTX, but is inferior to LTX.
<table>
<thead>
<tr>
<th>Classification</th>
<th>Examples</th>
<th>Mechanism of Action</th>
<th>Indication</th>
<th>Dosing</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop Diuretics</td>
<td>furosemide (Lasix®), hydrochlorothiazide (HCTZ)</td>
<td>Thick ascending of Loop of Henle</td>
<td>( \downarrow \text{Na}^+ / \downarrow \text{K}^+ / \downarrow \text{Cl}^- ) transport ± renal and peripheral vasodilatory effects (K⁺ loss; ( \uparrow ) H₂O secretion; ( \uparrow ) Ca²⁺ excretion) MANAGEMENT OF EDEMA SECONDARY TO CHF, NEPHROTIC SYNDROME, CINCHETIC ASCITES; ( \uparrow ) FREE WATER CLEARANCE (E.G. IN SIADH-INDUCED HYPERNATREMIA), ( \downarrow ) BP (LESS EFFECTIVE DUE TO SHORT ACTION)</td>
<td>furosemide: edema – 20–80 mg IV/IM/PO q6–8h (MAX 680 mg/d) UNTIL DESIRED RESPONSE HTN – 20–80 mg/d PO OD/bid DOSING</td>
<td>ALLERGY IN SULFA-SENSITIVE INDIVIDUALS, ELECTROLYTE ABNORMALITIES, HYPOKALEMIA, HYPOCALCEMIA, HYPERCALCERIA (WITH STONE FORMATION), VOLUME DEPLETION WITH METABOLIC ALKALOSIS, PRECIPITATES GOUTY ATTACKS</td>
</tr>
<tr>
<td>Thiazide Diuretics</td>
<td>hydrochlorothiazide (HCTZ), indapamide (Lozid®, Lozide®), metolazone (Zaroxolyn®), chlorothiazide (Hygroton®)</td>
<td>Distal convoluted tubule</td>
<td>INHIBIT ( \text{Na}^+ / \downarrow \text{Cl}^- ) TRANSPORT (K⁺ LOSS; ( \uparrow ) H₂O SECRECTION; ( \downarrow ) Ca²⁺ EXCRETION) 1st LINE FOR ESSENTIAL HTN TREATMENT OF EDEMA MANAGEMENT OF EDEMA SECONDARY TO CHF, NIEPHROTIC SYNDROME, CIRRHOTIC ASCITES; FREE WATER CLEARANCE (E.G. IN SIADH-INDUCED HYPERNATREMIA), DIABETES INSIPIDUS (NEPHROGENIC)</td>
<td>HCTZ: edema – 25–100 mg PO OD HTN – 12.5–25 mg PO OD (MAX 50 mg/d) NEPHROLITHIASIS/HYPERCALCERIA – 25–100 mg PO</td>
<td>HYPOCALCEMIA, INCREASED SERUM URATE LEVELS, PRECIPITATES GOUTY ATTACKS, HYPERCALCERIA, ELEVATED LIPOIDS, GLUCOSE INTOLERANCE</td>
</tr>
<tr>
<td>Potassium-Sparing Diuretics</td>
<td>spironolactone (Aldactone®), triamterene (Dyrenium®), amiloride (Midamor®)</td>
<td>Cortical collecting duct (( \downarrow ) ( \text{Na}^+ ) REABSORPTION)</td>
<td>REDUCES K⁺ LOSS CAUSED BY OTHER DIURETICS EDEMA/HYPERCALCERIA, DIABETIC KIDNEY DISEASE, IDIOPATHIC HYPERCALCIURIA AND STONES, GLANDULAR HYPERPLASIA, GYNECOMASTIA (ESTROGENIC EFFECT OF SPIRONOLACTONE)</td>
<td>spironolactone: 25–200 mg/d OD/bid DOSING HTN: 50–200 mg/d OD/bid DOSING HYPERCALCERIA – 100–400 mg/d OD/bid DOSING AMILORIDE: EDEMA/HTN: 5–10 mg PO OD</td>
<td>HYPERCALCEMIA (CAUTION WITH ACE INHIBITOR), TRAMTERENE CAN BE NEPHROTIC (RARE), NEPHROLITHIASIS, GYNECOMASTIA (ESTROGENIC EFFECT OF SPIRONOLACTONE)</td>
</tr>
<tr>
<td>Combination Agents</td>
<td>Dyazide® (triamterene + HCTZ), Aldactazide® (spironolactone + HCTZ), Moduretic® (amiloride + HCTZ), Vaserozide® (enalapril + HCTZ), Zestoretic® (lisinopril + HCTZ)</td>
<td>COMBINE ACE-INHIBITOR WITH THIAZIDE FOR SYNERGISTIC EFFECT COMBINE K⁺-SPARING DRUG WITH THIAZIDE TO REDUCE HYPOKALEMIA</td>
<td>REDUCES K⁺ LOSS CAUSED BY OTHER DIURETICS EDEMA/HYPERCALCERIA, DIABETIC KIDNEY DISEASE, IDIOPATHIC HYPERCALCIURIA AND STONES, GLANDULAR HYPERPLASIA, GYNECOMASTIA (ESTROGENIC EFFECT OF SPIRONOLACTONE)</td>
<td>REDUCES K⁺ LOSS CAUSED BY OTHER DIURETICS EDEMA/HYPERCALCERIA, DIABETIC KIDNEY DISEASE, IDIOPATHIC HYPERCALCIURIA AND STONES, GLANDULAR HYPERPLASIA, GYNECOMASTIA (ESTROGENIC EFFECT OF SPIRONOLACTONE)</td>
<td>REDUCES K⁺ LOSS CAUSED BY OTHER DIURETICS EDEMA/HYPERCALCERIA, DIABETIC KIDNEY DISEASE, IDIOPATHIC HYPERCALCIURIA AND STONES, GLANDULAR HYPERPLASIA, GYNECOMASTIA (ESTROGENIC EFFECT OF SPIRONOLACTONE)</td>
</tr>
<tr>
<td>Osmotic Diuretics</td>
<td>mannitol (Osmitrol®), glycerol urea</td>
<td>RENAL TUBULES (PROXIMAL AND COLLECTING DUCT)</td>
<td>NON-REABSORBABLE SOLUTES INCREASE OSMOTIC PRESSURE OF GLOMERULAR FIBRATE – INHIBITS REABSORPTION OF WATER AND ( \uparrow ) URINARY EXCRETION OF TOXIC MATERIALS</td>
<td>TO ( \downarrow ) INTRACRANIAL OR INTRACELLULAR PRESSURE RENAL FAILURE OR EDEMATOUS STATES</td>
<td>TRANSIENT VOLUME EXPANSION, ELECTROLYTE ABNORMALITIES (( \downarrow ) \text{Na}⁺, ( \downarrow ) \text{K}⁺)</td>
</tr>
<tr>
<td>ACEI</td>
<td>ramipril (Altace®), enalapril (Vasotec®), lisinopril (Prinivil®), torsemide (Maxipam®), captopril (Capoten®)</td>
<td>LUNGS, TISSUES DIFFUSELY</td>
<td>PREVENTS ANGIOTENSIN II VASOCONSTRICTING VASCULAR SMooth MUSCLE – INHIBITS REABSORPTION OF WATER AND ( \uparrow ) URINARY EXCRETION OF TOXIC MATERIALS HTN CARDIOPROTective EFFECTS (SEE CARDIOLOGY) RENOPROTECTive EFFECTS</td>
<td>HTN CARDIOPROTective EFFECTS (SEE CARDIOLOGY)</td>
<td>RENOPROTECTive EFFECTS</td>
</tr>
<tr>
<td>ARB</td>
<td>losartan (Cozaar®), candesartan (Atacand®), valsartan (Duosan®), telmisartan (Micardis®), eprosartan (Teveten®), olmesartan (Ometec®)</td>
<td>VASCULAR SMOOTH MUSCLE, ADRENAL CORTEX, PROXIMAL TUBULES</td>
<td>COMPETITIVE INHIBITOR AT THE ANGIOTENSIN II RECEPTOR: PREVENTS ANGIOTENSIN II VASOCONSTRICTING ACTION ON VASCULAR SMOOTH MUSCLE – ( \downarrow ) BP PREVENTS ANGIOTENSIN II MEDIATED ALDOSTERONE RELEASE FROM ADRENAL CORTEX AND ACTION ON PROXIMAL RENAL TUBULES – ( \uparrow ) \text{Na}⁺ AND ( \downarrow ) H₂O EXCRETION ( \rightarrow ) \text{BP REDUCES FIBROSIS AND ATEROSGEOGENCY} HTN CARDIOPROTective EFFECTS (SEE CARDIOLOGY) RENOPROTECTive EFFECTS</td>
<td>HTN: losartan 25–100 mg PO OD Candesartan 3–22 mg PO OD valsartan 150–300 mg PO OD telmisartan 80–320 mg PO OD eprosartan 600–800 mg PO OD olmesartan 20–40 mg PO OD</td>
<td>HYPERCALCEMIA, CAUTION – REDUCE DOSE IN HEPATIC IMPAIRMENT, ACUTE KIDNEY INJURY, TERATOGENIC</td>
</tr>
<tr>
<td>Renin Antagonists</td>
<td>aliskiren (Rasilez®)</td>
<td>DIRECT RENIN ANTAGONIST</td>
<td>INHIBITS RENIN PRODUCTION AND ACTIVITY CARDIOPROTective AND RENOPROTECTive ABILITIES BEING EVALUATED</td>
<td>HTN CARDIOPROTective EFFECTS (SEE CARDIOLOGY) RENOPROTECTive EFFECTS</td>
<td>HTN ALISKIREN 150–300 mg PO OD</td>
</tr>
</tbody>
</table>
# Landmark Nephrology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>4D</td>
<td>NEJM 2005; 353:238-48</td>
<td>Patients with type 2 DM receiving maintenance hemodialysis were randomized to 20 mg of atorvastatin per day or matching placebo. No difference in composite index of death from cardiac causes, nonfatal myocardial infarction, and stroke.</td>
</tr>
<tr>
<td>AASK</td>
<td>JAMA 2001; 285:2719-28</td>
<td>Ramipril, compared with amlodipine, slows progression of hypertensive renal disease and proteinuria and may benefit patients without proteinuria as well.</td>
</tr>
<tr>
<td>ACEI and Diabetic</td>
<td>NEJM 1993; 329:1456-62</td>
<td>Captopril protects against deterioration in renal function in insulin-dependent diabetic nephropathy and is significantly more effective than blood-pressure control alone.</td>
</tr>
<tr>
<td>ALTITUDE</td>
<td>Early Termination (Unpublished Results; protocol – NDT 2009; 24:1663-71)</td>
<td>Combining Aliskiren with ACEI or ARB in high-risk patients with type 2 diabetes leads to increased incidence of nonfatal stroke, hyperkalemia and hypertension.</td>
</tr>
<tr>
<td>ASTRAL</td>
<td>NEJM 2009; 361:1953-62</td>
<td>Renal artery revascularization compared to medical therapy does not improve renal function, BP, renal or cardiovascular events, or mortality and carries significant operative risks.</td>
</tr>
<tr>
<td>AURORA</td>
<td>NEJM 2009; 360:1395-407</td>
<td>Patients receiving maintenance hemodialysis randomized to rosuvastatin 10 mg daily or placebo. Rosuvastatin lowered the LDL cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.</td>
</tr>
<tr>
<td>BENEDICT</td>
<td>NEJM 2004; 351:1941-51</td>
<td>Treatment with ACEI candesartan alone or candesartan combined with verapamil decreased the incidence of microalbuminuria in patients with type 2 diabetes and hypertension with normal albuminuria.</td>
</tr>
<tr>
<td>CHOIR</td>
<td>NEJM 2006; 355:2085-98</td>
<td>Patients with CKD were randomly assigned to receive a dose of epoetin alfa targeted to achieve a hemoglobin level of 13.5 g/dL or 11.3 g/dL. The higher target group had an increased risk of death.</td>
</tr>
<tr>
<td>CREATE</td>
<td>NEJM 2006; 355:2071-84</td>
<td>Patients with CKD (15-35 mL/min) and mild to moderate anemia (11-12.5 g/dL) were randomized to normal (13-15 g/dL) or sub-normal (10.5-11.5 g/dL) hemoglobin levels. Early and complete correction of hemoglobin did not reduce the risk of cardiovascular events.</td>
</tr>
<tr>
<td>DETAIL</td>
<td>NEJM 2004; 351:1952-61</td>
<td>The ARB telmisartan and the ACEI enalapril are equally effective in slowing renal function deterioration in type 2 diabetes with mild to moderate hypertension and early nephropathy.</td>
</tr>
<tr>
<td>ELITE-SYMPHONY</td>
<td>NEJM 2007; 357:2562-75</td>
<td>Daclizumab induction, MMF, steroids and low-dose tacrolimus effectively maintain stable renal function following renal transplantation, without the negative effects on renal function commonly reported for standard CNI regimens.</td>
</tr>
<tr>
<td>FHN</td>
<td>NEJM 2010;363:2287-300</td>
<td>Patients were randomized to dialysis 6x/wk (frequent) or 3x/wk (conventional). Frequent hemodialysis was associated with improvement in composite outcomes of death or change in left ventricular mass and death or change in a physical-health composite score. Frequent hemodialysis caused more frequent interventions related to vascular access.</td>
</tr>
<tr>
<td>HEMO</td>
<td>NEJM 2002; 347:2010-19</td>
<td>Use of high dose dialysis or high flux membranes versus standard dose or low flux in thrice-weekly dialysis does not improve survival or outcomes. Possible benefit in cardiac-related outcomes with high flux membranes.</td>
</tr>
<tr>
<td>IDEAL</td>
<td>NEJM 2010; 363:609-19</td>
<td>Patients with progressive CKD and GFR between 10 and 15 mL/min randomized to initiate dialysis at GFR of 10-14 mL/min (early) or 5-7 mL/min (late). Early initiation of dialysis in patients with stage V chronic kidney disease was not associated with an improvement in survival or clinical outcomes.</td>
</tr>
<tr>
<td>IDNT</td>
<td>NEJM 2001; 345:851-60</td>
<td>Treatment with irbesartan reduced the risk of developing end-stage renal disease and worsening renal function in patients with type 2 DM and diabetic nephropathy.</td>
</tr>
<tr>
<td>IRMA</td>
<td>NEJM 2001; 345:870-8</td>
<td>Irbesartan is renoprotective independently of its blood-pressure lowering effect in patients with type 2 diabetes and microalbuminuria.</td>
</tr>
<tr>
<td>MDRD</td>
<td>Ann Intern Med 1995; 123:754-62</td>
<td>Blood pressure target for patients with proteinuria of more than 1 g/d should have a target BP of less than 125/75. For patients with proteinuria of 0.25 to 1.0 g/d should have a target BP of less than 130/80.</td>
</tr>
<tr>
<td>ONTARGET</td>
<td>Lancet 2008; 372:547-53</td>
<td>Telmisartan and ramipril monotherapy reduced proteinuria and rise in creatinine in patients with high vascular risk; combination of the two agents led to increased acute renal failure episodes, syncope and hypotension.</td>
</tr>
<tr>
<td>Model</td>
<td>Reference</td>
<td>Results</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>---------</td>
</tr>
<tr>
<td>REIN</td>
<td>Lancet 1999; 354:359-64</td>
<td>In non-diabetic nephropathy, ACEI were renoprotective in patients with non-nephrotic range proteinuria</td>
</tr>
<tr>
<td>REIN2</td>
<td>Lancet 2005; 365:939-46</td>
<td>In non-diabetic nephropathy already on ACEI, no further benefit from intensified BP control (sBP/dBP&lt;130/80) by adding a CCB versus conventional BP control (dBP&lt;90) on ACEI alone</td>
</tr>
<tr>
<td>RENAAL</td>
<td>NEJM 2001; 345:861-9</td>
<td>Losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy and was generally well-tolerated</td>
</tr>
<tr>
<td>RENAL</td>
<td>NEJM 2009; 361:1627-38</td>
<td>High intensity continuous renal-replacement therapy in acute kidney injury does not improve survival or outcomes compared to low intensity treatment, and is associated with higher rates of hypophosphatemia</td>
</tr>
<tr>
<td>ROAD</td>
<td>JASN 2007; 18:1889-98</td>
<td>Uptitration of either ACEI benazepril or ARB losartan to optimal anti-proteinuria doses conferred benefit on renal outcome in patients without diabetes who had proteinuria and renal insufficiency</td>
</tr>
<tr>
<td>SHARP</td>
<td>Lancet 2011; 377:2181-92</td>
<td>Randomized placebo-controlled trial in patients with CKD and no history of MI or coronary revascularization simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo. Reduction of LDL cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily reduced the incidence of major atherosclerotic events in patients with CKD</td>
</tr>
<tr>
<td>TREAT</td>
<td>NEJM 2009; 361:2019-32</td>
<td>Patients with type 2 DM, CKD and anemia were randomized to darbepoetin targeting a hemoglobin or 13 g/dL, or placebo. Darbepoetin did not reduce the risk of either death, a cardiovascular event or a renal event and was associated with an increased risk of stroke</td>
</tr>
</tbody>
</table>

**References**


Donadio JV and Grande JP. Medical progress: IgA nephropathy. NEJM 2002;347:738-748.


ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. NEJM 2009;359:1547-1559.


Acronyms .............................................. 2

The Neurological Exam .............................................. 2
General Exam and Mental Status
Cranial Nerves Exam
Motor Exam
Sensory Exam
Coordination Exam and Gait

Basic Anatomy Review .............................................. 4

Lumbar Puncture .............................................. 7

Approach to Common Presentations .............................................. 7
Weakness
Numbness/Altered Sensation

Cranial Nerve Deficits .............................................. 8
CN I: Olfactory
CN II: Optic
CN III: Oculomotor
CN IV: Trochlear
CN V: Trigeminal
CN VI: Abducens
CN VII: Facial
CN VIII: Vestibulocochlear
CN IX: Glossopharyngeal
CN X: Vagus
CN XI: Accessory
CN XII: Hypoglossal

NEURO-OPHTHALMOLOGY
Abnormalities of Vision .............................................. 11
Optic Neuritis
Anterior Ischemic Optic Neuropathy
Amaurosis Fugax
Central Retinal Vein Occlusion (CRVO)
Optic Disc Edema
Optic Disc Atrophy

Abnormalities of Visual Field .............................................. 12
Abnormalities of Eye Movements .............................................. 13
Disorders of Gaze
Internuclear Ophthalmoplegia (INO)
Diplopia
Nystagmus

Abnormalities of Pupils .............................................. 14
Seizure Disorders and Epilepsy .............................................. 14
Seizure
Status Epilepticus

Behavioural Neurology .............................................. 17
Acute Confusional State/Delirium
Dementia
Alzheimer’s Disease (AD)
Dementia with Lewy Bodies (DLB)
Frontotemporal Dementia (FTD)
Creutzfeldt-Jakob Disease (CJD)
Normal Pressure Hydrocephalus (NPH)
Aphasia
Apraxia
Agnosia

Mild Traumatic Brain Injury .............................................. 22
Neuro-oncology .............................................. 23
Paraneoplastic Syndrome
Tumours of the Nervous System

Movement Disorders .............................................. 24
Overview of Movement Disorders
Function of the Basal Ganglia
Movement Disorders
Parkinson’s Disease (PD)
Other Parkinsonian Disorders
Huntington’s Disease
Dystonia
Tic Disorders
Tourette’s Syndrome

Cerebellar Disorders .............................................. 28
Wernicke-Korsakoff Syndrome
Cerebellar Ataxias

Vertigo .............................................. OT12

Gait Disturbances .............................................. 29

Motor Neuron Disease .............................................. 30
Amyotrophic Lateral Sclerosis (ALS)
Other Motor Neuron Diseases

Peripheral Neuropathies .............................................. 31

Neuromuscular Junction Diseases .............................................. 32
Clinical Approach
Myasthenia Gravis (MG)
Lambert-Eaton Myasthenic Syndrome (LEMS)
Botulism
Myopathies .............................................. 34
Clinical Approach
Polymyositis/Dermatomyositis
Myotonic Dystrophy
Duchenne and Becker Muscular Dystrophy

Pain Syndromes .............................................. 35
Approach to Pain Syndromes
Neuropathic Pain
Tic Douloureux (Trigeminal Neuralgia)
Postherpetic Neuralgia (PHN)
Painful Diabetic Neuropathy
Complex Regional Pain Syndromes (CRPS)

Headache .............................................. 38
Migraine Headaches

Sleep Disorders .............................................. 41
Overview of Sleep
Disturbances of Alertness and Sleep

CNS Infections .............................................. ID19

Spinal Cord Syndromes .............................................. NS26

Stroke .............................................. 43
Terminology
Pathophysiology
Assessment and Treatment of Ischemic Stroke
Primary and Secondary Prevention of Ischemic Stroke
Cerebral Hemorrhage

Multiple Sclerosis (MS) .............................................. 46

Common Medications .............................................. 48

Landmark Neurology Trials .............................................. 50

References .............................................. 50
The Neurological Exam

General Exam and Mental Status

- **vitals**: pulse (especially rhythm), BP, temperature
- **H&N**: meningismus, head injury/bruises, (signs of basal skull fracture: Battle’s sign, raccoon eyes, hemotympanum, rhinorrhea), tongue biting
- **CVS**: carotid bruits, heart murmurs
- **mental status**: orientation (person, place, time), LOC (GCS)
  - GCS/15 = Motor/6, Verbal/5 (T = intubated), Eyes/4
- **cognition**:
  - Folstein MMSE – /30 (≤ 24 indicative of dementia)
  - MoCA – /30 (≥ 26 is considered normal)
- **clock drawing**

Cranial Nerves Exam

- **olfactory (CNI)**: odour sensation (test each nostril separately)
- **optic (CNII)**
  a. visual acuity: test each eye individually using best corrected vision
  b. visual fields
  c. pupil: direct and consensual pupillary reaction (afferent limb), accommodation, swinging flashlight test (see Relative Afferent Pupillary Defect, Ophthalmology, OP33)
  d. fundoscopy: optic disc edema, optic disc pallor, venous pulsations, hemorrhages
- **extra ocular movements (EOM)**
  a. **oculomotor (CNIII)**: levator palpebrae superioris, medial rectus, superior rectus, inferior rectus, inferior oblique, efferent limb of pupillary light response
  b. **trochlear (CNIV)**: superior oblique
  c. **abducens (CNVI)**: lateral rectus
- **trigeminal (CNV)**
  a. sensory: V1 (above supraorbital ridge), V2 (buccal area), V3 (mandible), corneal reflex (afferent)
  b. motor: temporalis, masseter, pterygoids, jaw jerk reflex
- **facial (CNVII)**
  a. sensorimotor: muscles of facial expression, hyperacusis (stapedius), corneal reflex (afferent)
  b. visceral sensory: taste of anterior 2/3 of tongue
  c. visceral motor: salivary and lacrimal glands
- **vestibulocochlear (CNVIII)**
  a. vestibular: nystagmus, caloric reflexes
  b. cochlear: Rinne, Weber
- **glossopharyngeal (CNIX) and vagus (CNX)**: palatal elevation, gag reflex, vocal cord function, swallowing, taste of posterior third of tongue
- **accessory (CNXI)**: trapezius and sternocleidomastoid strength
- **hypoglossal (CNXI)**: tongue muscle bulk, fasciculations, strength

Motor Exam

- **bulk**: atrophy, asymmetry
- **abnormal movements**: tremors, chorea, dystonia, dyskinesia, hemiballismus, myoclonus, athetosis, tics, fasciculations
- **abnormal posturing**: decerebrate, decorticate
- **tone**: hypotonia (flaccid), hypertonia (spasticity, rigidity, paratonia), cogwheeling
- **strength**
- **reflexes**: deep tendon reflexes, abdominal reflexes, primitive reflexes, Babinski, Hoffman, clonus

**Upper Motor Neuron Tests**

- **Babinski Reflex**: "Up-going" big toe ± fanning of toes indicates an UMN lesion.
- **Hoffman Reflex**: Flexion of IP joint of the thumb when tapping the nail of the index or ring finger may indicate an UMN lesion if asymmetrical.
- **Pronator Drift**: Patients are unable to maintain arm extension and supination in an UMN lesion.
Table 1. Localization of Motor Deficits

<table>
<thead>
<tr>
<th>LMN</th>
<th>UMN</th>
<th>Extrapyramidal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle Tone</td>
<td>Flaccid</td>
<td>Spastic</td>
</tr>
<tr>
<td>Involuntary Movements</td>
<td>Fasciculations</td>
<td>None</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Plantar Reflex</td>
<td>Down-going (flexor)</td>
<td>Up-going (extensor)</td>
</tr>
<tr>
<td>Pattern of Muscle Weakness</td>
<td>Proximal, distal or focal</td>
<td>Upper extremities: extensors weaker than flexors</td>
</tr>
</tbody>
</table>

Table 2. Overview of Neuromuscular Diseases

<table>
<thead>
<tr>
<th>Upper and Lower Motor Neuron Disease</th>
<th>Peripheral Neuropathy</th>
<th>Neuromuscular Junction</th>
<th>Myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>Segmental and asymmetrical, distal → proximal</td>
<td>Distal (except GBS) but may be asymmetrical</td>
<td>Proximal and fatiguable</td>
</tr>
<tr>
<td>Fasciculations</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Increased</td>
<td>Decreased/absent</td>
<td>Normal</td>
</tr>
<tr>
<td>Sensory</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Autonomic*</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

TESTS

<table>
<thead>
<tr>
<th>EMG</th>
<th>Denervation and reinnervation</th>
<th>Signs of demyelination ± axonal loss</th>
<th>Decremental response in MG on single fibre EMG</th>
<th>Small, short motor potentials</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCS</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Normal (until late)</td>
</tr>
<tr>
<td>Muscle enzyme</td>
<td>Normal</td>
<td>Increased</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*e.g. orthostatic hypotension, anhidrosis, visual blurring, urinary hesitancy or incontinence, constipation, erectile dysfunction

Table 3. Approach to Strength Testing of Radiculopathies versus Peripheral Neuropathies

How to use this table: For each nerve root, learn two (or more) peripheral nerves (and their associated muscles/movements). In radiculopathies, all associated peripheral nerves (and their movements) will be impaired, whereas in peripheral neuropathies, only one of the nerves (and its movement) will be impaired, sparing the other nerve. Especially useful peripheral nerve “pairs” are bolded for emphasis.

<table>
<thead>
<tr>
<th>Root</th>
<th>Peripheral Nerve</th>
<th>Movement</th>
<th>Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5</td>
<td>Musculocutaneous (C5/6)</td>
<td>Shoulder abduction</td>
<td>Biceps</td>
</tr>
<tr>
<td>C6</td>
<td>Radial (C6)</td>
<td>Elbow flexion</td>
<td>Brachioradialis</td>
</tr>
<tr>
<td>C7</td>
<td>Radial</td>
<td>Elbow flexion</td>
<td>Extensor carpi radialis longus</td>
</tr>
<tr>
<td></td>
<td>Posterior interosseus</td>
<td>Wrist extension</td>
<td>Triceps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Finger extension</td>
<td>Extensor digitorum communis</td>
</tr>
<tr>
<td>C8, T1</td>
<td>Median</td>
<td>Elbow extension</td>
<td>Flexor pollicis longus (look for thenar wasting)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wrist extension</td>
<td>Abductor pollicis brevis (look for thenar wasting)</td>
</tr>
<tr>
<td></td>
<td>Ulnar</td>
<td>Thumb flexion</td>
<td>Opponens pollicis (look for thenar wasting)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thumb abduction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Opposition</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Finger abduction</td>
<td>First dorsal interosseus (look for wasting in first dorsal webbed space)</td>
</tr>
<tr>
<td>L2, 3, 4</td>
<td>Femoral</td>
<td>Hip flexion</td>
<td>Iliopsoas</td>
</tr>
<tr>
<td></td>
<td>Obturator</td>
<td>Hip adduction</td>
<td>Adductor muscles</td>
</tr>
<tr>
<td>L3, 4</td>
<td>Femoral (L3/4)</td>
<td>Knee extension</td>
<td>Quadriceps</td>
</tr>
<tr>
<td></td>
<td>Deep peroneal (L4/5)</td>
<td>Dorsiflexion</td>
<td>Tibialis anterior</td>
</tr>
<tr>
<td>L5</td>
<td>Sciatic (L5, S1)</td>
<td>Hip extension</td>
<td>Gluteus maximus</td>
</tr>
<tr>
<td></td>
<td>Tibial</td>
<td>Ankle inversion</td>
<td>Tibialis posterior</td>
</tr>
<tr>
<td></td>
<td>Superficial peroneal</td>
<td>Ankle eversion</td>
<td>Peroneus muscles</td>
</tr>
<tr>
<td></td>
<td>Deep peroneal</td>
<td>Big toe extension</td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>Sciatic</td>
<td>Knee flexion</td>
<td>Hamstring muscles</td>
</tr>
<tr>
<td></td>
<td>Tibial</td>
<td>Plantar flexion</td>
<td>Gastrocnemius and soleus</td>
</tr>
</tbody>
</table>

Sensory Exam

- **primary sensation**
  - spinothalamic tract: pain and temperature
  - dorsal column: proprioception and vibration
- **cortical sensation**
  - graphesthesia, stereognosis, extinction, 2-point discrimination
Coordination Exam and Gait

• coordination exam
  • finger-to-nose, heel-to-shin, rapid alternating movements, “scanning” speech
• stance and gait
  • gait: antalgic, hemiplegic, ataxic, apraxic, festination, foot drop, broad-based
tandem gait (heel-to-toe walking)
  • Romberg test
  • pull test for retropulsion

Basic Anatomy Review

Figure 1. Brainstem (axial view)

Figure 2. Brainstem (posterior view)

A slow or uncoordinated rapid alternating movement can also be a sign of subtle weakness or Parkinsonism.

Romberg Test
Stable with eyes open and closed = normal.
Stable with eyes open, falls with eyes closed = +ve Romberg, suggesting loss of joint position sense.
Internal capsule

Upper motor neurons in motor cortex

Within 1-2 spinal levels of their entry, axons of first order neurons synapse onto second order neurons, whose axons then decussate before ascending as the spinothalamic tract.

**Figure 3.** Discriminative touch pathway (dorsal column) from body

**Figure 4.** Spinothalamic tract from body

**Figure 5.** Discriminative touch pathway (dorsal column) from face

**Figure 6.** Spinothalamic tract pathway from face

**Figure 7.** Corticospinal motor pathway
Figure 8. Sympathetic and parasympathetic pathway

Figure 9. Dermatome map

Myotomes
C5 – Shoulder abduction/elbow flexion
C6 – Wrist extensors
C7 – Elbow extension
C8 – Squeeze hand
T1 – Abduct fingers
T2-9 – Intercostal (abdominal reflexes)
T9-10 – Upper abdominals
T11-12 – Lower abdominals
L2 – Flex hip
L3 – Hip adduction
L4 – Knee extension and ankle dorsiflexion
L5 – Ankle dorsiflexion and big toe extension
S1 – Plantarflexion
Lumbar Puncture

Indications
• diagnostic: CNS infection (meningitis, encephalitis), inflammatory disorder (MS, Guillain-Barré, vasculitis), subarachnoid hemorrhage (if CT negative), CNS neoplasm (neoplastic meningitis)
• therapeutic: to administer anesthesia, chemotherapy, contrast media; to decrease intracranial pressure (pseudotumour cerebri, normal pressure hydrocephalus)

Contraindications
• mass lesion causing increased intracranial pressure (ICP) – could lead to cerebral herniation
  ▪ require CT first
• infection over lumbar puncture (LP) site/suspected epidural abscess
• low platelets (<50,000) or treatment with anticoagulation (high INR or aPTT)
• uncooperative patient

Complications
• tonsillar herniation
• post-LP headache (5-40%): worse when upright, better supine; generally onset within 24 h
  ▪ prevention: smaller gauge (i.e. 22) needle, reinsert stylet prior to needle removal, blunt-ended needle
  ▪ symptomatic treatment: caffeine and sodium benzoate injection
  ▪ corrective treatment: blood patch (autologous)
• spinal epidural hematoma
• infection

What to send LP for
• tube #1: cell count and differential: RBCs, WBCs and differential
  ▪ xanthochromia (yellow bilirubin pigmentation implies recent bleed into CSF)
• tube #2: chemistry: glucose (compare to serum glucose) and protein
• tube #3: microbiology: Gram stain and C&S
  ▪ specific tests depending on clinical situation/suspicion
  ▪ viral: PCR for herpes simplex virus (HSV) and other viruses
  ▪ bacterial: polysaccharide antigens of H. influenzae, N. meningitidis, S. pneumoniae
  ▪ fungal: Cryptococcal antigen, India ink stain (cryptococcus), culture
  ▪ TB: acid-fast stain, TB culture, TB PCR
• tube #4: cytology: for evidence of malignant cells
• tube #5: cell count: compare RBC count to that of tube #1
  ▪ note: tube 4 or 5 can be sent for repeat cell count

| Table 4. Lumbar Puncture Interpretation (Normal vs. Various Infectious Causes) |
|---------------------------------|-----------------|-----------------|-----------------|
| Condition                       | Colour          | Protein         | Glucose         | Cells            |
| NORMAL                          | Clear           | <0.45 g/L       | 60% of serum glc or >3.0 mmol/L | 0-5 WBC, 0 RBC, 0 PMNs |
| INFECTIOUS                      |                 |                 |                 |                  |
| Viral infection                 | Clear or opalescent | Normal or slightly increased <0.45-1 g/L | Normal | <1000x10⁵/L Lymphocytes mostly, some PMNs |
| Bacterial infection            | Opalescent yellow, may clot | >1 g/L | Decreased (<25% serum glc or <2.0 mmol/L) | >1000x10⁵/L PMNs |
| Granulomatous infection        | Clear or opalescent | Increased but usually <5 g/L | Decreased (usually <2.0-4.0 mmol/L) | <1000x10⁵/L Lymphocytes |

Approach to Common Presentations

Weakness

Approach
• mode of onset: abrupt (vascular, toxic, metabolic), subacute (neoplastic, infective, inflammatory), insidious (hereditary, degenerative, endocrinologic, neoplastic)
• course: worse at onset (vascular), progressive (neoplastic, degenerative, infective), episodic (vascular, inflammatory), activity dependent (NMJ, muscular)
• pattern: objective vs. subjective, generalized vs. localized, asymmetric vs. symmetric, proximal vs. distal, UMN vs. LMN, peripheral vs. myotomal
• associated symptoms: sensory symptoms, cortical symptoms, spinal symptoms (i.e. bowel/bladder dysfunction), signs/symptoms specific to various etiologies
• history: family history, developmental history, medications, risk factors, recent/preceding exposures
• investigations for LMN: NCS/EMG
• investigations for UMN: imaging (brain and/or spinal cord)
Differential Diagnosis
• objective muscle weakness
  ▪ generalized:
    • myopathy (muscular dystrophy, polymyositis, vasculitis, collagen vascular, HIV, CMV, influenza, steroids, statins, alcohol, hypothroidism, Cushings syndrome, electrolyte disorders)
    • NMJ (MG, botulism, LEMS, organophosphate poisoning)
  ▪ localized:
    • UMN (leukodystrophy, vasculitis, abscess, brain tumour, vitamin B₁₂ deficiency, MS, stroke)
    • anterior horn cell (spinal muscular atrophy, ALS, polio, paraneoplastic, lead toxicity)
    • peripheral neuropathy (peroneal muscle atrophy, GBS, leprosy, amyloid, myeloma, DM, lead toxicity)
• no objective muscle weakness
  ▪ chronic illness (cardiac, pulmonary, anemia, infection, malignancy)
  ▪ depression, deconditioning
• if loss of passive motion, consider intra-articular, peri-articular or extra-articular causes

Numbness/Altered Sensation

Approach
• positive sensory symptoms: parasthesia/dysesthesia = tingling, pins and needles, prickling, burning, stabbing
• negative sensory symptoms: hypoesthesia/anaesthesia = numbness, diminution or absence of feeling
• determine distribution of sensory loss: nerve root vs. peripheral nerve
• investigations: NCS, vitamin B₁₂ levels, imaging based on associated findings

Differential Diagnosis
• cerebral: stroke, demyelination, tumour
  ▪ associated symptoms: hemiplegia, aphasia, apraxia
• brainstem: stroke, demyelination, tumour
  ▪ associated symptoms: diplopia, vertigo, dysarthria, dysphagia
• spinal cord/radiculopathy: cord infarction, tumour, MS, syringomyelia, vitamin B₁₂ deficiency, disc lesion
  ▪ associated symptoms: back/neck pain, weakness (paraparesis or Brown-Séquard pattern)
• neuropathy: focal compressive neuropathy (based on location and distribution), DM, uremia, vasculitis, B₁₂ deficiency, HIV, Lyme disease, alcohol, paraneoplastic, amyloid

Cranial Nerve Deficits

CN I: Olfactory Nerve

Clinical Features
• absence of sense of smell associated with a loss of taste

Differential Diagnosis
• nasal: physical obstruction
  ▪ heavy smoking, chronic rhinitis, sinusitis, neoplasms, sepal deformity, choanal atresia, vestibular stenosis, foreign body
• olfactory neuroepithelial: destruction of receptors or their axon filaments
  ▪ influenza, herpes simplex, interferon treatment of hepatitis C virus, atrophic rhinitis (leprosy)
• central: lesion of olfactory pathway
  ▪ Kallmann’s syndrome, albinism, head injury, cranial surgery, SAH, chronic meningeal inflammation, meningioma, aneurysm, PD, stroke, MS
• endocrine/metabolic
  ▪ DM, adrenal hypo/hyperfunction, pseudohypoparathyroidism, hypothroidism, renal/liver failure, vitamin deficiency

CN II: Optic Nerve

• see Neuro-Ophthalmology, N11
CN III: Oculomotor Nerve

Clinical Features
- ptosis, resting eye position is “down and out” (depressed and abducted), pupil dilated (mydriasis)
- vertical and horizontal diplopia; paralysis of adduction, elevation and depression

Differential Diagnosis
- PCOM aneurysm: early mydriasis, then CN III palsy
- cavernous sinus (internal carotid aneurysm, meningioma, sinus thrombosis): associated with deficits in other CNs near the cavernous sinus (see Figure 11)
- ischemia of CNIII (DM, temporal arteritis, HTN, atherosclerosis): pupil sparing CN III palsy
- midbrain lesion: complete unilateral CNIII palsy with bilateral weakness of the superior rectus and ptosis with contralateral pyramidal signs ± mydriasis
- orbital lesion: associated with optic neuropathy, chemosis, proptosis
- other (inflammatory, infection, neoplasia, uncal herniation, trauma)

**Figure 11. Cavernous sinus (coronal view)**

CN IV: Trochlear Nerve

Clinical Features
- vertical and torsional diplopia; defect of intorsion and depression
- patient may complain of difficulty going down stairs or reading

Differential Diagnosis
- common: ischemic (DM, HTN), idiopathic, trauma (TBI or surgical), congenital
- other: cavernous sinus lesion, superior orbital fissure (tumour, granuloma)

CN V: Trigeminal Nerve

Clinical Features
- ipsilateral facial numbness, weakness of muscles of mastication (V3 only) with pterygoid deviation towards the side of the lesion

Differential Diagnosis
- brainstem (ischemia, tumour, syringobulbia, demyelination)
- peripheral (tumour, aneurysm, chronic meningitis, metastatic infiltration of nerve)
- trigeminal ganglion (acoustic neuroma, meningioma, fracture of middle fossa)
- cavernous sinus (carotid aneurysm, meningioma, sinus thrombosis)
- trauma
- note: other CN V lesions that cause facial pain = trigeminal neuralgia, herpes zoster

CN VI: Abducens Nerve

Clinical Features
- resting inward deviation (esotropia)
- horizontal diplopia; defect of lateral gaze

Differential Diagnosis
- pons (infarction, hemorrhage, demyelination, tumour): associated with facial weakness and contralateral pyramidal signs
- tentorial orifice (compression, meningioma, trauma): false localizing sign of increased ICP
- cavernous sinus (carotid aneurysm, meningioma, sinus thrombosis)
- ischemia of CN VI (DM, temporal arteritis, HTN, atherosclerosis)
- congenital (Duane’s syndrome)
CN VII: Facial Nerve

Clinical Features
- LMN lesion: ipsilateral facial weakness (facial droop, flattening of forehead, inability to close eyes, flattening of nasolabial fold)
- UMN lesion: contralateral facial weakness with forehead sparing (due to bilateral frontalis innervation)
- impaired lacrimation, decreased salivation, numbness behind auricle, hyperacusis, taste dysfunction of anterior 2/3 of tongue

Differential Diagnosis
- idiopathic = Bell's Palsy, 80-90% of cases (see Otolaryngology, OT22)
  - most often related to HSV, but other viruses may be implicated (CMV, herpes zoster, EBV)
- other: temporal bone fracture, EBV, Ramsay-Hunt (HSV), otitis media/mastoiditis, sarcoidosis, DM mononeuropathy, parotid gland disease, lyme meningitis, HIV

CN VIII: Vestibulocochlear Nerve

- see Otolaryngology, OT12

CN IX: Glossopharyngeal Nerve

Clinical Features
- unilateral lesion is rare
- taste dysfunction in posterior 1/3 of tongue
- absent gag reflex and dysphagia

Disorders
- glossopharyngeal neuralgia: sharp paroxysmal pain of posterior pharynx radiating to ear, triggered by swallowing
  - treated with carbamazepine or surgical ablation of CN IX

CN X: Vagus Nerve

Clinical Features
- oropharyngeal dysphagia (transfer dysphagia) due to palatal and pharyngeal weakness
- neuromuscular causes of dysphagia:
  - CNS: stroke, cerebral palsy, tumour, trauma, PD, AD, MS
  - CN: DM, laryngeal nerve palsy, polio, ALS
  - myopathic/NMJ: dermatomyositis, polymyositis, MG, sarcoidosis
- other causes of dysphagia: see Gastroenterology, G8
- dysarthria: inability to produce understandable speech due to impaired phonation and/or resonance
CN XI: Accessory Nerve

Clinical Features
• LMN lesion: paralysis of ipsilateral trapezius and sternocleidomastoid (ipsilateral shoulder drop, weakness on turning head to contralateral side)
• UMN lesion: paralysis of ipsilateral sternocleidomastoid and contralateral trapezius

CN XII: Hypoglossal Nerve

Clinical Features
• LMN lesion: tongue deviation towards lesion; ipsilateral tongue atrophy and fasciculations (if chronic)
• UMN lesion: tongue deviation away from lesion; absence of atrophy and fasciculations

NEURO-OPHTHALMOLOGY

Abnormalities of Vision
• see Ophthalmology, OP3

Acute Visual Loss
• see Ophthalmology, OP3

Optic Neuritis
• see Optic Disc Edema below, Multiple Sclerosis, N46

Anterior Ischemic Optic Neuropathy
• see also Optic Disc Edema, below
• non-arteritic (NAION): due to atherosclerosis
• arteritic (AION): due to giant cell arteritis (see Rheumatology, RH20)

Amaurosis Fugax
• see Ophthalmology, OP37 and Stroke, N43

Central Retinal Vein Occlusion (CRVO)
• see Ophthalmology, OP24

Optic Disc Edema

Table 5. Common Causes of Optic Disc Edema

<table>
<thead>
<tr>
<th></th>
<th>Optic Neuritis</th>
<th>Papilledema</th>
<th>AION</th>
<th>CRVO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;50</td>
<td>Any</td>
<td>&gt;50 but usually &gt;70</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Vision</td>
<td>Rapidly progressive monocular central vision loss with 4 acuity and colour vision with recovery</td>
<td>Late visual loss</td>
<td>Painless unilateral acute field defect over hours to days with 4 colour vision</td>
<td>Painless unilateral variable vision loss</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Pain (especially with eye movement)</td>
<td>Headache, n/v, local neurological deficits</td>
<td>If GCA: headache, scalp tenderness, jaw claudication, weight loss, fatigue</td>
<td>Cardiovascular risk factors</td>
</tr>
<tr>
<td>Pupil</td>
<td>RAPD</td>
<td>No RAPD</td>
<td>RAPD</td>
<td>± RAPD</td>
</tr>
</tbody>
</table>

CN XI is vulnerable to damage during neck surgery.

Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a medial medullary infarction.

If you suspect the diagnosis of giant cell arteritis do not wait for biopsy results. Begin treatment immediately!

NAION can be caused by use of Sildenafil (Viagra®) in rare cases.
Table 5. Common Causes of Optic Disc Edema (continued)

<table>
<thead>
<tr>
<th>Optic Neuritis</th>
<th>Papilledema</th>
<th>AION</th>
<th>CRVO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fundus</td>
<td>Disc swelling if anterior normal disc if retrobulbar</td>
<td>Bilateral disc swelling, retinal hemorrhage, no venous pulsations</td>
<td>Pale segmental disc edema, retinal dot, flame hemorrhages</td>
</tr>
<tr>
<td>Etiologies</td>
<td>MS, viral</td>
<td>Increased ICP</td>
<td>Giant cell arteritis</td>
</tr>
<tr>
<td>Investigations</td>
<td>MRI with gadolinium</td>
<td>Emergent CT; LP if CT is normal to measure opening pressure</td>
<td>CBC, ESR, CRP, temporal artery biopsy</td>
</tr>
<tr>
<td>Treatment</td>
<td>IV methylprednisolone</td>
<td>Treat cause</td>
<td>Consider ASA if non-arteritic; steroids if arteritic</td>
</tr>
</tbody>
</table>

Optic Disc Atrophy

- **etiologies:** glaucoma, AION, compressive tumour, optic neuritis, Leber’s hereditary optic neuropathy, congenital
- **presentation:** disc pallor, low visual acuity, peripheral vision defect, decreased colour vision
- **treatment:** none (irreversible), aim to prevent

Abnormalities of Visual Field

Figure 13. Characteristic visual field defects with lesions along the visual pathway

<table>
<thead>
<tr>
<th>Visual Fields Defects</th>
<th>Bitemporal Hemianopsia DDx by Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right anopsia (right optic nerve lesion)</td>
<td>Children: craniopharyngioma</td>
</tr>
<tr>
<td>Right anopsia and left upper quadrantanopsia (funcional scotoma)</td>
<td>Middle aged (20s to 50s): pituitary mass</td>
</tr>
<tr>
<td>Bitemporal hemianopsia (chiasmal lesion)</td>
<td>Elderly (&gt;60 yr): meningioma</td>
</tr>
<tr>
<td>Left homonymous hemianopsia (right optic tract lesion)</td>
<td>In homonymous hemianopsia, more congruent deficits are caused by more posterior lesions. Macular sparing may occur with occipital lesions.</td>
</tr>
<tr>
<td>Left upper quadrantanopsia (right temporal lesion)</td>
<td>Check all hemiplegic patients for homonymous hemianopsia (ipsilateral to side of hemiplegia).</td>
</tr>
<tr>
<td>Left lower quadrantanopsia (right parietal lesion)</td>
<td></td>
</tr>
</tbody>
</table>

Abnormalities of Eye Movements

Disorders of Gaze

Pathophysiology
- horizontal gaze: FEF → contralateral PPRF (midbrain/pons) → eyes saccade away from FEF
- vertical gaze: cortex → rostral interstitial nucleus in the MLF (midbrain)

Clinical Features
- unilateral lesion in one FEF → eyes deviate toward the side of the lesion
  - can be overcome with doll’s eye maneuver
- unilateral lesion in the PPRF → eyes deviate away from the lesion
  - cannot be overcome with doll’s eye maneuver if CN VI nucleus lesion as well
- seizure involving a FEF: eyes deviate away from the focus

Etiology
- common: infarcts (frontal or brainstem), MS, tumours

A lesion in a cerebral hemisphere causes eyes to “look away” from the hemiplegia, and to look towards the lesion.

A lesion in the brainstem causes the eyes to “look toward” the side of the hemiplegia, and to look away from the lesion.
**Internuclear Ophthalmoplegia (INO)**

**Pathophysiology**
- results from a lesion in MLF which disrupts coordination between CN VI nucleus in pons and the contralateral CN III nucleus in midbrain → disrupts conjugate horizontal gaze

**Clinical Features**
- horizontal diplopia on lateral gaze, oscillopsia
- on gaze away from the side of the lesion (see Figure 14)
  - ipsilateral adduction defect
  - contralateral abduction nystagmus
- cannot be overcome by caloric testing
- accommodation reflex intact
- may be bilateral (especially in MS)

**Etiology**
- common: MS, brain stem infarct

**Investigations**
- MRI

---

**Diplopia**

**Etiology – Monocular**
- mostly due to relatively benign optical problems (refractive error, cataract) or functional

**Etiology – Binocular** (due to ocular misalignment)
- muscle
  - Graves’ ophthalmopathy
  - EOM restriction/entrapment
- neuromuscular junction
  - MG (see Myasthenia Gravis, N32)
  - cranial nerve palsy (see Cranial Nerve Deficits, N8)
  - INO (see Internuclear Ophthalmoplegia, above)
- other
  - orbital trauma (orbital floor fracture), tumour, infection, inflammation
  - Miller-Fisher variant of GBS
  - Wernicke’s encephalopathy
  - leptomeningial disease

**Approach to Diplopia**
- monocular vs. binocular
- horizontal vs. vertical vs. oblique diplopia
- direction of gaze that exacerbates diplopia
- corrective head movements

**Workup**
- may observe isolated 4th or 6th nerve palsy for a few weeks, but workup if persistent or other symptoms develop
- indications for neuroimaging:
  - bilateral or multiple nerve involvement
  - severe sudden onset headache (rule out aneurysm)

**Nystagmus**

- **definition**: rapid, involuntary, small amplitude movements of the eyes that are rhythmic in nature
- direction of nystagmus is labelled by the **rapid** component of the eye movement
- can be categorized by movement type (pendular, jerking, rotatory, coarse) or as physiological vs. pathological
### Abnormalities of Pupils

- see Ophthalmology, OP30

### Seizure Disorders and Epilepsy

#### Seizure

**Definitions**
- seizure: transient neurological dysfunction caused by excessive activity of cortical neurons, resulting in paroxysmal alteration of behaviour and/or EEG changes
- epilepsy: chronic condition characterized by two or more unprovoked seizures

#### Classification

![Classification of seizures](image)

**NOTE:** seizures can also be classified using age of onset [childhood/adolescence, adulthood/late (i.e. > age 30)], setting (sleep, upon awakening), EEG (focal, generalized)

#### Signs and Symptoms

- generalized seizures (decreased LOC)
  - tonic-clonic [grand mal, generalized tonic-clonic (GTC)]:
    - prodrome of unease or irritability hours to days before the episode
    - tonic ictal phase: muscle rigidity
    - clonic ictal phase: repetitive violent jerking of face and limbs, tongue biting, cyanosis, frothing, incontinence
    - post-ictal phase: flaccid limbs, extensor plantar reflexes, headache, confusion, aching muscles, sore tongue, amnesia, elevated serum CK lasting hours
  - absence (petit mal): usually only seen in children, unresponsive for 5-10 s with arrest of activity, staring, blinking or eye-rolling, no post-ictal confusion; 3 Hz spike and slow wave activity on EEG
  - tonic: muscle rigidity in flexion or extension
  - clonic: repetitive rhythmic jerking movements
  - myoclonic: sporadic contractions localized to muscle groups of one or more extremities
  - atonic: loss of muscle tone leading to drop attack

#### Medical Emergency!

**Status epilepticus** can cause irreversible brain damage without treatment.

**Stroke** is the most common cause of late-onset (>50 yr of age) seizures, accounting for 50-60% of cases.

**Seizures and Dementia**

Neurodegenerative diseases can underlie seizures. Conversely, seizures can be a cause of dementia.
• partial seizures
  ▪ simple or complex can secondarily generalize, or simple → complex → generalized seizures
  ▪ simple (preserved LOC)
    • motor: postural, phonoitory, forceful turning of eyes and/or head, focal muscle rigidity/jerking ± Jacksonian march (spreading to adjacent muscle groups)
    • sensory: unusual sensations affecting vision, hearing, smell, taste or touch
    • autonomic: epigastric discomfort, pallor, sweating, flushing, piloerection, pupillary dilatation
    • psychiatric: symptoms rarely occur without impairment of consciousness and are more commonly complex partial
  ▪ complex (altered LOC)
    • patient may appear to be awake but with impairment of awareness
    • classic complex seizure is characterized by automatisms such as chewing, swallowing, lip-smacking, scratching, fumbling, running, disrobing and other stereotypic movements
    • other forms: dysphasic, dysmnesic (déjà vu), cognitive (disorientation of time sense), affective (fear, anger), illusions, structured hallucinations (music, scenes, taste, smells), epigastric fullness

Table 7. Classic Factors Differentiating Seizure versus Syncope

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Seizure</th>
<th>Syncope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of Onset</td>
<td>Day or night</td>
<td>Day</td>
</tr>
<tr>
<td>Position</td>
<td>Any</td>
<td>Upright, not recumbent</td>
</tr>
<tr>
<td>Onset</td>
<td>Sudden or brief</td>
<td>Gradual</td>
</tr>
<tr>
<td>Aura</td>
<td>Possible specific aura</td>
<td>Lightheaded sensation</td>
</tr>
<tr>
<td>Colour</td>
<td>Normal or cyanotic</td>
<td>Pallor</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Uncommon outside of ictal phase</td>
<td>Common; diaphoresis</td>
</tr>
<tr>
<td>Duration</td>
<td>Brief or prolonged</td>
<td>Brief</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Common</td>
<td>Possible but rare</td>
</tr>
<tr>
<td>Post-ictal</td>
<td>Occurs in tonic-clonic or complex partial</td>
<td>No</td>
</tr>
<tr>
<td>Motor Activity</td>
<td>Common</td>
<td>Occasional brief jerks</td>
</tr>
<tr>
<td>Injury</td>
<td>Common, tongue biting</td>
<td>Rare unless from fall</td>
</tr>
<tr>
<td>Automatisms</td>
<td>Common in absence or complex partial</td>
<td>None</td>
</tr>
<tr>
<td>EEG</td>
<td>Usually abnormal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Table 8. Classic Factors Differentiating Seizure versus Pseudoseizure (Conversion Disorder)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Seizure</th>
<th>Pseudoseizure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triggers</td>
<td>Uncommon</td>
<td>Emotional disturbance</td>
</tr>
<tr>
<td>Duration</td>
<td>Brief or prolonged</td>
<td>May be prolonged</td>
</tr>
<tr>
<td>Motor Activity</td>
<td>Synchronous, stereotypic, automatisms, lateral tongue biting, eyes rolled back</td>
<td>Opisthotonos, rigidity, forced eye closure, irregular extremity movements, shaking head, pelvic thrust, crying, geotropic eye movements, tongue biting at the tip</td>
</tr>
<tr>
<td>Timing</td>
<td>Day or night</td>
<td>Day; other people present</td>
</tr>
<tr>
<td>Physical Injury</td>
<td>May occur</td>
<td>Rare</td>
</tr>
<tr>
<td>Incontinence</td>
<td>May occur</td>
<td>Rare</td>
</tr>
<tr>
<td>Reproduction of Attack</td>
<td>Spontaneous</td>
<td>Suggestion ± stimulus</td>
</tr>
<tr>
<td>EEG</td>
<td>Often inter-ictal discharges</td>
<td>Normal</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Increased</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*Pseudoseizures do not rule out seizures (not uncommon to present with both)

Investigations
• CBC, electrolytes, fasting blood glucose, Ca²⁺, Mg²⁺, ESR, Cr, liver enzymes, CK, prolactin
• also consider toxicology screen, EtOH level, AED level (if applicable)
• CT/MRI (if new seizure without identified cause or known seizure history with new neurologic signs/symptoms)
• LP (if fever or meningismus)
• EEG
Treatment
- avoid precipitating factors
- indications for medical therapy (anticonvulsants): 2 or more unprovoked seizures, known organic brain disease, EEG with epileptiform activity, first episode of status epilepticus, abnormal neurologic examination or findings on neuroimaging
- psychosocial issues: stigma of seizures, education of patient and family, status of driver’s license, pregnancy issues
- safety issues: driving, operating heavy machinery, bathing, swimming alone
- consider surgical treatment if focal and refractory

Status Epilepticus
- definition: unremitting seizure of greater than 5 min; or successive seizures without return to a baseline state
- complications: anoxia, cerebral ischemia and cerebral edema, rhabdomyolysis and renal failure, aspiration pneumonia/pneumonitis, death (20%)
- initial measures: ABCs, vitals, monitors, fingerprick glucose (STAT), ECG, nasal O2, IV NS, IV glucose, IV thiamine, ABGs (if respiratory distress/cyanotic)
- bloodwork: electrolytes, Ca²⁺, Mg²⁺, PO₄³⁻, glucose, CBC, toxicology screen, EtOH level, AED levels
- focused history: onset, past history of seizures, drug and alcohol ingestion, past medical history, associated symptoms, witnesses/collateral history
- physical exam (once seizures controlled): LOC, vitals, HEENT (nuchal rigidity, head trauma, tongue biting, papilledema), complete neurological exam, signs of neurocutaneous disorders, decreased breath sounds, cardiac murmurs or arrhythmias, urinary incontinence, MSK exam (r/o injuries)

Figure 17. Status epilepticus treatment algorithm

Antiepileptic Drugs (AED)
- generalized-onset and partial-onset seizures: felbamate, lamotrigine, levetiracetam, refrinamide, topiramate, valproate, zonisamide
- partial seizures (simple partial, complex partial and secondarily generalized seizures): carbamazepine, gabapentin, lacosamide, oxcarbazepine, phenobarbital, phenytoin, pregabalain, primidone, tiagabine, vigabatrin (note: these drugs may exacerbate generalized seizures)
- absence seizures: ethosuximide
Behavioural Neurology

• see Psychiatry, PS19

Acute Confusional State/Delirium

Table 9. Selected Intracranial Causes of Acute Confusion

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>Thunderclap headache</td>
<td>CT (non-contrast)</td>
</tr>
<tr>
<td></td>
<td>Increased ICP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meningismus</td>
<td>LP</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>Focal neurological signs</td>
<td>Angiography if CT, LP negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>Fever, headache, nausea, photophobia</td>
<td>CT, LP</td>
</tr>
<tr>
<td></td>
<td>Meningismus</td>
<td></td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Focal neurological signs</td>
<td>CT, LP</td>
</tr>
<tr>
<td></td>
<td>Fever, headache, ± seizure</td>
<td>MRI</td>
</tr>
<tr>
<td>Abscess</td>
<td>Increased ICP</td>
<td>CT with contrast (often ring enhancing lesion)</td>
</tr>
<tr>
<td></td>
<td>Focal neurological signs</td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse axonal shear, epidural hematoma, subdural hematoma</td>
<td>Trauma hx</td>
<td>CT (non-contrast)</td>
</tr>
<tr>
<td></td>
<td>Increased ICP</td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td>Focal neurological signs</td>
<td></td>
</tr>
<tr>
<td>Autoimmune</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute CNS vasculitis</td>
<td>Skin rash, active joints</td>
<td>ANA, ANCA, RF</td>
</tr>
<tr>
<td></td>
<td>Systemic Lupus Erythematosis</td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angiography</td>
</tr>
<tr>
<td>Neoplastic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass effect/edema, hemorrhage, seizure</td>
<td>Increased ICP</td>
<td>CT (non-contrast)</td>
</tr>
<tr>
<td></td>
<td>Focal neurological signs</td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td>Papilledema</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>Status epilepticus</td>
<td>See Seizure Disorders and Epilepsy, N14</td>
</tr>
<tr>
<td>Primary Psychiatric</td>
<td>Psychotic disorder, mood disorder, anxiety disorder</td>
<td>No specific tests</td>
</tr>
</tbody>
</table>

Dementia

• see Psychiatry, PS20

Definition
• an acquired, generalized and (usually) progressive impairment of cognitive function (i.e. memory, recall, orientation, language, abstraction) associated with impairment in activities of daily living (i.e. planning, shopping, food preparation, difficulties with finances)
• effect on content, but not level of consciousness
• see Psychiatry, PS20 for DSM-IV diagnostic criteria
• see Geriatric Medicine, GM5
• differentiated from Mild Cognitive Impairment (MCI) by the extent to which the impairment affects ADLs
  • MCI represents an intermediate stage between dementia and normal aging
  • by definition, IADLs are not affected in MCI

Epidemiology
• 15% of those >65 yr of age have dementia
• <5% reversible

Etiology
• see Table 10 for common causes of dementia
• see Table 11 for acquired causes of dementia
• reversible causes: alcohol (intoxication or withdrawal, Wernicke's encephalopathy), medication (benzodiazepines, anticholinergics), heavy metals toxicity, hepatic or renal failure, Wilson's disease, B12 deficiency, ↑/↓ glucose, ↑/↓ cortisol, thyroid dysfunction, normal pressure hydrocephalus, depression (pseudodementia), intracranial tumour, subdural hematoma
• must rule out delirium

Delirium is a medical emergency carrying significant risk of morbidity and mortality. It is characterized by acute onset, disorientation, fluctuating level of consciousness, poor attention, and marked psychomotor changes.

Visual hallucinations more commonly indicate organic disease.
**History**

- "geriatric giants"
  - confusion/incontinence/falls/polypharmacy
  - memory and safety (wandering, leaving doors unlocked, leaving stove on, losing objects)
  - behavioural (mood, anxiety, psychosis, suicidal ideation, personality changes, aggression)
- ADLs and IADLs
- cardiovascular, endocrine, neoplastic, renal ROS
- alcohol, smoking
- OTCs, herbal remedies, medications (sedative hypnotics, antipsychotics, antidepressants, anticholinergics), compliance, accessibility
- history of vascular disease or head trauma
- collateral history

**Physical Examination**

- blood pressure
- hearing and vision
- neurological exam with attention to signs of parkinsonism, UMN findings, cerebrovascular disease
- general physical exam depending on risk factors and history
- MMSE or MoCA, clock drawing, frontal lobe testing (go/no-go, word lists, similarities, proverb)

**Investigations**

- depends on suspected etiologies (see Tables 10 and 11)
  - CBC (note MCV for evidence of alcohol use and B12 deficiency), glucose, TSH, B12, RBC folate
  - electrolytes, LFTs, renal function, lipids, serum calcium
  - CT head, MRI as indicated, SPECT – optional
  - as clinically indicated: VDRL, HIV, ANA, anti-dsDNA, ANCA, ceruloplasmin, copper, cortisol, toxicology, heavy metals
- issues to consider
  - failure to cope, fitness to drive, caregiver education and stress, power of attorney, legal will, advanced medical directives

**Table 10. Common Causes of Dementia**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY DEGENERATIVE</td>
<td></td>
<td>CT or MRI, SPECT</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>Memory impairment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aphasia, apraxia, agnosia</td>
<td></td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Visual hallucinations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parkinsonism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluctuating cognition</td>
<td></td>
</tr>
<tr>
<td>Frontotemporal dementia (e.g. Pick’s disease)</td>
<td>Behavioural presentation: disinhibition, perseveration, decreased social awareness, mental rigidity, memory relatively spared</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Language presentation: Progressive non-fluent aphasia, semantic dementia</td>
<td></td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Chorea</td>
<td>Genetic testing</td>
</tr>
<tr>
<td>VASCULAR</td>
<td></td>
<td>CT or MRI, SPECT</td>
</tr>
<tr>
<td>Multi-infarct dementia</td>
<td>May be abrupt onset</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stepwise deterioration is classic but progressive deterioration is most common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dysexecutive syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Focal neurological findings</td>
<td></td>
</tr>
<tr>
<td>CNS vasculitis</td>
<td>Systemic S&amp;S of vasculitis</td>
<td>ANA; ANCA; RF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT or MRI, Angiography</td>
</tr>
</tbody>
</table>

**Table 11. Acquired Causes of Dementia**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFECTIOUS</td>
<td></td>
<td>CT, LP</td>
</tr>
<tr>
<td>Chronic meningitis</td>
<td>Fever, headache, nausea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meningismus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Localizing neuro deficits</td>
<td></td>
</tr>
<tr>
<td>Chronic encephalitis</td>
<td>Fever, headache</td>
<td>CT or MRI</td>
</tr>
<tr>
<td>Chronic abscess</td>
<td>Increased ICP</td>
<td>CT with contrast</td>
</tr>
<tr>
<td>HIV</td>
<td>See Infectious Diseases, ID41</td>
<td>HIV serology</td>
</tr>
<tr>
<td>Creutzfeld-Jacob disease</td>
<td>Rapidly progressive, myoclonus</td>
<td>EEG, CT or MRI, LP</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Ataxia, myoclonus, tabes dorsalis</td>
<td>LP, CT or MRI, VDRL</td>
</tr>
</tbody>
</table>
Table 11. Acquired Causes of Dementia (continued)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAUMATIC</td>
<td>Diffuse axonal shear, epidural hematoma, subdural hematoma</td>
<td>Trauma Hx, Increased ICP, papilledema, Localizing neuro signs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHEUMATOLOGIC</td>
<td>SLE</td>
<td></td>
</tr>
<tr>
<td>NEOPLASTIC</td>
<td>Mass effect/edema, hemorrhage, seizure</td>
<td>Increased ICP, Localizing neuro signs</td>
</tr>
<tr>
<td></td>
<td>Paraneoplastic encephalitis</td>
<td>Systemic symptoms of cancer</td>
</tr>
</tbody>
</table>

Alzheimer’s Disease (AD)

• see Psychiatry, PS20

Definition
• progressive cognitive decline interfering with social and occupational functioning characterized by the following
  1. anterograde amnesia: impaired ability to learn new information
  2. one of the following cognitive disturbances
     a. aphasia: language disturbance
     b. apraxia: impaired ability to carry out motor activities despite intact motor function
     c. agnosia: failure to recognize or identify objects despite intact sensory function
     d. disturbance in executive function: impaired planning, organizing, sequencing, abstracting

Pathophysiology
• genetic factors
  - minority (<7%) of AD cases are familial (autosomal dominant)
  - 3 major genes for autosomal dominant AD have been identified:
    - amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14), presenilin 2 (chromosome 1)
  - the E4 polymorphism of apolipoprotein E is a susceptibility genotype (E2 is protective)
• pathology (although not necessarily specific for AD)
  - gross pathology
    - diffuse cortical atrophy, especially frontal, parietal, and temporal lobes (hippocampi)
  - microscopic pathology
    - senile plaques (extracellular deposits of amyloid in the grey matter of the brain)
    - loss of synapses
    - neurofibrillary tangles (intracytoplasmic paired helical filaments with β-amyloid and hyperphosphorylated Tau protein)
    - loss of cholinergic neurons in nucleus basalis of Meynert that project to the frontal cortex
  - biochemical pathology
    - 50-90% reduction in action of choline acetyltransferase

Epidemiology
• 1/12 of population 65-75 yr of age
• 1/3 of population >85 yr of age
• accounts for 60-80% of all dementias

Risk Factors
• age, family history, smoking, head injury, low education level, Down’s syndrome

Signs and Symptoms
• cognitive impairment
  - memory impairment for newly acquired information (early)
  - deficits in language, abstract reasoning and executive function
• psychiatric manifestations
  - major depressive disorder (5-8%)
  - psychosis (20%)
  - apathy
• motor manifestations (late)
  - parkinsonism (if present consider DLB)

Investigations
• perform investigations to rule out other causes of dementia as necessary
• EEG: usually normal, may observe generalized slowing (nonspecific)
• MRI: preferential atrophy of the hippocampi and precuneus of the parietal lobe; dilatation of lateral ventricles; widening of cortical sulci
• SPECT: hypoperfusion in temporal and parietal lobes

Cholinesterase Inhibitors for Dementia with Lewy bodies (DLB), Parkinson’s Disease Dementia (PDD) and Cognitive Impairment in Parkinson’s Disease (CIND-PD)
Cochrane DB Syst Rev 2012;3:CD006504
Study: Meta-analysis of RCTs assessing efficacy of treatment with cholinesterase inhibitors in DLB, PDD, and CIND-PD.
Results: The six trials (n=1238) included demonstrated therapeutic benefit of cholinesterase inhibitor for global assessment, cognitive function, behavioural disturbance, and activities of daily living. Cholinesterase Inhibitor was associated with increased adverse events (OR 1.64) and drop out (OR 1.94). Adverse events were more common with rivastigmine but not with donepezil. Fewer deaths occurred in the treatment group (OR 0.28).
Conclusion: Current evidence supports use of cholinesterase Inhibitors for patients with PDD but its role in DLB and CIND-PD is still unclear.

4 As and one D of AD
Anterograde amnesia
Aphasia
Apraxia
Agnosia
Disability in executive function
(Anterograde amnesia plus at least one of the other features is required for AD diagnosis)

Down’s syndrome predisposes to early onset of Alzheimer’s (i.e. age of ~40) due to three copies of the amyloid gene (APP)
**Treatment**

- acetylcholinesterase inhibitors have been shown to slow decline in cognitive function
  - donepezil, rivastigmine, galantamine
  - relative contraindications: bradycardia, heart block, arrhythmia, CHF, CAD, asthma, COPD, ulcers or risk factors for ulcers and GI bleeding
- galantamine is contraindicated in patients with hepatic/renal impairment
- memantine is an NMDA-receptor antagonist that has some benefits in later stage AD (i.e. when MMSE <17)
- symptomatic management
  1. pharmacologic
     - low dose neuroleptics for agitation (neuroleptics may worsen cognitive decline)
     - trazodone for sleep disturbance
     - antidepressants (SSRIs)
  2. non-pharmacologic
     - redirection
     - explore inciting factors for behaviour and modify behavior of patient or caregiver
     - family support and day care facilities

**Prognosis**

- progressive with mean duration of disease 10 yr

---

### Dementia with Lewy Bodies (DLB)

**Definition**

- progressive cognitive decline interfering with social or occupational function; memory loss usually not an early feature
- one (possible DLB) or two (probable DLB) of the following:
  - fluctuating cognition with pronounced variation in attention and alertness
  - recurrent visual hallucinations
  - parkinsonism (not to be confused with Parkinson’s disease dementia)
  - suggestive or supportive features include REM sleep disorder, sensitivity to neuroleptic medications (rigidity, neuroleptic malignant syndrome, extrapyramidal symptoms), repeated falls (late disease)

**Etiology and Pathogenesis**

- Lewy bodies (eosinophilic cytoplasmic inclusions) found in both cortical and subcortical structures
- mixed DLB and AD pathology is common

**Epidemiology**

- 15-25% of all dementias

**Treatment**

- acetylcholinesterase inhibitors (e.g. donepezil)

**Prognosis**

- typical survival 3-6 yr

---

### Frontotemporal Dementia (FTD)

**Definition**

- FTD is a progressive dementia; third most common cause of cortical dementia
- behavioural variant of FTD (more common) presents with social conduct disorder predominantly
- language variants:
  1. progressive nonfluent aphasia: non-fluent, laboured articulation/speech, anoma, preserved single word comprehension, word-finding deficit, impaired repetition
  2. semantic dementia: fluent, normal rate, anoma, impaired single word comprehension, intact repetition, use words of generalization (“thing”) or superordinate categories (“animal” for “dog”)

**Etiology and Pathogenesis**

- unknown, likely genetic/familial component
- two main histological types:
  1. frontal lobe degeneration with microvacuolar change
  2. Pick type with astrocytic gliosis ± ballooned cells and inclusion bodies

**Epidemiology**

- 10% of all dementias
Signs and Symptoms
- diagnosis of behavioural variant of FTD:
  - core features:
    1. insidious onset and gradual progression
    2. early decline in social interpersonal conduct
    3. early impairment in regulation of personal conduct
    4. early emotional blunting
    5. early loss of insight
  - supportive features:
    1. behavioural (decline in personal hygiene, mental rigidity, distractibility, hyperorality, perseverative or utilization behaviour)
    2. speech and language (perseverative or stereotyped speech, echolalia, mutism)
    3. physical signs (primitive reflexes, incontinence, akinesia, rigidity, tremor, low and labile blood pressure)
- severe frontal lobe impairment in absence of severe amnesia, aphasia, perceptual disorder
- imaging: predominant frontal and/or anterior temporal atrophy
- EEG usually normal

Creutzfeldt-Jakob Disease (CJD)
- rare degenerative fatal brain disorder caused by prion proteins causing spongiform changes, astrocytosis, and neuronal loss
- most common forms are sporadic (85%), hereditary (5-10%), and acquired (<1%)
- investigations: CSF analysis, MRI brain (cortical and/or subcortical FLAIR changes), EEG (periodic complexes)
- definitive diagnosis is by brain biopsy
- no treatments currently exist

Normal Pressure Hydrocephalus
- see Neurosurgery, NS8

Aphasia
Definition
- an acquired disturbance of language characterized by errors in speech production, writing, comprehension, or reading

Neuroanatomy of Aphasia
- Broca’s area (posterior inferior frontal lobe) involved in speech production (expressive)
- Wernicke’s area (posterior superior temporal lobe) involved in comprehension of language (receptive)
- angular gyrus is responsible for relaying written visual stimuli to Wernicke’s area for reading comprehension
- arcuate fasciculus association bundle connects Wernicke’s and Broca’s areas

Assessment of Language
- assessment of context
  - handedness (writing, drawing, toothbrush, scissors), education level, native language, learning difficulties
- assessment of aphasia
  - spontaneous speech (fluency, paraphasias, repetition, naming, comprehension – auditory and reading, writing, neologisms)

<table>
<thead>
<tr>
<th>Table 12. Approach to Aphasias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluency</td>
</tr>
<tr>
<td>Broca’s</td>
</tr>
<tr>
<td>Motor TCA*</td>
</tr>
<tr>
<td>Mixed TCA*</td>
</tr>
<tr>
<td>Global</td>
</tr>
<tr>
<td>Wernicke’s</td>
</tr>
<tr>
<td>Conduction</td>
</tr>
<tr>
<td>Sensory TCA*</td>
</tr>
<tr>
<td>Anomic</td>
</tr>
</tbody>
</table>

*Transcortical aphasias are typically associated with cerebral anoxia (e.g. post-MI, CO poisoning, hypotension)
Apraxia

Definition
• inability to perform skilled voluntary motor sequences that cannot be accounted for by weakness, ataxia, sensory loss, impaired comprehension or inattention

Clinicopathological Correlations

Table 13. Apraxia

<table>
<thead>
<tr>
<th>Description</th>
<th>Tests</th>
<th>Hemispheres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideomotor</td>
<td>Inability to perform skilled learned motor sequences</td>
<td>Left</td>
</tr>
<tr>
<td>Ideational</td>
<td>Inability to sequence actions</td>
<td>Right and left</td>
</tr>
<tr>
<td>Constructional*</td>
<td>Inability to draw or construct</td>
<td>Right and left</td>
</tr>
<tr>
<td>Dressing*</td>
<td>Inability to dress</td>
<td>Right</td>
</tr>
</tbody>
</table>

*Arefers specifically to the inability to carry out the learned movements involved in construction, drawing, or dressing; not merely the inability to construct, draw, or dress. Many skills aside from praxis are needed to carry out these tasks.

Agnosia

Definition
• disorder in the recognition of the significance of sensory stimuli in the presence of intact sensation and naming

Clinicopathological Correlations

Table 14. Agnosias

<table>
<thead>
<tr>
<th>Description</th>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aperceptive visual agnosia</td>
<td>Bilateral temporo-occipital cortex</td>
</tr>
<tr>
<td>Associative visual agnosia</td>
<td>Bilateral inferior temporo-occipital junction</td>
</tr>
<tr>
<td>Prosopagnosia</td>
<td>Bilateral occipitotemporal areas or right inferior temporo-occipital region</td>
</tr>
<tr>
<td>Colour agnosia</td>
<td>Bilateral inferior temporo-occipital lesions</td>
</tr>
<tr>
<td>Astereognosis</td>
<td>Anterior parietal lobe in the hemisphere opposite the affected hand</td>
</tr>
<tr>
<td>Finger agnosia</td>
<td>Dominant hemisphere parietal-occipital lesions</td>
</tr>
</tbody>
</table>

Mild Traumatic Brain Injury

Definition
• mild TBI = concussion
• trauma induced transient alteration in mental status that may involve loss of consciousness
• hallmarks of concussion: confusion and amnesia, which may occur within minutes
• loss of consciousness (if present) must be less than 30 min, initial GCS must be between 13-15 and post-traumatic amnesia must be less than 24 h

Epidemiology
• 75% of TBIs are estimated to be mild; remainder are moderate or severe (see Neurosurgery, NS30 and Emergency Medicine, ER7)
• highest rates in children 0-4 yr, adolescents 15-19 yr and elderly >65 yr

Clinical Features
• impairments following mild TBI:
  ▪ somatic: headache, sleep disturbance, nausea, vomiting, blurred vision
  ▪ cognitive dysfunction: attentional impairment, reduced processing speed, drowsiness, amnesia
  ▪ emotion and behaviour: impulsivity, irritability, depression
• severe concussion: may precipitate seizure, bradycardia, hypotension, sluggish pupils
• associated conditions: brain contusion, diffuse axonal injury, C-spine injury
Investigations
• neuro exam to identify focal neurologic deficits
• neurocognitive assessment:
  ▪ simple orientation questions are inadequate to detect cognitive changes
  ▪ initial assessment of severity is determined by:
    • Glasgow Coma Scale: mild: 13-15, moderate: 9-12, severe: 3-8
    • sideline evaluation: Standardized Assessment of Concussion, Westmead Post-Traumatic Amnesia Scale, Sport Concussion Assessment Tool
• neuroimaging:
  ▪ x-ray of skull: not indicated for routine evaluation of MTBI
  ▪ CT head as indicated by Canadian CT Head Rules (see Emergency Medicine, ER10)
  ▪ MRI not indicated in initial evaluation – indicated in presence of continued or worsening symptoms despite normal CT

Treatment
• observation for first 24 h after mild TBI in all patients because of risk of intracranial complications
• emergency department for assessment if any loss of consciousness or persistent symptoms
• hospitalization if: with normal CT (GCS <15, seizures, bleeding diathesis), abnormal CT scan
• early rehabilitation to maximize outcomes
  ▪ OT, PT, SLP, vestibular therapy, driving, therapeutic recreation
• pharmacological management of headaches, pain, depression
• cognitive behavioural therapy, relaxation therapy
• follow Return to Play guidelines (www.thinkfirst.ca)

Prognosis
• most recover from mild TBI with minimal treatment, but some experience long-term consequences
• athletes with a previous concussion are at increased risk of subsequent concussion and cumulative brain injury
• repeat TBI can lead to life threatening cerebral edema (controversially known as second impact syndrome) or permanent impairment
• sequelae include
  ▪ postconcussion syndrome: dizziness, headache, neuropsychiatric symptoms, cognitive impairment (usually resolves within weeks to months)
  ▪ post-traumatic headaches: begin within seven days of injury
  ▪ post-traumatic epilepsy: twofold increase in risk of epilepsy in 5 yr post TBI, prophylactic anticonvulsants not effective
  ▪ post-traumatic vertigo

Neuro-oncology

Paraneoplastic Syndromes
• see Endocrinology, E51

Tumours of the Nervous System
• see Neurosurgery, NS10
Movement Disorders

Overview of Movement Disorders

Table 15. Movement Disorder Definitions

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia</td>
<td>Subjective restlessness relieved by stereotypic movements (e.g. squirming)</td>
</tr>
<tr>
<td>Asterix</td>
<td>Loss of muscle contraction (negative myoclonus)</td>
</tr>
<tr>
<td>Athetosis</td>
<td>Slow writhing movements, especially distally</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>Slow and/or small amplitude movements</td>
</tr>
<tr>
<td>Chorea</td>
<td>Brief, abrupt, irregular movements; can appear purposeful in milder forms</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>Any sudden involuntary movement, but the term is often used to describe the stereotypical movements that come with long term neuroleptic or dopaminergic use</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Co-contraction of agonist and antagonists causing sustained twisting movements</td>
</tr>
<tr>
<td>Freezing</td>
<td>Episodes of halted motor action, especially during walking</td>
</tr>
<tr>
<td>Hemiballismus</td>
<td>Unilateral violent flinging movement</td>
</tr>
<tr>
<td>Myokimia</td>
<td>Brief muscle group contraction that is either focal, segmental, or generalized</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Spontaneous, fine, fascicular contraction of muscle</td>
</tr>
<tr>
<td>Tics</td>
<td>Stereotyped repetitive actions due to inner urge; can be suppressed</td>
</tr>
<tr>
<td>Tremor</td>
<td>Rhythmic alternating muscle contraction and relaxation</td>
</tr>
</tbody>
</table>

Function of the Basal Ganglia

- The cerebral cortex initiates movement via excitatory (glutamatergic) projections to the striatum, which then activate two pathways: direct and indirect
  - Direct: cortex → striatum → GPi/SNr → thalamus → motor cortex
    - Activation of this pathway removes the inhibitory effect of the GPi on the thalamus, letting the thalamus activate the cortex and ultimately allowing movement
  - Indirect: cortex → striatum → GPe → STN → GPi/SNr → thalamus → motor cortex
    - Activation of this pathway causes inhibition of the thalamus and ultimately prevents movement

Figure 20. Neural connections of the basal ganglia

In some cases, dystonias may only occur during voluntary movement and sometimes only during specific activities such as writing, chewing, or speaking.

Hemiballismus is a prominent unilateral chorea that is most often due to a vascular lesion of the contralateral subthalamic nucleus.

Some myoclonus is stimulus sensitive and can be induced by noise, movement, light, visual threat or pinprick.
**Movement Disorders**

**Differential Diagnoses**

1. **Tremor:**
   - **postural:** physiologic, anxiety, sedative/alcohol withdrawal, drug toxicity, heavy metal poisoning, carbon monoxide poisoning, thyrotoxicosis, benign essential tremor, cerebellar, Wilson's disease
   - **benign essential tremor** is a common autosomal dominant trait that presents as a bilateral postural tremor of the vertical axis, especially in the upper extremities
   - **intention:** brainstem lesion, cerebellar lesion, alcohol, anticonvulsants, sedatives, Wilson's disease
   - **resting:** Parkinsonism, Wilson's disease, mercury poisoning

   ![Image of basal ganglia](https://via.placeholder.com/150)

   **Figure 21. Horizontal section of basal ganglia**

   **Table 16. Approach to Tremors**

<table>
<thead>
<tr>
<th>Body Part</th>
<th>Resting</th>
<th>Postural</th>
<th>Intention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Part</td>
<td>Distal UE</td>
<td>UE/head/voice</td>
<td>Anywhere</td>
</tr>
<tr>
<td>Characteristics</td>
<td>3-7 Hz pill rolling</td>
<td>6-12 Hz fine tremor</td>
<td>&lt;5 Hz coarse tremor</td>
</tr>
<tr>
<td>Worse with</td>
<td>Rest while concentrating</td>
<td>Sustained posture (outstretched arms)</td>
<td>Finger to nose</td>
</tr>
<tr>
<td>Associated Sx</td>
<td>&quot;TRAP&quot;</td>
<td>Autosomal dominant FHx</td>
<td>Cerebellar findings</td>
</tr>
<tr>
<td>DDx</td>
<td>PD, Parkinsonism, Wilson's disease</td>
<td>Physiologic, benign essential, drugs, hyperthyroid, hyperglycemic</td>
<td>Cerebellar disorders, Wilson's disease, alcohol, MS</td>
</tr>
<tr>
<td>Treatment</td>
<td>Sinemet, surgery, DBS</td>
<td>Propranolol, anticonvulsants, primidone</td>
<td>Treat underlying cause</td>
</tr>
</tbody>
</table>

2. **Chorea:** Huntington\'s disease, neuroacanthocytosis, SLE, APLA syndrome, Wilson\'s disease, cerebrovascular disease, tardive dyskinesia, senile chorea, Sydenham\'s chorea, pregnancy chorea

3. **Dystonia**
   - **primary dystonia:** familial, sporadic (torticollis, blepharospasm, writer\'s cramp)
   - **dystonia-plus syndromes:** dopa-responsive dystonia, myoclonus-dystonia
   - **secondary dystonia:** thalamotomy, stroke, CNS tumour, demyelination, PNS injury, drugs/toxins (L-dopa, neuroleptics, anticonvulsants, Mn, CO, cyanide, methanol)
   - **heterodegenerative dystonias:** Parkinsonian disorders, Wilson\'s disease, Huntington\'s disease

4. **Myoclonus**
   - **physiologic myoclonus:** hiccups, nocturnal myoclonus
   - **essential myoclonus**
   - **epileptic myoclonus**
   - **symptomatic myoclonus:**
     - degenerative disorders (Wilson\'s disease, Huntington disease, Alzheimers)
     - infectious disorders (CJD, viral encephalitis, AIDS-dementia complex)
     - metabolic disorders (drug intoxication/withdrawal, hypoglycemia, hyponatremia, HONK, hepatic encephalopathy, uremia, hypoxia)
     - focal brain damage (head injury, stroke, mass)

   ![Palatal myoclonus](https://via.placeholder.com/150)

   Palatal myoclonus can result from lesion to the dentatorubroolivary pathway, and is associated with an audible clicking.

   ![In a young patient (<45) must do TSH (thyroid disease), ceruloplasmin (Wilson\'s disease), and CT/MRI (cerebellar disease) as indicated by type of tremor.](https://via.placeholder.com/150)

   In a young patient (<45) must do TSH (thyroid disease), ceruloplasmin (Wilson\'s disease), and CT/MRI (cerebellar disease) as indicated by type of tremor.

   ![Alcohol](https://via.placeholder.com/150)

   Alcohol
   - Dampens essential tremor
   - Potentiates intention tremor
   - Does not improve resting tremor of PD

   ![> 90% of essential tremor does not need treatment.](https://via.placeholder.com/150)

   > 90% of essential tremor does not need treatment.

   ![Most common cause of chorea is drug therapy for PD.](https://via.placeholder.com/150)

   Most common cause of chorea is drug therapy for PD.
5. Tics
- **primary tic disorders**: transient tic disorder, chronic tic disorder, Gilles de la Tourette, adult onset or senile
- **secondary tic disorders**: encephalitis, CJD, Sydenham's chorea, head trauma, drugs, mental retardation syndromes
- association with OCD and ADHD

## Parkinson's Disease (PD)

### Etiology
- **sporadic**: combination of oxidative stress to dopaminergic neurons, environmental toxins (e.g., pesticides), accelerated aging, genetics
- **familial** (10%): autosomal dominant α-synuclein mutations, autosomal recessive Parkin gene or DJ-1 gene mutation (juvenile onset)
- **MPTP** (neurotoxin)

### Epidemiology
- mean age of onset is 60 yr
- family history, male, head injury, rural living, exposure to certain neuro toxins

### Pathophysiology
- loss of dopaminergic neurons in pars compacta of substantia nigra, thus reduced dopamine in striatum leading to disinhibition of the indirect pathway and decreased activation of the direct pathway causing increased inhibition of cortical motor areas
- α-synucleinopathy: α-synuclein accumulates in Lewy bodies and causes neuritoxicity in substantia nigra

### Signs and Symptoms
- **positive motor**
  - resting tremor: asymmetric 4-5Hz "pill-rolling" tremor, especially in hands
  - rigidity: lead-pipe rigidity with cogwheeling due to superimposed tremor
- **negative motor**
  - bradykinesia: slow small amplitude movements, fatiguing of rapid alternating movements, difficulty initiating movement
- related findings: masked facies, hypophonia, aprosody (monotonous speech), dysarthria, micrographia, shuffling gait with decreased arm swing
- freezing: occurs with walking triggered by initiating stride or barriers/destinations, lasting seconds
- postural instability: late finding presenting as falls, festinating gait
- cognition: bradyphrenia (slow to think/respond), dementia (late finding)
- behavioural: decreased spontaneous speech, depression, sleep disturbances, anxiety
- autonomic: constipation, urinary retention, sexual dysfunction, later findings of orthostatic hypotension

### Treatment
- pharmacologic
  - mainstay of treatment: Sinemet® (levodopa/carbidopa). Levodopa is a dopamine precursor; carbidopa decreases peripheral metabolism of levodopa, decreasing side effects and increasing half-life of levodopa
  - levodopa related fluctuation: delayed onset of response (affected by mealtime), end-of-dose deterioration ("wearing-off"), random oscillations of on-off symptoms
  - major complication of levodopa is dyskinesia
  - treatment of early PD: dopamine agonists, amantadine, MAOI
  - adjuncts: dopamine agonists, MAOI, anticholinergics (especially if prominent tremors), COMT inhibitors
- surgical: thalamotomy, pallidotomy, DBS (thalamic, pallidal, subthalamic), embryonic dopaminergic stem cell transplantation
- psychiatric (see Psychiatry, PS21)

### Consider an Alternative Diagnosis if Atypical Parkinsonism
- **poor response to L-dopa**
- **abrupt onset of symptoms**
- **rapid progression**
- **early falls**
- **early autonomic dysfunction**
- **symmetric symptoms at onset**
- **early age of onset (<50)**
- **early cognitive impairment**
- **Fx of psychiatric/dementing disorders**
- **recent diagnosis of psychiatric disease**
- **history of encephalitis**
- **unusual toxin exposure**
- **extensive travel history**

### Dopamine Agonist Therapy in Early Parkinson's Disease
- **Cochrane DB Syst Rev 2009;2:CD006564**
- **Study**: Meta-analysis of trials of dopamine agonists in early Parkinson's disease.
- **Results**: Twenty-nine trials were included (n=5247). Dopamine agonists were found to have decreased motor side effects (dyskinesia OR 0.51, dystonia OR 0.64, motor fluctuations OR 0.51) compared to levodopa, but provided poorer symptom control compared to levodopa. Also, other side effects were increased (constipation OR 1.69, hallucinations OR 1.90, dizziness OR 1.45).
- **Conclusion**: Dopamine agonists have fewer motor side effects than levodopa, but provide worse symptom control and increased rate of other side effects.
Other Parkinsonian Disorders

- dementia with Lewy bodies (see Behavioural Neurology, N20)
- progressive supranuclear palsy: tauopathy with limited vertical gaze (classically downgaze), early falls, axial rigidity and akinesia, dysarthria and dysphagia
- corticobasal degeneration: tauopathy with varied presentations but classically presents with unilateral parkinsonism, dystonia/myoclonus, apraxia ± “alien limbs” phenomenon
- multiple system atrophy: synucleinopathy presenting as either cerebellar predominant (previously olivo-ponto cerebellar atrophy or OPCA) or parkinsonism predominant (previously striato-nigral degeneration). Both are associated with early autonomic dysfunction (previously Shy-Drager syndrome)
- vascular parkinsonism: multi-infarct presentation with lower body parkinsonism

Huntington’s Disease

Etiology and Pathogenesis
- genetics: autosomal dominant CAG repeats (with anticipation) in Huntington gene on Chromosome 4, which leads to accumulation of defective protein in neurons
- pathology: global cerebral atrophy, especially affecting the striatum, leading to increased activity of the direct pathway and decreased activity of the indirect pathway

Epidemiology
- North American prevalence 4-8/100,000
- mean age of onset 35-44 yr; but varies with degree of anticipation from 5-70

Signs and Symptoms
- typical progression: insidious onset with clumsiness, fidgetiness and irritability, progressing over 15 yr to frank dementia, psychosis and chorea
  - dementia: progressive memory impairment and loss of intellectual capacity
  - chorea: begins as movement of eyebrows and forehead, shrugging of shoulders, and parakinesia (pseudopurposeful movement to mask involuntary limb jerking)
  - progresses to dance-like or ballism, and in late stage is replaced by dystonia and rigidity
  - mood changes: irritability, depression, anhedonia, impulsivity, bouts of violence

Investigations
- MRI: enlarged ventricles, atrophy of cerebral cortex and caudate nucleus
- genetic testing
  - expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeats in the HTT gene
  - CAG repeats on chromosome 4p16.3 that encodes the protein huntingtin

Treatment
- no disease altering treatment
- psychiatric symptoms: antidepressants and antipsychotics
- chorea: neuroleptics and benzodiazepines
- dystonia: botulinum toxin

Dystonia

Epidemiology
- second most common movement disorder, after parkinsonism

Clinical Features
- symptoms exacerbated by fatigue, stress, emotions; relieved by sleep or specific tactile/proprioceptive stimuli (‘geste antagoniste’, e.g. place hand on face for cervical dystonia)
- more likely to be progressive and generalize if younger onset or leg dystonia

Treatment
- local medical: botulinum toxin
- systemic medical: anticholinergics (benztropine), muscle relaxants (baclofen), benzodiazepines, antiparkinsonergics (reserpine, neuroleptics); dopamine for dopa-responsive dystonia
- surgical: surgical denervation of affected muscle, stereotaxic thalamotomy (unilateral dystonia), posteroverentral pallidotomy
Tic Disorders

Clinical Classification
- **motor tics**
  - *simple*: blinking, head jerking
  - *dystonic*: bruxism, grinding teeth, abdominal tension, sustained mouth opening
  - *complex*: copropraxia (obscene gestures), echopraxia (imitate gestures), throwing, touching
- **vocal tics**
  - *simple*: blowing, coughing, grunting, throat clearing
  - *complex*: coprolalia (shout obscenities), echolalia (repeat others’ phrases), palilalia (repeat own phrases)

Treatment
- dopamine blocker

Tourette’s Syndrome (aka Gilles de la Tourette’s Syndrome)

Definition according to DSM IV
1. Presence of motor and vocal tics at some point during illness, not necessarily concurrently
2. Multiple tics a day nearly everyday or intermittently throughout 1 yr with no tic-free periods greater than 3 mo
3. Onset prior to 18 yr of age
4. Not due to effect of a substance or general medical condition

Epidemiology
- prevalence among adolescents 3-5/100,000; M>F

Signs and Symptoms
- **tics**: wide variety that wax and wane in type and severity
  - can be voluntarily suppressed for some time but are preceded by unpleasant sensation that is relieved once tic is carried out
- psychiatric: compulsive behaviours (associated with OCD and ADHD), hyperactive behaviour, rages, sleep-wake disturbances, learning disabilities

Treatment
- clonidine, clonazepam

Prognosis
- begins at 5 yr of age progressively increasing until 10 yr; often improves in adolescence and 50% are tic-free by 18 yr of age

Cerebellar Disorders

Clinico-Anatomic Correlations
- **vermis**: trunk/gait ataxia
- **cerebellar lobe (i.e. lateral)**: rebound phenomenon, scanning dysarthria, dysdiadochokinesia, dysmetria, nystagmus

Symptoms and Signs of Cerebellar Dysfunction
- nystagmus: observe on extra-ocular movement testing (most common is gaze-evoked nystagmus)
- dysarthria (ataxic): abnormal modulation of speech velocity and volume – elicit scanning/telegraphic/slurred speech on spontaneous speech (see CN X Vagus Nerve, N10)
- ataxia: broad-based, uncoordinated, lurching gait
- dysmetria: irregular placement of voluntary limb or ocular movement
- dysdiadochokinesia: impairment of rapid alternating movements (e.g. pronation – supination task)
- postural instability: truncal ataxia on sitting, titubation (rhythmic rocking of trunk and head), difficulty with tandem and broad-based gait
- intention tremor: typically orthogonal to intended movement, and increases as target is approached
- hypotonia: decreased resistance to passive muscular extension (occurs shortly after injury to lateral cerebellum)
- pendular patellar reflex: knee reflex causes pendular motion of leg (occurs after injury to cerebellar hemispheres)
- rebound phenomenon: overcorrection after displacement of a limb
- ocular apraxia: gaze dysmetria

<table>
<thead>
<tr>
<th></th>
<th>Vestibular</th>
<th>Cerebellar</th>
<th>Sensory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nystagmus/Vertigo</td>
<td>+</td>
<td>=</td>
<td>–</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>=</td>
<td>=</td>
<td>–</td>
</tr>
<tr>
<td>Limb ataxia</td>
<td>–</td>
<td>+</td>
<td>+esp.leg</td>
</tr>
<tr>
<td>Slant</td>
<td>Worsewith</td>
<td>Poorwith</td>
<td>+ve</td>
</tr>
<tr>
<td></td>
<td>eyes closed</td>
<td>eyes open</td>
<td>Romberg</td>
</tr>
<tr>
<td>Vibration/Proprioception</td>
<td>Normal</td>
<td>Normal</td>
<td>Impaired</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>esp. distal</td>
</tr>
<tr>
<td>Achilles reflexes</td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>absent</td>
</tr>
</tbody>
</table>
**Wernicke-Korsakoff Syndrome**

- see Psychiatry, PS23
- note that alcohol can also cause a cerebellar ataxia separate from thiamine deficiency; this ataxia can be due to cerebellar atrophy or alcohol polyneuropathy

**Cerebellar Ataxias**

**Congenital Ataxias**
- early onset nonprogressive ataxias associated with various syndromes as well as developmental abnormalities (e.g. Arnold-Chiari malformation, Dandy-Walker cysts)

**Hereditary Ataxias**
- autosomal recessive: includes Friedrich’s ataxia, ataxia telangiectasia, vitamin E deficiency
  - signs: gait and limb ataxia, weakness, areflexia, extensor plantar reflex, impaired proprioception and vibration, dysarthria
  - death in 10-20 yr from cardiomyopathy or kyphoscoliotic pulmonary restriction
- autosomal dominant: most commonly spinocerebellar ataxias (30 types, most due to CAG repeats)
  - signs: ataxia and dysarthria; ± myoclonus, chorea, polyneuropathy, pyramidal or extrapyramidal features, hyporeflexia, seizures, dementia

**Acquired Ataxias**
- neurodegeneration (e.g. multiple system atrophy)
- systemic: alcohol, celiac sprue, hypothyroidism, Wilson’s, thiamine deficiency
- toxins: carbon monoxide, heavy metals, lithium, anticonvulsants, solvents
- vascular: infarct, bleed, basilar migraine
- autoimmune: MS, Miller-Fischer (GBS)

**Vertigo**

- see Otolaryngology, OT12

**Gait Disturbances**

**Approach to Gait Disturbances**

1. **Characterization of the gait disturbance**
   - posture, stride length, width between feet, height of step, stability of pelvis, symmetry, arm swing, elaborate/inconsistent movements, standing from sitting

2. **Identification of accompanying neurologic signs**
   - full neurological exam required (diagnosis often can be made by P/E alone)

3. **Identify red flags**
   - sudden onset, cerebellar ataxia, paresis (hemi, para or quadra), bowel/bladder incontinence

4. **Work up**
   - based on etiology – requires blood work, neuroimaging and urgent neurologist referral

**Table 17. Types of Gait Disturbance**

<table>
<thead>
<tr>
<th>Location</th>
<th>Description</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual loss</td>
<td>Broad based gait with tentative steps</td>
<td>Cataract surgery without lens replacement</td>
</tr>
<tr>
<td>Proprioceptive loss</td>
<td>Sensory ataxia: wide-based with high stepping posture and positive Romberg</td>
<td>Demyelinating neuropathies, paraneoplastic syndrome, tabes dorsalis, MS, compressive myelopathy, B12 deficiency</td>
</tr>
<tr>
<td>Peripheral vestibular lesion</td>
<td>1. Vestibular ataxia</td>
<td>1. Tumour, trauma, infectious, Ménière’s disease</td>
</tr>
<tr>
<td>1. Acute</td>
<td>2. Disequilibrium</td>
<td>2. Ototoxic drugs</td>
</tr>
<tr>
<td>2. Bilateral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral nerve disorder</td>
<td>Steppage gait</td>
<td>Acquired/hereditary peripheral neuropathy, compressive peroneal neuropathy, L4-5 radiculopathy</td>
</tr>
<tr>
<td>1. Foot drop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Lumbosacral radiculopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myopathies</td>
<td>Waddling gait: broad based, short stepped gait with pronounced lumbar lordosis, rotation of pelvis</td>
<td>Progressive muscular dystrophy</td>
</tr>
</tbody>
</table>
**Motor Neuron Disease**

### Amyotrophic Lateral Sclerosis (ALS) (aka Lou Gehrig’s Disease)

**Definition**
- progressive neurodegenerative disease that causes UMN and LMN symptoms and is ultimately fatal

**Etiology**
- idiopathic (most), genetic (5-10% familial, especially SOD1 mutation, other: C9orf72, TARDBP)

**Pathology**
- disorder of anterior horn cells of spinal cord, cranial nerve nuclei, and corticospinal tract

**Epidemiology**
- 5/100,000; incidence increases with age

**Signs and Symptoms**
- limb motor symptoms: segmental and asymmetrical UMN and LMN symptoms
- bulbar findings: dysarthria (flaccid or spastic), dysphagia, tongue atrophy and fasciculations, facial weakness and atrophy
- pseudobulbar affect, frontotemporal dementia (up to 10%)
- sparing of sensation, ocular muscles and, sphincters

**Investigations**
- EMG: chronic denervation and reinnervation, fasciculations
- NCS: to rule out peripheral neuropathy (i.e. multifocal motor neuropathy with conduction block)
- CT/MRI: to rule out cord disease/compression

**Management**
- riluzole (modestly slows disease progression)
- symptomatic relief
  - spasticity/cramping: baclofen, tizanidine, regular exercise and physical therapy
  - sialorrhea: TCA (i.e. amitriptyline), sublingual atropine drops, parotid/submandibular botox (rare)
  - pseudobulbar affect: dextromethorphan/quinidine, TCA, SSRI
  - non-pharmacologic: high caloric diet, ventilatory support (especially BiPAP), early nutritional support (i.e. PEG tube), rehabilitation (PT, OT, SLP), psychosocial support

**Prognosis**
- median survival 3 yr; death due to respiratory failure

### Other Motor Neuron Diseases

- degenerative
  - progressive muscular atrophy (progressive bulbar palsy): only LMN symptoms with asymmetric weakness, later onset than ALS, 5-10% of patients in ALS centres
  - primary lateral sclerosis (progressive pseudobulbar palsy): UMN symptoms, later onset, not fatal with variable disability; 5-10% of patients in ALS centres
  - spinal muscular atrophy: pediatric disease with symmetric LMN symptoms
- infectious
  - post-polio syndrome: residual asymmetric muscle weakness, atrophy
- acquired
  - multifocal motor neuropathy: conduction block on NCS, asymmetric LMN symptoms, ± anti-GM1 Ab, treatable with IVlg

---

Table 17. Types of Gait Disturbance (continued)

<table>
<thead>
<tr>
<th>Location</th>
<th>Description</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyramidal/Corticospinal tract</td>
<td>Spastic gait: spastic foot drop,</td>
<td>Unilateral: stroke (ischemic/hemorrhagic)</td>
</tr>
<tr>
<td>lesion</td>
<td>circumduction, scissoring of legs or</td>
<td>Bilateral: cervical spondylosis, cerebral palsy,</td>
</tr>
<tr>
<td>1. Unilateral</td>
<td>toe walking with bilateral</td>
<td>spinal cord tumour, combined spinal cord</td>
</tr>
<tr>
<td>2. Bilateral</td>
<td>circumduction</td>
<td>degeneration, MS, motor neuron disease</td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>1. Parkinsonian gait: small paces,</td>
<td>Infarct, Huntington’s, Sydenham’s chorea,</td>
</tr>
<tr>
<td></td>
<td>stooped posture, reduced armswing</td>
<td>Wilson’s disease, lupus, neuroleptic medications,</td>
</tr>
<tr>
<td></td>
<td>2. Choreic/semiballistic/dystonic gait</td>
<td>polycythemia vera, genetic dystonia</td>
</tr>
<tr>
<td>Cerebellar Disorder</td>
<td>Cerebellar ataxic gait: wide-based without</td>
<td>Primary and secondary neoplasm, toxins</td>
</tr>
<tr>
<td></td>
<td>high stepping; veers to side of lesion</td>
<td>(alcohol), vit. E deficiency, hypothyroid, hypoxia,</td>
</tr>
<tr>
<td></td>
<td>Alcoholic gait</td>
<td>hypoglycemia, paraneoplastic syndrome</td>
</tr>
</tbody>
</table>
## Peripheral Neuropathies

### Diagnostic Approach to Peripheral Neuropathies

1. Differentiate: motor vs. sensory vs. autonomic vs. mixed
2. Pattern of deficit: symmetry; focal vs. diffuse; upper vs. lower limb; cranial nerve involvement
3. Temporal pattern: acute vs. chronic; relapsing remitting vs. constant vs. progressive
4. History: PMH, detailed FHx, exposures (e.g. insects, toxins, sex, travel), systemic symptoms
5. Detailed peripheral neuro exam: LMN findings, differentiate between root and peripheral nerves, cranial nerves, respiratory status

### Classification

- **mononeuropathy**: dermatomal deficit due to single nerve root lesion
  - due to disc herniation or root compression causing radicular pain
  - little tactile anaesthesia, as dermatomes overlap
- **polyneuropathy**: single nerve deficit
  - one type is cauda equina syndrome (lumbosacral roots)
- **plexopathy**: deficit matching distribution of a nerve plexus
  - **brachial plexopathy**
    - upper (C5–C7): LMN sx of shoulder and upper arm muscles (Erb’s palsy)
    - lower (C8-T1): LMN sx and sensory sx of forearm and hand (Klumpke's palsy)
  - **lumbosacral plexopathy** (rare, especially unilateral)
  - **Dx**: idiopathic neuritis, infarction (i.e. diabetes), compression
- **mononeuropathy**: single nerve deficit
  - **carpal tunnel syndrome** (most common): compression of median nerve at wrist
    - symptoms: wrist pain, paresthesia first 3 and ½ digits, ± radiation to elbow, worse at night
    - signs: Tinel’s sign, Phalen’s test, thenar muscle wasting, sensory deficit
  - **EMG and NCS**: slowing at wrist (both motor and sensory)
  - **Bell’s palsy** (most common cranial neuropathy): see Otolaryngology, OT22
    - *other less common* mononeuropathies due to entrapment/compression: ulnar (compression at elbow), median (at pronator teres), radial (at spiral groove of humerus), obturator (femoral canal), peroneal (due to crossing legs or surgical positioning), posterior tibial (tarsal canal)
- **mononeuropathy multiple**: deficit affecting multiple discrete nerves (asymmetric)
  - *must rule out vasculitis or collagen vascular disease*
- **polyneuropathy**: symmetrical distal stocking-glove pattern
  - symmetrical distal sensorimotor deficit affecting longest fibres first (stocking-glove distribution), hypotonia; progression of dysesthesia early and weakness later
  - *etiologies*: DM (most common), renal disease, substances, toxins, genetics, SLE, HIV, leprosy, alcohol, B12 deficiency, uremia
- **chronic inflammatory demyelinating polyneuropathy (CIDP)**
  - chronic relapsing sensorimotor polyneuropathy with increase protein in CSF and demyelination (shown on EMG/NCS)
  - *course* is fluctuating, in contrast with the acute onset of GBS
  - *treatment*: first-line is prednisone; alternatives are plasmapheresis, IVIg, and azathioprine

### Table 18. Differential Diagnosis of Symmetric Polyneuropathy*

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Mechanism</th>
<th>Course</th>
<th>Modalities</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAN</td>
<td>Ischemic</td>
<td>Chronic</td>
<td>S/M</td>
<td>see Rheumatology, RH19</td>
</tr>
<tr>
<td>SLE</td>
<td>Ischemic</td>
<td>Chronic</td>
<td>S/M</td>
<td>see Rheumatology, RH11</td>
</tr>
<tr>
<td>RA</td>
<td>Ischemic</td>
<td>Chronic</td>
<td>S/M</td>
<td>see Rheumatology, RH8</td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/A</td>
<td>HIV serology</td>
</tr>
<tr>
<td>Leptosy</td>
<td>Infiltrative</td>
<td>Chronic</td>
<td>S/A</td>
<td>Leprosy serology</td>
</tr>
<tr>
<td>Lyme</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>M</td>
<td>Nerve biopsy</td>
</tr>
<tr>
<td>Immune</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GBS</td>
<td>Demyelination</td>
<td>Acute</td>
<td>M</td>
<td>LP († protein; no † cells)</td>
</tr>
<tr>
<td>CIDP</td>
<td>Demyelination</td>
<td>Chronic</td>
<td>S/M</td>
<td>LP († protein)</td>
</tr>
<tr>
<td>Hereditary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMSN</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/M</td>
<td>Genetic testing</td>
</tr>
<tr>
<td>Neoplastic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraneoplastic Myeloma</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/M</td>
<td>Paraneoplastic antibodies</td>
</tr>
<tr>
<td>Myeloma</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/M</td>
<td>SPEP</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Axonal</td>
<td>Chronic</td>
<td>M</td>
<td>SKELETON BONE SURVEY</td>
</tr>
<tr>
<td>Monoclonal gammopathy</td>
<td>Demyelination</td>
<td>Chronic</td>
<td>S/M</td>
<td>Bone marrow biopsy</td>
</tr>
<tr>
<td>Toxin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EtOH</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
<td>GGT, MCV</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
<td>Urine heavy metals</td>
</tr>
<tr>
<td>Medications</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
<td>Drug levels</td>
</tr>
</tbody>
</table>

* DDx of Demyelinating Neuropathy
  - GBS, CIDP, paraproteinemia, diphtheria, amiodarone, Charcot-Marie-Tooth, storage diseases, pressure palsies, predisposition, paraneoplastic.
  - Axonal neuropathies have decreased amplitude on NCS; demyelinating neuropathies have decreased velocity on NCS.
  - Otoxic drugs (e.g. aminoglycosides) should not be given to diabetics.
  - Sensory neuropathy of the feet prevent them from adequately compensating for loss of vestibular function.

- **Tinel’s Sign**: tap lightly over the median nerve at the wrist. The patient’s symptoms of carpal tunnel will be elicited in a positive test.
- **Phalen’s Test**: hold both wrists in forced flexion (with the dorsal surfaces of the hands pressed against each other) for 30-60 s. Test is positive if symptoms of carpal tunnel are elicited.

- **Toronto Notes 2014**
- **Role of Laboratory and Genetic Testing**
  - **Evaluation of Distal Symmetric Polyneuropathy**
    - **Rule of Laboratory and Genetic Testing**
      - **Neurology** 2009/12:185-192
      - Screening lab tests: Blood glucose, serum B12 with metabolites, serum protein immunofixation electrophoresis.
      - Genetic testing: Indicated for cryotogenic polyneuropathy exhibiting classic hereditary neuropathy phenotype. Screen for CMT1A duplication/deletion and Cx32 mutations.
Table 18. Differential Diagnosis of Symmetric Polyneuropathy* (continued)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Mechanism</th>
<th>Course</th>
<th>Modalities</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic</td>
<td>Diabetic</td>
<td>Chronic</td>
<td>S/A</td>
<td>Fasting glucose, Hba1c, 2 h OGTT</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Axonal</td>
<td>Chronic</td>
<td>S/M</td>
<td>TSH, T3, T4</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Axonal</td>
<td>Chronic</td>
<td>S/A</td>
<td>Electrolytes, Cr, BUN</td>
</tr>
<tr>
<td>Nutritional</td>
<td>B12 deficiency</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
</tr>
<tr>
<td>Other</td>
<td>Porphyrin</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>Amyloid</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S</td>
</tr>
</tbody>
</table>

*Abbreviations: CIDP – chronic inflammatory demyelinating polyradiculoneuropathy; GGT – gamma-glutamyl transferase; HMSN – hereditary motor sensory neuropathy; OGTT – oral glucose tolerance test; PAN – polyarteritis nodosa; RA – rheumatoid arthritis; SLE – systemic lupus erythromatosus; SPEP – serum protein electrophoresis; S – sensory; M – motor; A – autonomic

Guillain-Barré Syndrome (GBS)

- **Definition:** acute rapidly evolving polyneuropathy that often starts in the distal lower limbs and ascends
- **Etiology**
  - autoimmune attack and damage to peripheral nerve myelin
  - sometimes preceded by viral/bacterial infections
- **Signs and Symptoms**
  - sensory: distal and symmetric paresthesias, loss of proprioception and vibration sense, neuropathic pain
  - motor: weakness starting distally in legs, areflexia
  - autonomic: blood pressure dysregulation, arrhythmias, bladder dysfunction
- **Investigations**
  - CSF: albuminocytological dissociation (high protein, normal WBC)
  - EMG/NCS: conduction block, differential or focal (motor>sensory) slowing, decreased F-wave, sural sparing
- **Subtypes**
  1. acute inflammatory demyelinating polyneuropathy (AIDP)
  2. acute motor-sensory axonal neuropathy (AMSAN)
  3. acute motor axonal neuropathy (AMAN)
- **Treatment**
  - IVIg or plasmapheresis, ± pain management, monitor vitals and vital capacity
- **Prognosis**
  - peak of symptoms at 2-3 wk, resolution at 4-6 wk
  - 5% mortality (higher if require ICU); up to 15% have permanent deficits

Neuromuscular Junction Diseases

Clinical Approach to Disorders of the Neuromuscular Junction

Table 19. Common Disorders of the Neuromuscular Junction

<table>
<thead>
<tr>
<th></th>
<th>Myasthenia Gravis</th>
<th>Lambert-Eaton</th>
<th>Botulism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular/bulbar paresis</td>
<td>+</td>
<td>-</td>
<td>+ + (early)</td>
</tr>
<tr>
<td>Limb weakness</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fatiguability</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Post-exercise enhancement</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reflexes</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Anticholinergic sx</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sensory sx</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Associated conditions</td>
<td>Thymoma</td>
<td>Small cell carcinoma</td>
<td>GI S&amp;S</td>
</tr>
<tr>
<td>Repetitive EMG stimulation</td>
<td>Decremental response</td>
<td>Incremental response</td>
<td>↑ (rapid stimulation) ↓ (slow stimulation)</td>
</tr>
</tbody>
</table>

Myasthenia Gravis (MG)

**Etiology and Pathophysiology**

- progressive autoimmune disorder due to anti-AChR antibodies, resulting in early saturation at the NMJ and inadequate muscle activation with increasing nerve stimulation
- 15% of patients with MG have associated thymic neoplasia, 85% have thymic hyperplasia
Epidemiology
• bimodal age of onset – 20s (mostly women) and 60s (mostly men)

Signs and Symptoms
• see Table 19
• fatiguable, symmetric or asymmetric weakness without reflex changes, sensory changes, or coordination abnormalities
• ocular (diplopia/ptosis), bulbar (dysarthria/dysphagia), and/or proximal limb weakness
• symptoms may be exacerbated by infection, pregnancy, menses, and various drugs
• respiratory muscle weakness may lead to respiratory failure

Investigations
• edrophonium (Tensilon*) test
  ▪ assess for improvement over 2 min following edrophonium injection
• EMG
  ▪ repetitive stimulation → decremental response
  ▪ single fibre electromyography shows increased jitter (80-100% sensitivity)
  ▪ spirometry – forced vital capacity may be used to monitor adequacy of respiratory effort over time
• anti-acetylcholine receptor antibody assay (70-80% sensitivity)
• MUSK antibody may be used if seronegative for AChR antibody
• CT/MRI to screen for thymoma/thymic hyperplasia

Treatment
• thymectomy
  ▪ 85% of patients show improvement or remission
• symptomatic relief
  ▪ acetylcholinesterase inhibitors (e.g. pyridostigmine)
  ▪ does not affect primary pathologic process so rarely results in control of disease when used alone
• immunosuppression
  ▪ steroids are mainstay of treatment (70-80% remission rate)
  ▪ azathioprine, cyclophosphamide and mycophenolate as adjuncts or as steroid sparing therapy
  ▪ short-term immunomodulation (for crises)
  ▪ IVlg and plasmapheresis

Prognosis
• 30% eventual spontaneous remission
• with treatment, life expectancy is equal to that of a person without MG, but quality of life may vary

Lambert-Eaton Myasthenic Syndrome (LEMS)

Etiology and Pathophysiology
• autoimmune disorder due to antibodies against presynaptic voltage-gated calcium channels, causing decreased ACh release at the NMJ
• 50-66% are associated with small cell carcinoma of the lung

Signs and Symptoms
• see Table 19
• weakness of skeletal muscles without sensory or coordination abnormalities
• reflexes are diminished or absent, but increase after active muscle contraction
• bulbar and oculomotor muscles affected in 25% (vs. 90% in MG)
• prominent anticholinergic autonomic symptoms (dry mouth > impotence > constipation > blurred vision)

Investigations
• edrophonium test (see Myasthenia Gravis, N32) → no response
• EMG
  ▪ rapid (>10 Hz) repetitive stimulation → incremental response
  ▪ post-exercise facilitation → an incremental response with exercise
  ▪ screen for malignancy, especially small cell lung cancer

Treatment
• tumour removal
• acetylcholine modulation
  ▪ increased acetylcholine release (3,4-diaminopyridine)
  ▪ decreased acetylcholine degradation (pyridostigmine)
• immunomodulation
  ▪ steroids, plasmapheresis, IVlg

Figure 22. Myasthenia gravis
Tensilon® is a drug that inhibits acetylcholinesterase. It improves muscle function immediately in myasthenia gravis, but not in a cholinergic crisis. This test is infrequently used. When performed, a crash cart should be nearby as respiratory difficulty and/or bradycardia may occur.

Figure 23. Lambert-Eaton myasthenic syndrome (LEMS)
Botulism

Etiology and Pathophysiology
- caused by a toxin produced by spores of *Clostridium botulinum* bacteria, which is found in soil and water throughout the world. Bacteria can enter the body through wounds or by ingesting improperly preserved foods
- infantile botulism is the most common form, and is usually from ingestion of honey or corn syrup

Signs and Symptoms
- occur 6–48 h after ingestion
- difficulty with convergence, ptosis, paralysis of extraocular muscles
- dilated, poorly reactive pupils
- other autonomic dysfunction: jaw weakness, dysarthria, dysphagia
- spreads to trunk and limbs
  - abdominal cramps with nausea and vomiting
  - symmetric weakness with paralysis and absent/decreased deep tendon reflexes
  - anticholinergic symptoms: dry mouth, constipation, urinary retention
- rarely respiratory distress, potentially advancing to respiratory failure

Investigations
- blood test for toxin
- stool culture

Treatment
- botulinum anti-toxin – good prognosis with prompt treatment
- supportive therapy as required

Myopathies

Clinical Approach to Muscle Diseases

Table 20. Myopathies

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Key Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Myalgias, Pharyngeal involvement</td>
<td>CK↑, Biopsy: endomysial infiltrates; necrosis</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Myalgias, Characteristic rashes</td>
<td>CK↑, Biopsy: perifascicular atrophy</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>See Respirology, R13</td>
<td>ACE↑, Biopsy: granulomas</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
<td>Weak quadriceps and deep finger flexors</td>
<td>CK↑, Biopsy: inclusion bodies</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid († or ↓)</td>
<td>See Endocrinology, E20, E33</td>
<td>TSH↑, serum cortisol, calcium panel</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parathyroid († or ↓)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>Medication or toxin history</td>
<td>Toxicology screen</td>
</tr>
<tr>
<td>Critical illness myopathy</td>
<td>ICU patient steroids and nondepolarizing paralyzing agents</td>
<td>Biopsy: selective loss of thick myosin filaments</td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parastatic, bacterial or viral</td>
<td>Myalgias, Inflammatory myopathy</td>
<td>CK↑, myoglobin</td>
</tr>
<tr>
<td>Hereditary dystrophy</td>
<td>Early onset (Duchenne and Becker)</td>
<td>Dystrophin analysis: absent</td>
</tr>
<tr>
<td>Becker</td>
<td>Progressive proximal muscle weakness</td>
<td>Dystrophin analysis: abnormal</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>Distal myopathy, Myotonia</td>
<td>Genetic testing</td>
</tr>
<tr>
<td>Hereditary metabolic</td>
<td>Exercise-related myalgias, cramping, and myoglobinuria</td>
<td>CK↑, lactate, serum/urinary myoglobin↑</td>
</tr>
<tr>
<td>Hereditary periodic paralysis</td>
<td>“Channelopathy” Episodic weakness</td>
<td>Normal, up or down K↑</td>
</tr>
</tbody>
</table>

Myopathies are characterized by prominent symmetric proximal weakness and absent sensory changes.

Good Questions to Assess Proximal Weakness
- Legs: climbing stairs, stand from sit
- Arms: reach above head, wash hair

Common Medications that Cause Myopathy: steroids, statins, antiretrovirals, thyroxine, fibrates, cyclosporine, ipecac.

Common Drugs that Cause Myopathy: ethanol, cocaine, heroin.
Table 20. Myopathies (continued)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Key Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary mitochondrial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MERRF</td>
<td>Myoclonus, generalized seizures, dementia, myopathy</td>
<td>Biopsy: ragged red fibres</td>
</tr>
<tr>
<td>MELAS</td>
<td>Pediatric onset, stroke-like symptoms, episodic vomiting, dementia</td>
<td>Increased lactate</td>
</tr>
<tr>
<td>Kearns Sayre</td>
<td>Progressive ophtalmoplegia, retinal pigment degeneration, cardiac conduction abnormalities</td>
<td></td>
</tr>
</tbody>
</table>

MERRF = mitochondrial encephalomyopathy with ragged red fibers; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

**Polymyositis/Dermatomyositis**

- see Rheumatology, RH15

**Myotonic Dystrophy**

Etiology and Pathophysiology
- unstable trinucleotide (CTG) repeat in DMK gene (protein kinase) at 19q13.3, number of repeats correlates with severity of symptoms
- autosomal dominant

Epidemiology
- most common adult muscular dystrophy
- prevalence 3-5/100,000

Signs and Symptoms
- appearance: ptosis, bifacial weakness, frontal baldness (including women), triangular face giving a drooping/dull appearance
- physical exam
  - distribution of weakness: distal weaker than proximal (in contrast to other myopathies), steppage gait
  - myotonia: delayed relaxation of muscles after exertion (elicit by tapping on thenar muscles with hammer)
  - cardiac: 90% have conduction defects (1st heart block; atrial arrhythmias)
  - respiratory: hypoventilation 2nd to muscle weakness
  - ocular: subcapsular cataracts, retinal degeneration, decreased intraocular pressure
  - other: diabetes, infertility, testicular atrophy
- EMG: subclinical myotonia – long runs with declining frequency and amplitude

Treatment and Prognosis
- no cure, progressive, death usually around 50 yr
- management of myotonia: phenytoin

**Duchenne and Becker Muscular Dystrophy**

- see Pediatrics, P44

**Pain Syndromes**

**Approach to Pain Syndromes**

Definitions
- nociceptive pain: pain arising from normal activation of peripheral nociceptors
- neuropathic pain: pain arising from direct injury to neural tissue, bypassing nociceptive pathways
- spontaneous pain: unprovoked burning, shooting, or lancinating pain
- paresthesiae: spontaneous abnormal nonpainful sensations (e.g. tingling)
- dyesthesiae: evoked pain with inappropriate quality or excessive quantity
- allodynia: a dyesthetic response to a non-noxious stimulus
- hyperalgesia: an exaggerated pain response to a noxious stimulus

- Pinprick sensation mediated by Aδ fibers
- Pain due to tissue damage is mediated by C fibers
Non-pharmacological Management
- physical (PT, acupuncture, chiropractic manipulation, massage)
- psychoeducational (CBT, family therapy, education, psychotherapy)

Medical Pain Control
- combination multi-modal therapy is important
- primary analgesics: acetaminophen, NSAIDs (often used for soft tissue injuries, strains, sprains, headaches and arthritis), opiates
- adjuvants: antidepressants (TCAs, SSRIs), anticonvulsants (gabapentin, carbamazepine, pregabalin), baclofen, sympatholytics (phenoxybenzamine), α2-adrenergic agonists (clonidine)

Surgical Pain Control
- peripheral ablation: nerve blocks, facet joint denervation
- direct delivery: implantable morphine pump
- central ablation: stereotactic thalamotomy, spinal tractotomy or dorsal root entry lesion
- DBS or dorsal column stimulation

**Neuropathic Pain**

Definition
- pain resulting from a disturbance of the central or peripheral nervous system

Symptoms and Signs
- hyperalgesia/allodynia
- subjectively described as burning, heat/cold, pricking, electric shock, perception of swelling, numbness (i.e. stocking/sock distribution)
- can be spontaneous or stimulus evoked
- distribution may not fall along classical neuro-anatomical lines
- associated issues: sleep difficulty, anxiety/stress/mood alteration

Causes of Neuropathic Pain
- sympathetic
  - complex regional pain syndrome
- central: abnormal CNS activity
  - phantom limb, post spinal cord injury, post stroke, MS
- non-sympathetic: damage to peripheral nerves
  - systemic disease: DM, thyroid disease, renal disease, rheumatoid arthritis
  - nutritional/toxicity: alcoholism, pernicious anemia, chemotherapy
  - infectious: post-herpetic, HIV
  - trauma/compression: nerve entrapment, trigeminal neuralgia, post surgical, nerve injury, cervical/lumbar radiculopathy, plexopathy

Treatment
- identify/treat underlying cause
- pharmacotherapy
  - Stepwise approach (Canadian Pain Society, 2007): TCA, anticonvulsant, SNRI, topical lidocaine, long acting opiate (caution), tramadol
  - other: capsaicin cream, intrathecal opioid or clonidine, botulinum toxin injection, nerve block
- common non-pharmacologic therapies
  - neuropsychiatry: cognitive behavioural therapy, psychotherapy
  - rehabilitation: physiotherapy
  - complementary and alternative medicine: acupuncture, meditation, massage therapy, traditional Chinese medicine
- surgical therapies: dorsal column neurostimulator, DBS (thalamus)

**Tic Douloureux (Trigeminal Neuralgia)**

Clinical Features
- recurrent episodes of sudden onset, excruciating unilateral paroxysmal shooting “electric” pain in trigeminal root territory (V3\(\geq\)V2\(\geq\)V1)
- may have normal sensory exam
- pain lasts seconds/minutes over days/weeks; may remit for weeks/months
- triggers: touching face, eating, talking, cold wind, shaving, applying make-up
Etiology
- **classic TN:** idiopathic
- **secondary TN:** compression by tortuous blood vessel (superior cerebellar artery), cerebellopontine angle tumour (5%), multiple sclerosis (5%)

Epidemiology
- **F > M:** usually middle-aged and elderly

Diagnosis
- clinical diagnosis
- investigate for secondary causes, which are more likely if bilateral TN or associated sensory loss
  - MRI to rule out structural lesion, MS or vascular lesion

Treatment
- first line: carbamazepine or oxcarbazepine
- second line: baclofen or lamotrigine
- narcotics not generally recommended
- if medical treatment fails: Gasserian ganglion percutaneous technique, gamma knife, invasive percutaneous denervation (radiofrequency/glycerol), percutaneous balloon microcompression, microvascular decompression

---

**Postherpetic Neuralgia (PHN)**

Clinical Features
- pain persisting in the region of a cutaneous outbreak of herpes zoster
- constant deep ache or burning, intermittent spontaneous lancinating/jabbing pain, allodynia
- distribution: thoracic, trigeminal, cervical > lumbar > sacral
- associated impaired sleep, decreased appetite, decreased libido

Etiology and Pathogenesis
- destruction of the sensory ganglion neurons (e.g. dorsal root, trigeminal, or geniculate ganglia) secondary to reactivation of herpes zoster infection

Epidemiology
- incidence in those with zoster increases with age (2% in <60 yr, 19% in >70 yr)
- risk factors: older age, greater acute pain, greater rash severity

Prevention
- varicella zoster vaccine in childhood reduces incidence of varicella zoster
- herpes zoster vaccine (Zostavax®) reduces incidences of shingles, PHN and other herpetic sequel (currently recommended in Canada for those >60 yr old)

Treatment
- medical: TCA (i.e. amitryptiline), anti-convulsants (i.e. pregabalin, gabapentin), analgesia (i.e. opiates, lidocaine patch), intrathecal methylprednisolone, topical capsaicin
  - early treatment of acute herpes zoster with antivirals (acyclovir; longer-acting famciclovir and valacyclovir more effective)
  - treatment of herpes zoster with corticosteroids DOES NOT decrease PHN
- surgical: spinal tractotomy, dorsal root entry zone lesion, DBS of thalamus

---

**Painful Diabetic Neuropathy**

Approach
- determine if pain is neuropathic or vascular
- more likely neuropathic if:
  - foot > calves
  - sharp/tingling pain
  - pain present at rest and improves with walking

Treatment
- **Level A:** pregabalin
- **Level B:** venlafaxine, duloxetine, amitryptyline, gabapentin, valproate, rarely opioids, capsaicin
Complex Regional Pain Syndromes (CRPS)

Clinical Features
• presence of an initiating noxious event (MI, stroke)
• continuing pain, allodynia, or hyperalgesia with pain disproportionate to inciting event
• evidence during the course of symptoms of edema, changes in skin blood flow or abnormal vasomotor activity
• absence of conditions that would otherwise account for degree of pain and dysfunction
• other features can include edema, osteoporosis, hyperhydrosis, hair loss, fascial thickening

Classification
• CRPS type I (reflex sympathetic dystrophy): minor injuries of limb or lesions in remote body areas precede onset of symptoms
• CRPS type II (causalgia): injury of peripheral nerves precedes the onset of symptoms

Investigations
• trial of differential neural blockade may be helpful in diagnosis
• autonomic testing (evidence of sympathetic dysfunction)
• bone scan, plain radiography, MRI

Prevention
• early mobilization after injury/infarction

Treatment
• goal of treatment: to facilitate function
• conservative treatment: education, support groups, PT/OT, smoking cessation
• medical: topical capsaicin, TCA, NSAID, tender point injections with corticosteroid/lidocaine, gabapentin/pregabalin/lamotrigine, calcitonin or bisphosphonates, oral corticosteroids
• surgical: paravertebral sympathetic ganglion blockade
• refer to pain management clinic

Headache

Clinical Approach
• history
  ▪ pain characteristics: onset, frequency, duration, intensity, location, radiation, other specific features (e.g. worse in AM, worse with bending/cough/Valsalva)
  ▪ associated symptoms: visual changes, change in mental status, nausea/vomiting, fever, meningismus, photophobia, phonophobia, TMJ popping/clicking, jaw claudication, neurological sx
  ▪ precipitating/accelerating factors (triggering factors, analgesics), medications (esp. nitrates, CCBs, NSAIDs, anticoagulants), PMH, FHx
  ▪ red flags (possible indications for CT scan/further investigation): new-onset headache (esp. if age <5 or >50), quality worse/different than previous headaches, sudden and severe (‘thunderclap’), immunocompromised, fever, focal neurological deficits, trauma
• physical
  ▪ vitals (including BP and temp), Kernig’s/Brudzinski’s, MSK examination of head and neck
  ▪ HEENT: fundi (papilledema, retinal hemorrhages), red eye, temporal artery tenderness, sinus palpation, TMJ
  ▪ full neurologic exam (including LOC, orientation, pupils (symmetry), and focal neurological deficits)
  ▪ red flags: papilledema, altered LOC, fever, meningismus, focal neurological deficits, signs of head trauma

Classification
• primary
  ▪ tension, migraine, cluster, exertional, cervical OA, TMJ syndrome
• secondary
  ▪ SAH, ICH, stroke, venous sinus thrombosis, meningitis/encephalitis, trauma, increased ICP (space-occupying lesion, malignant HTN or pseudotumour cerebri), temporal arteritis, sinusitis, acute-angle closure glaucoma, pre-eclampsia, post lumbar puncture, drugs/toxins (e.g. nitroglycerin use and analgesia withdrawal); all can be associated with serious morbidity or mortality
Table 21. Headaches – Selected Primary Types

<table>
<thead>
<tr>
<th>Tension-Type</th>
<th>Migraine</th>
<th>Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>70%</td>
<td>12%</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>15-40</td>
<td>10-30</td>
</tr>
<tr>
<td>Sex Bias</td>
<td>F &gt; M</td>
<td>F &gt; M</td>
</tr>
<tr>
<td>Family History</td>
<td>None</td>
<td>+</td>
</tr>
<tr>
<td>Location</td>
<td>Bilateral frontal</td>
<td>Unilateral &gt; bilateral Fronto-temporal</td>
</tr>
<tr>
<td>Duration</td>
<td>Minutes – days</td>
<td>Hours – days</td>
</tr>
<tr>
<td>Onset/Course</td>
<td>Gradual; worse in PM</td>
<td>Gradual; worse in PM</td>
</tr>
<tr>
<td>Quality</td>
<td>Band-like; constant</td>
<td>Throbbing</td>
</tr>
<tr>
<td>Severity</td>
<td>Mild-moderate</td>
<td>Moderate-severe</td>
</tr>
<tr>
<td>Triggers/Provoking</td>
<td>Depression Anxiety Noise Hunger Sleep deprivation</td>
<td>Noise/light Caffeine/alcohol Hunger Stress Sleep deprivation</td>
</tr>
<tr>
<td>Palliating</td>
<td>Rest</td>
<td>Rest</td>
</tr>
<tr>
<td>Associated Sx</td>
<td>No vomiting</td>
<td>Nausea/vomiting Photo/phonophobia Aura</td>
</tr>
</tbody>
</table>

Management

- Non-pharmacological
  - Psychological counseling
  - Physical modalities (e.g. heat, massage)
  - Simple analgesics
  - Tricyclic antidepressants

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Evidence</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>Propranolol</td>
<td>A</td>
<td>Asthma, DM (mask) Hypoglycemia</td>
<td>Fatigue Depression Light-headedness</td>
</tr>
<tr>
<td></td>
<td>Timolol</td>
<td>A</td>
<td>Hypoglycemia</td>
<td>CHF</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>B</td>
<td>CHF</td>
<td></td>
</tr>
<tr>
<td>TCA</td>
<td>Amitriptyline</td>
<td>A</td>
<td>Heart disease, glaucoma Avoid in elderly</td>
<td>Sedation Dry mouth Weight gain Light-headedness</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td>C</td>
<td>Heart disease</td>
<td>Sedation</td>
</tr>
<tr>
<td>CCB’s</td>
<td>Flunarizine</td>
<td>A</td>
<td>Depression, obesity</td>
<td>Weight gain, depression, PD (rare)</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>B</td>
<td>Heart disease</td>
<td>Weight gain (10-20 lb), constipation</td>
</tr>
<tr>
<td>AED</td>
<td>Valproate</td>
<td>A</td>
<td>Liver, renal, pancreatic diseases</td>
<td>Weight gain, tremor, alopecia, teratogenic: N.T. defect</td>
</tr>
<tr>
<td></td>
<td>Topiramate + folic acid supplement</td>
<td>A</td>
<td>Renal</td>
<td>Paresthesia, weight loss, cognitive: memory loss, difficulty concentrating, renal stone (rare)</td>
</tr>
</tbody>
</table>

Table 22. Prophylactic Management of Migraine Headaches

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Evidence</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>Propranolol</td>
<td>A</td>
<td>Asthma, DM (mask) Hypoglycemia</td>
<td>Fatigue Depression Light-headedness</td>
</tr>
<tr>
<td></td>
<td>Timolol</td>
<td>A</td>
<td>Hypoglycemia</td>
<td>CHF</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>B</td>
<td>CHF</td>
<td></td>
</tr>
<tr>
<td>TCA</td>
<td>Amitriptyline</td>
<td>A</td>
<td>Heart disease, glaucoma Avoid in elderly</td>
<td>Sedation Dry mouth Weight gain Light-headedness</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td>C</td>
<td>Heart disease</td>
<td>Sedation</td>
</tr>
<tr>
<td>CCB’s</td>
<td>Flunarizine</td>
<td>A</td>
<td>Depression, obesity</td>
<td>Weight gain, depression, PD (rare)</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>B</td>
<td>Heart disease</td>
<td>Weight gain (10-20 lb), constipation</td>
</tr>
<tr>
<td>AED</td>
<td>Valproate</td>
<td>A</td>
<td>Liver, renal, pancreatic diseases</td>
<td>Weight gain, tremor, alopecia, teratogenic: N.T. defect</td>
</tr>
<tr>
<td></td>
<td>Topiramate + folic acid supplement</td>
<td>A</td>
<td>Renal</td>
<td>Paresthesia, weight loss, cognitive: memory loss, difficulty concentrating, renal stone (rare)</td>
</tr>
</tbody>
</table>

Table 23. Headaches – Selected Serious but Rare Secondary Types

<table>
<thead>
<tr>
<th>Meningeal Irritation</th>
<th>Increased ICP</th>
<th>Temporal Arteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Onset</td>
<td>Any age</td>
<td>Any age</td>
</tr>
<tr>
<td>Location</td>
<td>Generalized</td>
<td>Any location</td>
</tr>
<tr>
<td>Onset/Course</td>
<td>Meningitis: hours-days SAH: thunderclap onset</td>
<td>Gradual; worse in AM</td>
</tr>
<tr>
<td>Severity</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Provoking</td>
<td>Head movement</td>
<td>Lying down</td>
</tr>
<tr>
<td></td>
<td>Valsalva</td>
<td>Head low</td>
</tr>
<tr>
<td></td>
<td>Exertion</td>
<td>Exertion</td>
</tr>
<tr>
<td>Associated Sx</td>
<td>Neck stiffness</td>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td></td>
<td>Photophobia</td>
<td>Focal neuro symptoms</td>
</tr>
<tr>
<td></td>
<td>Focal deficits (e.g. CN palsies)</td>
<td>Decreased level of consciousness</td>
</tr>
</tbody>
</table>

The Rational Clinical Examination: Does this Patient with Headache have a Migraine or Need Neuroimaging?

JAAMA 2006;296:1274-1283

Does this patient with headache have a migraine?

The most useful panel of questions for diagnosing migraine is summarized by the POUNDING mnemonic:

- **P** – Pulsatile quality
- **D** – Duration of 4-72 hrs
- **O** – Unilateral location
- **U** – Unbilaterial
- **N** – Nausea or vomiting
- **A** – Allodynia
- **D** – Disability

The LR for definite or possible migraine diagnosis varies with the number of features present; with ≥4, 3 and ≥2 features, the LRs are 24 (1.5-388), 3.9 (1.3-9.2) and 0.41 (0.32-0.52) respectively.

Anticonvulsants in Migraine Prophylaxis

Cochrane DB Syst Rev 2009;3:CD003228

Study: Meta-analysis of prospective, controlled trials of anticonvulsant drugs in migraine headache prophylaxis.

Results: Twenty-three studies (n=2927) were included. Anticonvulsants reduce migraine frequency by 1.3 attacks per 28 days compared to placebo and double the number of patients for whom migraine frequency is reduced by 50% (RR: 2.25, NNT: 3.9). Valproate and topiramate are better than placebo, while clonazepam, acetazolamide, lamotrigine and vigabatrin are not.

Clinical impact: Decrease in headache frequency by 1.3 attacks per 28 days compared to placebo and double the number of patients for whom migraine frequency is reduced by 50%. Anticonvulsants reduce migraine frequency by 1.3 attacks per 28 days compared to placebo and double the number of patients for whom migraine frequency is reduced by 50% (RR: 2.25, NNT: 3.9). Valproate and topiramate are better than placebo, while clonazepam, acetazolamide, lamotrigine and vigabatrin are not. Several individual clinical features were found to be predictive of significant intracranial pathology:

- **Symptom:** \( \text{OR} = 2.2 \) (2.1-2.3)
- **Cluster-type headache:** \( \text{OR} = 3.5 \) (2.6-4.4)
- **Unilateral headache:** \( \text{OR} = 3.2 \) (2.9-3.5)
- **Cluster headache:** \( \text{OR} = 3.5 \) (2.8-4.0)

Acute and Preventive Pharmacologic Treatment of Cluster Headache

Neurology 2010;75:463-473

Study: Meta-analysis of prospective, double-blind, RCTs of pharmacologic agents for prevention or treatment of CH.

Results: 27 trials were included. Sumatriptan 6 mg SC, zolmitriptan nasal spray 5-10 mg, and 100% oxygen 6-12 L/min received Level A recommendation for acute treatment. For prevention, Level B recommendations were given for intranasal cyclooxygen 100 ug daily and subcutaneous steroid injections.

Conclusion: Sumatriptan, zolmitriptan, and mid flow oxygen are effective acute treatments for CH.
Table 23. Headaches – Selected Serious but Rare Secondary Types (continued)

<table>
<thead>
<tr>
<th>Physical Signs</th>
<th>Increased ICP</th>
<th>Temporal Arteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kemig’s sign</td>
<td>Focal neuro symptoms</td>
<td>Papilledema</td>
</tr>
<tr>
<td>Brudzinski’s sign</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningismus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management</td>
<td>CT/MRI with gadolinium/ LP, antibiotics for bacterial meningoitis</td>
<td>CT/MRI and treatment to reduce pressure</td>
</tr>
<tr>
<td></td>
<td>See Neurosurgery, NS6</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Etiology</td>
<td>Meningitis, SAH</td>
<td>Tumour, IIIH, malignant hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vasculitis (GCA)</td>
</tr>
</tbody>
</table>

IH – idiopathic intracranial hypertension

Migraine Headaches

Definition (common migraine)
- ≥5 attacks fulfilling each of the following criteria
  - 4-72 h duration
  - 2 of the following: unilateral, pulsating, moderate-severe (interferes with daily activity), aggravated by routine physical activity
  - 1 of the following: nausea/vomiting, photophobia/phonophobia

Epidemiology
- 18% females, 6% males; frequency decreases with age (especially at menopause)

Etiology and Pathophysiology
- theories of migraine etiology:
  - depolarizing wave of “cortical spreading depression” across the cerebral cortex that may cause an aura (e.g. visual symptoms due to wave through occipital cortex) and also activate trigeminal nerve afferent fibres
  - possible association with vasoconstriction/dilation
  - significant genetic contribution
- triggers: stress, sleep excess/deprivation, drugs (estrogen, nitroglycerin), hormonal changes, caffeine withdrawal, chocolate, tyramines (e.g. red wine), nitrates (e.g. processed meats)

Signs and Symptoms
- stages of uncomplicated migraine
  i. prodrome (hours to days before headache onset)
  ii. aura
  iii. headache (see Table 21 for description of typical headache)
  iv. postdrome
- aura
  - fully reversible symptom of focal cerebral dysfunction lasting <60 min
  - examples: visual disturbance (fortification spectra – zigzags; scintillating scotomata – spots), unilateral paresthesia and numbness or weakness, aphasia
- prodrome/postdrome: appetite change, autonomic symptoms, altered mood, psychomotor agitation/retardation
- classification of migraines
  - common migraine: no aura
  - classic migraine: with aura (headache follows reversible aura within 60 min)
  - complicated migraine: with severe/persistent sensorimotor deficits
    - examples:
      - basilar-type migraine (occipital headache with diplopia, vertigo, ataxia, and altered level of consciousness)
      - hemiplegic/hemisensory migraine
      - ophthalmoplegic migraine
  - acephalic migraine (i.e. migraine equivalent): aura without headache

Management
- avoid triggers
- mild to moderate migraine
  - 1st line: NSAIDs (ibuprofen, naproxen)
  - moderate to severe migraine
    - triptans (most effective), ergots (dihydroergotamine, DHE)
    - migraine prophylaxis: anticonvulsants (divalproex, topiramate, gabapentin), TCA (amitryptiline, nortriptyline), propranolol, calcium channel blocker (verapamil)
  - prophylactic agent is recommended only if migraine attacks are severe enough to cause impairment of a patient’s quality of life or if a patient has >3 migraines/month that have not responded adequately to treatment.

Pharmacological Treatments for Acute Migraine

Meta-analysis of 54 double-blind, placebo-controlled RCTs of pharmacological treatment of acute migraine of moderate to severe intensity (21,022 patients in total).

Main Results:
- Data were available for 9 oral medications, 2 intranasal medications, and subcutaneous sumatriptan.
- For h/a relief at 2 h, all interventions were effective except Cafergot®, with NNTs ranging from 2.0 for sumatriptan 6 mg SC to 5.4 for naratriptan 2.5 mg. The lowest NNT for oral medication was 2.4 for eletriptan 80 mg.
- For patients pain free at 2 h, the lowest NNT was 2.1 for sumatriptan 6 mg SC, with the lowest NNT for oral medication being 3.1 for naratriptan 10 mg.
- For sustained relief over 24 h, NNT ranged from 2.0 for eletriptan 80 mg to 3.3 for rizatriptan 5 mg. Side effects could not be analyzed systematically. There were no drug-to-drug comparisons.

Conclusion: Overall, most treatments were effective. Subcutaneous sumatriptan and oral triptans were most effective.
Sleep Disorders

Overview of Sleep

Definition
- newborn: 18 h sleep (50% REM), adolescents: 10 h, adults: 7-9 h but most get insufficient amounts
- many elderly have reduced sleep as a consequence of underlying sleep disorders

Sleep Architecture
- polysomnogram (PSG) measures: EEG, eye movements (electro-oculogram – EOG), EMG, respiratory effort, oxygenation, ECG

Table 24. Sleep Stage Characteristics

<table>
<thead>
<tr>
<th>Waking State</th>
<th>EEG</th>
<th>EOG</th>
<th>Muscle Tone</th>
<th>Other Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low voltage high frequency,</td>
<td>Rapid, blinking</td>
<td>High</td>
<td>Marker for very light quality sleep or sleep disruption</td>
</tr>
<tr>
<td></td>
<td>dominant α rhythm (8-13 Hz)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage N1 (~5%)</td>
<td>&lt;50% α activity replaced with θ (4-7 Hz).</td>
<td>Slow, roving eye movements</td>
<td>High, but gradually dropping</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vertex waves</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage N2 (~50%)</td>
<td>K complexes high voltage negative and positive discharges with spindles (11-16 Hz)</td>
<td>Still</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Stage N3 (previously 3 and 4)/Slow Wave/Delta Sleep (~20%)</td>
<td>Slow wave activity – high voltage (&gt;75 μV), low frequency (&lt;2 Hz)</td>
<td>Still</td>
<td>Low</td>
<td>Homeostatic sleep Reduced BP, HR, cardiac output, RR Growth hormone release</td>
</tr>
<tr>
<td>Rapid Eye Movement (REM) Sleep (~25%)</td>
<td>Mixed frequency, low voltage, sawtooth waves</td>
<td>Rapid eye movements</td>
<td>Very low</td>
<td>Irregular respiration Arrhythmias, heart rate variation Classical dreaming state</td>
</tr>
</tbody>
</table>

Disturbances of Alertness and Sleep

Coma
- see Neurosurgery, NS34

Insomnia
- difficulty initiating or maintaining sleep, or waking up earlier than desired (leading to sleep that is chronically non-restorative/poor quality) despite adequate opportunity and circumstances for sleep
- types:
  - sleep state misperception, psychophyslogic insomnia (learned sleep-preventing associations – i.e. clock watching), fatal familial insomnia (rare prion protein mutation causing autonomic dysfunction), idiopathic (lifelong difficulty)
- secondary causes:
  - psychiatric disorders (80% of psychiatric patients): anxiety and depression (see Psychiatry, PS10, PS13)
  - neurologic disorders: neurodegenerative disease, epilepsy, neuromuscular disorders, many others
  - sleep disorders: restless legs syndrome (sleep initiation difficulties), sleep apnea (sleep maintenance difficulties)
  - medical conditions: pregnancy, cardiorespiratory (COPD/HF), GERD, pain (arthritis, fibromyalgia, cancer)
  - drugs/toxins: caffeine, alcohol, stimulants, antidepressants, glucocorticoids, sedative withdrawal
- treatment:
  - sleep log, sleep hygiene, stimulus control, sleep restriction, relaxation response, cognitive behavioral therapy

Drug Effects on Wakefulness and Sleep
- Antihistamines associated with increased sleepiness
- Stimulants increase arousal
- Caffeine (an adenosine antagonist) increase wakefulness
- Benzodiazepines reduce slow wave sleep
- Antidepressants (TCA/MAO-I/SSRI) reduce REM, prolong REM latency
- Alcohol may hasten sleep onset but associated with increased arousals

Avoid sleep medications (esp. in elderly patients) due to increased risk of falls, pseudodepression, memory loss.
Sleep Apnea
- definition
  - disorder of breathing in sleep associated with sleep disruption and consequent excessive somnolence
- epidemiology:
  - >2-4% of the population
  - increasing obesity
  - significant morbidity: HTN, stroke, heart failure, sleepiness, mortality (accidents)
- types:
  - obstructive sleep apnea: see Respirology, R31
  - central sleep apnea: no effort to breathe over 10 s
  - mixed apnea: starts as central, but eventually becomes obstructive
- etiology of central apnea:
  - heart failure, opiates, brainstem pathology, myotonic dystrophy
- diagnosis: apnea hypopnea index (AHI) or respiratory disturbance index (RDI) should be <5 in the normal or pathologic state
- treatment: conservative measures, dental devices, CPAP (common), surgery (rare), ensure driving safety

Restless Leg Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD)
- definition:
  - urge to move with accompanied uncomfortable sensations that begin or worsen with rest, are partially or totally relieved with movement, and are worse in evening/night
  - RLS refers to sensation
  - PLMD refers to the manifestation
- epidemiology:
  - 10% North Americans, 90% of RLS have PLMD, 50% of PLMD have RLS
- etiology:
  - central (spasticity), or peripheral nervous system (radiculopathy, neuropathy), pregnancy, iron deficiency, alcohol use
- treatment:
  - underlying contributors (iron and B₁₂ supplementation), dopaminergic agonists (first line), clonazepam (causes tachyphylaxis), opioids (only exceptional circumstances)
  - NOT recommended: Sinemet®, causes augmentation

Narcolepsy
- definition/clinical features:
  - excessive daytime sleepiness (all narcolepsy), cataplexy = loss of muscle tone with emotional stimuli (pathognomonic), sleep paralysis (unable to move upon wakening for 2-3 min), hypnagogic hallucinations (vivid dreams or hallucinations at sleep onset)
- epidemiology:
  - prevalence 1:2000, onset in adolescence/early adulthood; life-long disorder
- etiology:
  - presumed autoimmune attack on orexin/hypocretin system, post head injury, multiple sclerosis, hypothalamic tumours; rarely familial
- diagnosis: based on clinical history + multiple sleep latency test findings of short sleep latency <8 min and REM within 15 min of sleep onset on 2/4 naps
- treatment:
  - sleep hygiene and scheduled brief naps, restricted driving
  - alerting agents modafinil (non-amphetamine stimulant), stimulant (i.e. methylphenidate)
  - anti-cataplectic: TCAs, SSRIs, sodium oxybate

Parasomnias
- definition/clinical features: unusual behaviors in sleep with clinical features appropriate to stage of sleep
- etiology: in elderly, REM sleep behavior disorder may be associated with Parkinson’s disease; in children slow wave sleep arousals (sleep walking) may be associated with sleep disordered breathing
- diagnosis: clinical history in children, polysomnography in adults to exclude nocturnal seizures
- treatment: behavioral management (safety, adequate sleep); clonazepam for REM sleep behavior, tonsillectomy if appropriate in children

Circadian Rhythm
- definition/clinical features: abnormalities based on time of day rather than sleep (i.e. jet lag, shift work)
- diagnosis: clinical history

CNS Infections
- see Infectious Diseases, ID19

Spinal Cord Syndromes
- see Neurosurgery, NS28
**Terminology**

- **stroke**: sudden onset of neurological deficits of a vascular basis with infarction of CNS tissue
  - **transient ischemic attack (TIA)**: sudden onset of neurological deficits of a vascular basis without infarction (i.e. resolution)

**Pathophysiology**

- two major types: ischemic (~80%) and hemorrhagic (~20%)
  1. Ischemic
    - **arterial thrombosis**: thrombus formation in artery (local/in situ)
      - **large vessel**: stenosis or occlusion of the internal carotid artery, vertebral, or intracranial arteries
        - mechanisms:
          - insufficient blood flow beyond lesion (hemodynamic stroke)
          - underlying processes: atherosclerosis (most common cause), dissection and vasculitis
      - **small vessel/lacunar**
        - mechanism: chronic hypertension and diabetes cause vessel wall thickening and decreased luminal diameter
        - affects mainly small penetrating arteries (primarily basal ganglia, internal capsule and thalamus)
    - **cardioembolic**: blockage of cerebral arterial blood flow due to particles originating from a cardiac source
      - atrial fibrillation (most common), rheumatic valve disease, prosthetic heart valves, recent MI, fibrous and infectious endocarditis
    - **systemic hypoperfusion** (global cerebral ischemia)
      - inadequate blood flow to brain, usually secondary to cardiac pump failure (e.g. cardiac arrest, arrhythmia or MI)
      - primarily affects watershed areas (between the major cerebral arterial territories)
  2. Hemorrhagic
    - **intracerebral hemorrhage (ICH)**
      - mechanisms:
        - hypertensive (most common): rupture of small microaneurysms (Charcot-Bouchard aneurysms) causing intraparenchymal hemorrhage
        - most common sites: putamen, thalamus, cerebellum, andpons
        - other: trauma, amyloid angiopathy (associated with lobar hemorrhage), vascular malformations, vasculitis, drug use (cocaïne or amphetamines)
    - **subarachnoid hemorrhage (SAH)** see Neurosurgery, NS18

**Stroke Syndromes According to Vascular Territory**

- **ACA**: contralateral leg paresis and sensory loss
- **MCA**: proximal occlusion involves:
  1. contralateral weakness and sensory loss of face and arm
  2. cortical sensory loss
  3. may have contralateral homonymous hemianopia or quadrantanopia
  4. if left hemisphere: aphasia
  5. if right hemisphere: neglect
  6. eye deviation towards the side of the lesion and away from the weak side
- **PCA**:
  1. contralateral hemianopia or quadrantanopia
  2. midbrain findings: CN III and IV palsy/pupillary changes, hemiparesis
  3. thalamic findings: sensory loss, amnesia, decreased level of consciousness
  4. if bilateral: cortical blindness or prosopagnosia
- **basilar artery** (locked-in syndrome):
  1. quadriparesis
  2. dysarthria
  3. impaired eye movements
- **PICA (lateral medullary or Wallenburg syndrome)**: ipsilateral ataxia, ipsilateral Horner's, ipsilateral facial sensory loss, contralateral limb impairment of pain and temperature sensation, nystagmus, vertigo, nausea/vomiting, dysphagia, dysarthria, hiccup
- **medial medullary infarct** (anterior spinal artery, which can be associated with anterior cord infarct): contralateral hemiparesis (facial sparing), contralateral impaired proprioception and vibration sensation, ipsilateral tongue weakness
• lacunar infarcts (deep hemispheric white matter):
  • pure motor hemiparesis: posterior limb of internal capsule: contralateral arm, leg, and face
  • pure sensory loss: thalamic: hemisensory loss
  • ataxic hemiparesis: ipsilateral ataxia and leg paresis
  • dysarthria-clumsy hand syndrome: dysarthria, facial weakness, dysphagia, mild hand weakness and clumsiness

Assessment and Treatment of Ischemic Stroke

General Assessment
• ABCs, full vital sign monitoring, check glucose, urgent CODE STROKE if <4.5 h from symptom onset (for possible thrombolysis)
• history
  • onset: time when last known to be awake and symptom free
  • mimics to rule out: seizure/post-ictal, hypoglycemia, migraine, conversion disorder
• investigations:
  • non-contrast CT head (STAT): to rule out hemorrhage and assess extent of infarct
  • ECG: to rule out atrial fibrillation (cardioembolic cause)
  • CBC, electrolytes, creatinine, PTT/INR, blood glucose
• imaging (i.e. CT) signs of stroke:
  • loss of cortical white-grey differentiation
  • sulcal effacement (i.e. mass effect decreases visualization of sulci)
  • hypodensity of parenchyma
  • insular ribbon sign
  • hyperdense MCA sign

ACUTE STROKE MANAGEMENT

1. Thrombolysis
• rtPA (recombinant tissue plasminogen activator)
  • given within 4.5 h of acute ischemic stroke onset provided there are clinical indications and no contraindications to use:
    • indications: based on NIH Stroke Scale (NIHSS – see sidebar)
    • contraindications: see sidebar

2. Anti-Platelet Therapy
• give at presentation of TIA or stroke if rtPA not received
• antiplatelet agents:
  • ASA: recommended dose 81 mg chewed
  • if patient intolerant to ASA, use other antiplatelet agent (i.e. clopidogrel)

3. Acute Anti-Coagulant Therapy
• for patients with TIA or stroke and atrial fibrillation if rtPA not received
  • recommend IV heparin (or ensuring INR between 2-3 if already anticoagulated on warfarin)

Other Acute Management Issues
• avoid hyperglycemia which can increase the infarct size
• lower temperature if febrile
• prevent complications:
  • NPO if dysphagia (to be reassessed by SLP)
  • DVT prophylaxis if bed-bound
  • initiate rehabilitation early

Blood Pressure Control
• do NOT lower the blood pressure unless the hypertension is severe
  • antihypertensive therapy is withheld for at least 5 d after thromboembolic stroke unless SBP >120 mmHg or DBP >120 mmHg, or in the setting of acute MI, renal failure, aortic dissection
• acutely elevated BP is necessary to maintain brain perfusion to the ischemic penumbra
• most patients with an acute cerebral infarct are initially hypertensive and their BP will fall spontaneously within 1-2 d
• IV labetalol first-line if needed

Etiological Diagnosis
• further investigations:
  • additional neuroimaging (MRI)
  • vascular imaging: CTA/MRA/carotid dopplers
  • cardiac tests: ECHO, holter monitoring
  • correct etiological diagnosis is critical for appropriate secondary prevention strategies
Primary and Secondary Prevention of Ischemic Stroke

Anti-Platelet Therapy
- **primary prevention**
  - current evidence has not firmly established a protective role for antiplatelet agents for low-risk patients without a prior stroke/TIA
- **secondary prevention**
  - ASA is the initial antiplatelet of choice for stroke prevention
  - other agents (generally reserved for those who suffer cerebrovascular symptoms while on ASA or in unable to tolerate ASA)
  - Aggrenox® (ESPRIT trial)
  - clopidogrel (CAPRIE trial)
  - there is no benefit (and increased risk of major bleeding) to combining ASA and clopidogrel (MATCH and CHARISMA trials)

Carotid Stenosis
- **primary prevention (asymptomatic)**
  - carotid endarterectomy is controversial: if stenosis >60%, risk of stroke is 2% per year; carotid endarterectomy reduces the risk of stroke by 1% per year (but 5% risk of complications)
- **secondary prevention (previous stroke/TIA in carotid territory)**
  - carotid endarterectomy clearly benefits those with symptomatic severe stenosis (70-99%), and is less beneficial for those with symptomatic moderate stenosis (50-69%) (NASCET trial), see Neurosurgery, NS25
- according to the CREST trial, endarterectomy and carotid stenting have similar benefits in a composite endpoint of reduction of stroke, MI and death. However, in the periprocedural period, stenting results in a higher rate of stroke, while endarterectomy results in a higher rate of MI

Atrial Fibrillation
- primary and secondary prevention with anticoagulation
  - risk stratification using CHADS2 score (see sidebar)
  - 0 (very low risk): antiplatelet
  - 1 (low risk): anticoagulant or antiplatelet – patient specific decision
  - >2 (mod-high risk): anticoagulant
  - anticoagulation therapy
  - warfarin (titrate to INR 2-3)
  - dabigatran (110 or 150 mg bid) may be an option to warfarin, but should be used cautiously due to lack of a reversal agent should bleeding occur

Hypertension
- **primary prevention**
  - targets: BP <140/90 (or <130/80 for diabetics or renal disease)
  - ramipril 10 mg PO OD is effective in patients at high risk for cardiovascular disease (HOPE trial)
  - ACEI reduce the risk of stroke beyond their antihypertensive effect
- **secondary prevention**
  - ACEI and thiazide diuretics are recommended in patients with previous stroke/TIA (PROGRESS trial)

Hypercholesterolemia
- **primary prevention**
  - statins reduce the risk of stroke in patients with CAD or at high risk for cardiovascular events, even with normal cholesterol (CARE trial)
- **secondary prevention**
  - statins reduce risk of subsequent stroke – best evidence is for high dose atorvastatin (SPARCL trial) but lower doses may be more appropriate if patient cannot tolerate high dose

Diabetes
- ideal management: HbA1c <7%, fasting blood glucose between 4 and 7

Smoking
- **primary prevention**
  - smoking increases risk of stroke in a dose-dependent manner
- **secondary prevention**
  - after smoking cessation, the risk of stroke decreases to baseline within 2-5 yr

Ischemic Stroke
**Primary and Secondary Prevention of**

High-dose Atorvastatin after Stroke or Transient Ischemic Attack (SPARCL trial)
NEJM 2003;359:549-559
Method: Multicenter double-blind RCT
Population: 4731 patients with stroke or TIA within 1-4 mo before study entry, LDL 100-190 mg/dl, no coronary heart disease.
Intervention: 80 mg atorvastatin PO OD or placebo.
Outcome: Final non-fatal or fatal stroke over 5 yr
Results: Patients receiving atorvastatin had a lower rate of stroke (ARI 2.2%, hazard ratio 0.84; P = 0.003). There was a five-year absolute reduction in risk of 3.5% (95% CI: 0.02-0.16). There was no significant change in mortality rate, but a small significant increase in the risk of hemorrhage.
Conclusions: High-dose atorvastatin decreases overall incidence of strokes and cardiovascular events in patients with a history of recent stroke or TIA.

Dabigatran vs. Warfarin in Patients with Atrial Fibrillation (The RE-LY Trial)
NEJM 2011;365:898-907
Study Type: Prospective, multi-center RCT. Double-blinded comparison between dabigatran and warfarin.
Population: 18,113 patients with atrial fibrillation and a risk of stroke followed over 2 yr.
Primary Outcome: Stroke or systemic embolism.
Results: Rates of outcome were 1.69% per year in warfarin group and a 1.53% per year in dabigatran group (RR 0.87, P = 0.003). Risk of hemorrhagic stroke was lower with dabigatran (0.12% versus 0.38%; P <0.001). Minor bleeds were slightly increased in warfarin group (3.66% versus 2.71% with dabigatan; P = 0.033). Risk of hemorrhagic stroke was lower with dabigatran (0.12% versus 0.38%; P <0.001). Conclusions: Dabigatan at 110 mg PO bid was associated with similar rates of stroke and systemic embolism and lower rates of major hemorrhage compared to warfarin in patients with atrial fibrillation. The 150 mg PO bid dose of dabigatran was more effective at stroke prevention and had a similar bleeding risk to warfarin.

tPA in Acute Stroke – NINDS Trial
NEJM 1995;333:1581-1588
Study: Randomized, double-blind, placebo-controlled trial (3 mo follow-up).
Patients: 624 patients (mean age 79 yr) with ischemic stroke of recent onset, and no evidence of intracranial hemorrhage on CT. Exclusions included hx of recent stroke or recent surgery, DBP >185, DBP >110, symptoms of SAH, recent GI or GU hemorrhage, seizure with onset of stroke, and recent use of anticoagulants.
Intervention: IV tPA or placebo within 180 min of the onset of symptoms.
Outcomes: Neurologic deficit at 24 h (NIHSS scale) and functional outcome at 3 mo.
Results: There was no significant difference between groups at 24 h. At 3 mo, there were more patients in the tPA group with minimal or no disability (52% vs. 38%, P = 0.03). Intracranial hemorrhage was more common in the tPA group (p=0.001). There was no difference in mortality.
Conclusion: IV tPA given within 3 h of onset of acute ischemic stroke improves functional outcome at 3 mo. The risk of hemorrhage is increased.

Dr. et al. Neurology, 2014
Physical Activity
- regular physical activity is an important lifestyle measure in stroke prevention and its beneficial effect has a dose-related response in terms of intensity and duration of activity

Stroke Rehabilitation
- individualized based on severity and nature of impairment; may require inpatient program and continuation through home care or outpatient services
- multidisciplinary approach includes dysphagia assessment and dietary modifications, communication rehabilitation, cognitive and psychological assessments including screen for depression, therapeutic exercise programs, assessment of ambulation and evaluation of need for assistive devices, splints or braces, vocational rehabilitation

Cerebral Hemorrhage

Investigations
- general investigations, see Assessment and Treatment of Ischemic Stroke, N44
- further investigations:
  - lumbar puncture (if suspect subarachnoid hemorrhage despite negative CT)
  - may require cerebral angiogram if suspect aneurysm or AVM
  - if typical location for hypertensive hemorrhage, repeat CT head in 4-6 wk after hemorrhage has resolved to rule out an underlying lesion
- surgical: see Neurosurgery, NS7

Management
- medical
  - anti-hypertensives: no conclusive BP target ranges for managing ICH exist; 2010 AHA/ASA guidelines suggest that reducing sBP to as low as 140 mmHg with IV anti-hypertensives is safe and appropriate management (target BP 140-160 systolic)
  - ICP lowering medical management (if necessary): see Neurosurgery, NS7

Multiple Sclerosis (MS)

Definition
- a chronic inflammatory disease of the CNS characterized by relapsing remitting, or progressive neurologic symptoms due to inflammation, demyelination and axonal degeneration

Clinical Patterns of MS (Figure 25)
- relapsing remitting (RRMS) 85%, primary progressive (PPMS) 10%, progressive relapsing (PRMS) 5%, secondary progressive (SPMS)
- most RRMS goes on to become SPMS

MS Variants
- Devic’s = neuromyelitis optica (NMO): severe optic neuritis and extensive transverse myelitis extending >3 vertebral segments (NMO antibody positive)
- clinically isolated syndrome (CIS): single MS-like episode, which may progress to MS
- tumefactive MS: solitary lesion >2 cm mimicking neoplasms on MRI
- fulminant MS (Marburg): rapidly progressive and fatal MS associated with severe axonal damage, inflammation, and necrosis
- acute disseminated encephalomyelitis (ADEM): monophasic demyelinating disorder with multifocal neurologic symptoms seen mainly in children often following infection or vaccination

Etiology
- genetic
  - polygenetic: the HLA-DRB1 gene has been demonstrated to be a genetically susceptible area
  - 30% concordance for monozygotic twins, 2-4% risk in offspring of affected mother or father
- environmental
  - MS is more common in regions with less sun exposure and lower stores of vitamin D (Europe, Canada, US, New Zealand, SE Australia)
  - MS has also been linked to certain viruses (EBV is associated with MS)

Epidemiology
- onset 17-35 yr; 3F:1M
- PPMS occurs in an older population with 1F:1M
Diagnosis
- dissemination in space and in time as based on the revised McDonald criteria
- dissemination in time: 2 or more attacks, new gadolinium enhancing lesion 3 mo later, or new T2 lesions >1 mo after first attack
- dissemination in space: clinical evidence of 2 or more lesions; or three of [1 gadolinium enhancing or 9 T2 lesions], [1 infratentorial lesion], [1 juxtacortical lesion], [3 periventricular lesions]

Clinical Features
- symptoms include numbness, visual disturbance (optic neuritis), weakness, spasticity, diplopia (e.g. INO), impaired gait, vertigo, bladder dysfunction
- Lhermitte's sign: flexion of neck causes electric shock sensation down back into limbs indicating cervical cord lesion
- Uhthoff's phenomenon: worsening of symptoms (classically optic neuritis) in heat
- SPMS: classically weakness of legs in pyramidal distribution paired with cerebellar findings of arms (i.e. intention tremor)
- symptoms not commonly found in MS: visual field defects, aphasia, apraxia, progressive hemiparesis
- relapse: acute/subacute onset of clinical dysfunction that peaks from days to weeks, followed by remission with variable symptom resolution (symptoms must last at least 24 h)
- in RRMS, average 0.4 to 0.6 relapses/yr, but higher disease activity in first year of disease

Investigations
- MRI: demyelinating plaques appear as hyperintense lesions on T2 weighted MRI, with active lesions showing enhancement with gadolinium
- typical locations: periventricular, corpus callosum, cerebellar peduncles, brainstem, juxta cortical region, and dorsolateral spinal cord
- Dawson's fingers: periventricular lesions extending into corpus callosum
- cranial MRI is more sensitive than spinal MRI
- CSF: oligoclonal bands in 90%, increased IgG concentration
- evoked potentials (visual/auditory/somatosensory): delayed but well-preserved wave forms

Treatment
- acute treatment: methylprednisolone 1000 mg IV daily x 3-7 d (no taper required); if poor response to corticosteroids may consider plasma exchange
- disease modifying therapy (DMT):
  - goals: decrease relapse rate, decrease progression of disability, slow accumulation of MRI lesions
  - first line: interferon-β (injection: Betaseron®, Avonex®, Rebif®), glatiramer acetate (injection: Copaxone®)
  - second line: natalizumab (Tysabri®) (monthly IV infusion)
  - new oral agents: fingolimod (available) and cladribine (not yet available)
  - indications for fingolimod: newly diagnosed patients with active RRMS who prefer oral treatment despite increased risks or those intolerant of first line therapies
  - CIS: early treatment with interferons may delay potential second attack
  - RRMS: DMT reduces rate of relapse by about 30%
  - PPMS/SPMS: no proven efficacy of DMTs
- symptomatic treatment
  - spasticity: baclofen, tizanidine, dantrolene, benzodiazepine, botulinum toxin
  - bladder dysfunction: oxybutynin
  - pain: TCA, carbamazepine, gabapentin
  - fatigue: amantidine, modafinil, methylphenidate
  - depression: antidepressant, lithium
  - constipation: high fibre intake, stool softener, laxatives
  - sexual dysfunction: sildenafil, tadalafil, vardenafil
- education and counseling: MS society, support groups, psychosocial issues

Prognosis
- good prognostic indicators: female, young, RRMS, presenting with optic neuritis, low burden of disease on initial MRI, low rate of relapse early in disease
- PPMS: poor prognosis, higher rates of disability, poor response to therapy
<table>
<thead>
<tr>
<th>Indications</th>
<th>Mechanism of Action/Class</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s disease</td>
<td>Dopamine precursor</td>
<td>levodopa + carbidopa</td>
<td>Sinemet®</td>
<td>Carbidopa 25 mg/levodopa 100 mg PO tid Max 200 mg carbidopa and 2000 mg levodopa per day</td>
<td>Narrow-angle glaucoma, use of MAO inhibitor in last 14 d, history of melanoma or undiagnosed skin lesions</td>
<td>Nausea, hypotension, hallucinations, dyskinesias in last 14 d, history of melanoma or undiagnosed skin lesions</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Dopamine agonist</td>
<td>bromocriptine</td>
<td>Parlodel®</td>
<td>1.25 mg PO bid, increase by 2.5 mg/d q2-4wk, up to 10-30 mg PO tid</td>
<td>Concomitant use of potent inhibitors of CYP3A4, uncontrolled hypertension, ischemic heart disease, peripheral vascular disease. Caution with renal or hepatic disease</td>
<td>Hypotension, nausea, dizziness, constipation, diarrhea, vomiting, abdominal cramps, headache, nasal congestion, drowsiness, hallucinations</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>MAO B inhibitor</td>
<td>selegiline</td>
<td>Eldepryl®</td>
<td>5 mg PO bid</td>
<td>Concomitant use of meperidine or tricyclic antidepressants</td>
<td>Headache, insomnia, dizziness, nausea, dry mouth, hallucinations, confusion, orthostatic hypotension, increased akinsia, risk of hypertensive crisis with tyramine-containing foods</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholinesterase inhibitor</td>
<td>pyridostigmine</td>
<td>Mestinon®</td>
<td>600 mg/d PO divided in 5-6 doses Range 60-1500 mg/d</td>
<td></td>
<td>Nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis, diaphoresis, muscle cramps, fasciculations, muscle weakness</td>
</tr>
<tr>
<td>Acute migraine</td>
<td>Triptan (selective 5-hydroxytryptamine receptor agonist)</td>
<td>sumatriptan</td>
<td>Imitrex®</td>
<td>25-100 mg PO pm, maximum 200 mg/d</td>
<td>Hemiplegic/basilar migraine, ischamic heart disease, cerebrovascular disease, uncontrolled hypertension, use of ergotamine/5-HT1 agonist in past 24 h, use of MAO inhibitor in last 14 d, severe hepatic disease</td>
<td>Vertigo, chest pain, flushing, sensation of heat, hypertensive crisis, peripheral vascular disease, coronary artery vasospasm, cardiac arrest, nausea, vomiting, headache, hyposalivation, fatigue</td>
</tr>
<tr>
<td>Acute migraine</td>
<td>Ergot (5-HT1D receptor agonist)</td>
<td>dihydroergotamine</td>
<td>Migranal®</td>
<td>Nasal spray 0.5 mg/spray, maximum 4 sprays/d</td>
<td>Hemiplegic/basilar migraine, high-dose ASA therapy, uncontrolled hypertension, ischemic heart disease, peripheral vascular disease, severe hepatic or renal dysfunction, use of triptans in last 24 h, use of MAO inhibitors in last 14 d</td>
<td>Coronary artery vasospasm, transient myocardial ischemia, myocordial infarction, ventricular tachycardia, ventricular fibrillation. May cause significant rebound headache</td>
</tr>
<tr>
<td>Migraine prophylaxis</td>
<td>Anticonvulsant</td>
<td>topiramate</td>
<td>Topamax®</td>
<td>25 mg OD PO (in evening); may increase weekly by 25 mg/d to a max 50 mg bid</td>
<td></td>
<td>Sedation, mood disturbance, cognitive dysfunction, anorexia, nausea, diarrhea, parathesias, metabolic acidosis, glaucoma, SJS/TEN</td>
</tr>
<tr>
<td>Migraine prophylaxis</td>
<td>β-blocker</td>
<td>propranolol</td>
<td>Inderal®</td>
<td>80 mg/d divided every 6-8 h; increase by 20-40 mg/dose every 3-4 wk to max 160-240 mg/d in divided doses q6-8h</td>
<td>Uncompensated CHF, severe bradycardia or heart block, severe COPD or asthma</td>
<td>Fatigue, cognitive dysfunction, disturbed sleep, rashes, dyspepsia, dry eyes, heart failure, bronchospasm, risk of acute tachycardia and HTN if withdrawal</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Anticonvulsant for partial ± 2º generalization, generalized tonic-clonic</td>
<td>carbamazepine</td>
<td>Tegretol® (Carbatrol)</td>
<td>Start at 100-200 mg PO OD-bid, increase by 200 mg/d up to 800-1200 mg/d</td>
<td>History of bone marrow depression, hepatic disease, hypersensitivity to the drug, use of MAO inhibitor in last 14 d</td>
<td>Drowsiness, headache, unsteadiness, dizziness, n/v, skin rash, agranulocytosis/aplastic anemia (rare)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Anticonvulsant for partial, tonic-clonic, status epilepticus</td>
<td>phenytoin</td>
<td>Dilantin®</td>
<td>100 mg PO bid, maintenance dose up to 200 mg PO tid SE: 10-15 mg/kg IV loading dose then maintenance doses of 100 mg PO or IV q6-8h</td>
<td>Hypersensitivity, pregnancy, breast-feeding; caution with F-450 interactions</td>
<td>Hypotension, SJS/TEN, SLE-type symptoms, gingival hypertrophy, peripheral neuropathy, headache, blood dyscrasias, nystagmus, n/v, constipation, sedation, teratogenic</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Anticonvulsant for partial or generalized, absence seizures</td>
<td>valproic acid</td>
<td>Depacon®</td>
<td>10-15 mg/kg/d PO, increase incrementally until therapeutic dose to max of 60 mg/kg/d</td>
<td>Hypersensitivity, hepatic disease, urea cycle disorders</td>
<td>Hepatic failure, headache, somnolence, alopecia, n/v, diarrhea, tremor, diplopia, thrombocytopenia, hypothermia, pancreatitis, encephalopathy</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Anticonvulsant for absence seizures</td>
<td>ethosuximide</td>
<td>Zarontin®</td>
<td>500 mg/d PO, increase by 250 mg every 4-7 d to max 1.5 g/d in divided doses</td>
<td>Hypersensitivity (succinimides)</td>
<td>CNS depression, blood dyscrasias, SLE, SJS, GI symptoms</td>
</tr>
<tr>
<td>Indications</td>
<td>Mechanism of Action/Class</td>
<td>Generic Name</td>
<td>Trade Name</td>
<td>Dosing</td>
<td>Contraindications</td>
<td>Side Effects</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------------------</td>
<td>--------------</td>
<td>------------</td>
<td>-------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Stroke prevention in AF</strong></td>
<td>Anticoagulant (direct thrombin inhibitor)</td>
<td>dabigatran</td>
<td>Pradax®</td>
<td>110 mg PO bid or 150 mg PO bid</td>
<td>CrCl &lt; 30 mL/min, significant hemostatic impairment or CNS lesions within 6 mo with high risk of bleeding</td>
<td>Dyspepsia, gastritis, bleeding</td>
</tr>
<tr>
<td><strong>Mild to moderate AD or DLB</strong></td>
<td>Cholinesterase Inhibitor</td>
<td>donepezil</td>
<td>Aricept®</td>
<td>5 mg PO OD, may increase to 10 mg PO OD after 4-6 wk</td>
<td>Hypersensitivity to donepezil or to piperidine derivatives</td>
<td>Diarrhea, n/v, insomnia, muscle cramps, fatigue, anorexia, HTN, syncope, AV block</td>
</tr>
<tr>
<td><strong>Multiple sclerosis</strong></td>
<td>MS Disease Modifying Therapy</td>
<td>interferon-β-1b</td>
<td>Betaseron®</td>
<td>0.25 mg (8 MU) SC every other day</td>
<td>Pregnancy, hypersensitivity to natural or recombinant interferon β</td>
<td>Injection site reactions, injection site necrosis, flu-like symptoms (fever, chills, myalgia; tend to decrease over time)</td>
</tr>
<tr>
<td></td>
<td>MS Disease Modifying Therapy</td>
<td>interferon-β-1a SC</td>
<td>Rebif®</td>
<td>44 µg SC 3 times/wk</td>
<td>Hypersensitivity to interferon β</td>
<td>Injection site reactions, nausea, transient chest pain, vasodilation</td>
</tr>
<tr>
<td></td>
<td>MS Disease Modifying Therapy</td>
<td>interferon-β-1a IM</td>
<td>Avonex®</td>
<td>39 µg IM once weekly</td>
<td>Hypersensitivity to interferon β</td>
<td>Injection site reactions, nausea, transient chest pain, vasodilation</td>
</tr>
<tr>
<td><strong>Spasticity (i.e. MS)</strong></td>
<td>Muscle Relaxant – Antispastic</td>
<td>baclofen</td>
<td>Lioresal®</td>
<td>5 mg PO tid, increase by 15 mg/d q3d to max dose 80 mg/d in three divided doses</td>
<td>Hypersensitivity to baclofen</td>
<td>Transient drowsiness, daytime sedation, dizziness, weakness, fatigue, convulsions, constipation, nausea</td>
</tr>
</tbody>
</table>
Landmark Neurology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREST</td>
<td>NEJM 2010; 363:11-23</td>
<td>Carotid stenting and endarterectomy had similar benefits in reduction of stroke, MI and death in carotid stenosis, but in the periprocedural period, stenting had a higher rate of stroke, while endarterectomy had a higher rate of MI.</td>
</tr>
<tr>
<td>ECASS 3</td>
<td>NEJM 2008; 359:1317-29</td>
<td>rtPA improved clinical outcomes when administered within 3 to 4.5 h of acute ischemic stroke.</td>
</tr>
<tr>
<td>Interferon-β Multiple Sclerosis Study Group Trial</td>
<td>Neurology 1993; 43:655-81</td>
<td>Interferon-β-1b reduces relapse rate and severity of relapses in RRMS.</td>
</tr>
<tr>
<td>NASCET</td>
<td>NEJM 1991; 355:549-59</td>
<td>Patients with symptomatic carotid stenosis of 70-99% benefited more from carotid endarterectomy than best medical therapy.</td>
</tr>
<tr>
<td>NINDS rtPA</td>
<td>NEJM 1995; 333:1581-7</td>
<td>rtPA reduces mortality and long-term disability when administered within 3 h of acute stroke.</td>
</tr>
<tr>
<td>PROFESS</td>
<td>NEJM 2008; 359:1238-51</td>
<td>ASA + dipyridamole and clopidogrel showed similar benefits in secondary stroke prevention.</td>
</tr>
<tr>
<td>SPARCL</td>
<td>NEJM 2006; 355:549-59</td>
<td>The observed benefit of statins in cardiovascular disease is also extended to patients with a recent stroke or TIA.</td>
</tr>
</tbody>
</table>

References

Coma

Common Presenting Complaints

Headache
Detsky, ME, McDonald DR, Baehrlecher MD, et al. Does this patient with headache have a migraine or need neuroimaging. JAMA 2006;296:1274-1283.

Traumatic Brain Injury

Movement Disorders

Multiple Sclerosis

Acronyms .................................................. 2
Basic Anatomy Review ............................... 2
Differential Diagnoses of Common Neurosurgical Presentations .......... 4
INTRACRANIAL PATHOLOGY
Intracranial Pressure (ICP) Dynamics ...... 4
ICP/Volume Relationship
Cerebral Blood Flow (CBF)
ICP Measurement
Elevated ICP
Herniation Syndromes ......................... 7
Treatment of Elevated ICP
Hydrocephalus ........................................ 8
Idiopathic Intracranial Hypertension
(Pseudotumour Cerebri) ......................... 10
Tumours ................................................. 10
Metastatic Tumours
Astrocytoma
Meningioma
Vestibular Schwannoma (Acoustic Neuroma)
Pituitary Adenoma
Pus ....................................................... 15
Cerebral Abscess
Blood ..................................................... 16
Extradural ("Epidural") Hematoma
Subdural Hematoma (SDH)
Cerebrovascular Disease ...................... 18
Subarachnoid Hemorrhage (SAH)
Intracerebral Hemorrhage (ICH)
Intracranial Aneurysms
Carotid Stenosis
Vascular Malformations ....................... 23
Arteriovenous Malformations (AVMs)
Cavernous Malformations
EXTRACRANIAL PATHOLOGY
Approach to Limb/Back Pain ................. 24
Extradural Lesions ............................... 24
Root Compression
Cervical Disc Syndrome
Cervical Stenosis (Cervical Spondylosis)
Lumbar Disc Syndrome
Cauda Equina Syndrome
Lumbar Spinal Stenosis
Neurogenic Claudication
Intradural Intramedullary Lesions ........ 28
Syringomyelia (Syrinx)
Spinal Cord Syndromes ..................... 28
Peripheral Nerves ............................... 29
SPECIALTY TOPICS
Neurotrauma ....................................... 30
Trauma Assessment
Head Injury
Brain Injury
Late Complications of Head/Brain Injury
Spinal Cord Injury (SCI)
Fractures of the Spine
Neurologically Determined Death
Coma
Persistent Vegetative State
Pediatric Neurosurgery ...................... 35
Spinal Dysraphism
Intraventricular Hemorrhage (IVH)
Hydrocephalus in Pediatrics
Dandy-Walker Malformation
Chiari Malformations
Craniostenosis
Pediatric Brain Tumours
Functional Neurosurgery .................. 39
Movement Disorders
Neuropsychiatric Disorders
Chronic Pain
Surgical Management of Epilepsy ........ 40
Surgical Management for Trigeminal Neuralgia .................. 41
Common Medications ....................... 41
References .......................................... 42
**Acronyms**

AVF  arteriovenous fistula  GPI  globus pallidus pars interna  OPLL  ossification of posterior longitudinal ligament

AVM  arteriovenous malformation  H/A  headache  PAG  periaqueductal grey matter

CBF  cerebral blood flow  HTN  hypertension  PET  positron emission tomography

CSF  cerebrospinal fluid  IC  internal capsule  PLL  posterior longitudinal ligament

CPA  cerebellar pontine angle  ICF  intracellular fluid  PIV  periventricular grey matter

CPP  cerebral perfusion pressure  ICP  intracranial pressure  SAH  subarachnoid hemorrhage

CVR  cerebral vascular resistance  IVH  intraventricular hemorrhage  SDH  subdural hemorrhage

DBS  deep brain stimulation  LMN  lower motor neuron  SIADH  syndrome of inappropriate antidiuretic hormone

DI  diabetes insipidus  LOC  loss of consciousness  SRS  stereotactic radiosurgery

ECF  extracellular fluid  LP  lumbar puncture  STN  subthalamic nucleus

ECT  electroconvulsive therapy  MAP  mean arterial pressure  UMN  upper motor neuron

EEG  electroencephalography  MSL  midline shift  VPL  ventral posterolateral

EMG  electromyography  NC  neurogenic claudication  VPM  ventral posteromedial

EVB  external ventricular drain  NPH  normal pressure hydrocephalus

GCS  glasgow coma scale  N/V  nausea/vomiting

**Basic Anatomy Review**

**MRI Brain**

A. Sagittal Section

- Frontal lobe
- Cingulate gyrus
- Septum pellucidum
- Parietal lobe

- Corpus callosum
- Thalamus
- Hypothalamus
- Occipital lobe

- Midbrain
- Pons
- Fourth ventricle
- Cerebellum

- Medulla
- Dens of C2
- Spinal cord
- Body of C3

B. Axial Section

- Frontal lobe
- Caudate lobe
- Lateral nucleus
- Internal capsule
- Insula
- Thalamus
- Parietal lobe
- Occipital lobe

**Cervical Region**

- C1
- C2
- C3
- C4
- C5
- C6
- C7
- C8
- T1

**Lumbar Region**

- T12
- L1
- L2
- L3
- L4
- L5
- S1
- S2
- S3
- S4
- S5
- Co1

**Figure 1.** Magnetic resonance imaging (MRI) neuroanatomy


**Figure 2.** Relationship of nerve roots to vertebral level in the cervical and lumbar spine

*Note: AP views depict left-sided C4-5 and L4-5 disc herniation, and correlating nerve root impingement*
Figure 3. Vascular supply of the brain. Please refer to legend for artery names. 3A. Circle of Willis, most common variant. 3B. Vascular territories of the brain and brainstem, sagittal view, seen laterally. 3C. Vascular territories of the brain and brainstem, sagittal view, seen medially.

Figure 4. Aneurysms of the Circle of Willis

1. Anterior communicating artery, 30%
2. Middle cerebral artery, 20%
3. Internal carotid/posterior communicating artery, 30%
4. Basilar tip, 7%
5. Superior cerebellar artery, 3%
6. Vertebrobasilar junction, 2%
7. Posterior inferior cerebellar artery, 3%
## Differential Diagnoses of Common Neurosurgical Presentations

<table>
<thead>
<tr>
<th>Intracranial Mass Lesions</th>
<th>Disorders of the Spine</th>
<th>Peripheral Nerve Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astrocytoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vestibular schwannoma (acoustic neuroma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pus/inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral abscess, extradural abscess, subdural empyema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalitis (see Infectious Diseases, ID20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumefactive multiple sclerosis (MS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extradural (epidural) hematoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage: SAH, ICH, IVH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyst</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extradural</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Degenerative: disc herniation, canal stenosis, spondylolisthesis/spondylosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infection/inflammation: osteomyelitis, discitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ligamentous: ossification of posterior longitudinal ligament (PLL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trauma: mechanical compression/instability, hematoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumours (55% of all spinal tumours): lymphoma, metastases (lymphoma, lung, breast, prostate), neurofibroma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intradural extramedullary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vascular: dural arterio-venous fistula, subdural hematoma (especially if on anticoagulants)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumours (40% of all spinal tumours): meningioma, schwannoma, neurofibroma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intramedullary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumours (5% of all spinal tumours): astrocytomas and ependymomas most common; also hemangioblastomas and dermoids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Syringomyelia (common causes: trauma, congenital, idiopathic)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infectious/inflammatory: TB, sarcoid, transverse myelitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vascular: AVM, ischemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neuropathies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Traumatic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Entrapments</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Iatrogenic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inflammatory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumours</td>
<td></td>
</tr>
</tbody>
</table>

## INTRACRANIAL PATHOLOGY

### Intracranial Pressure (ICP) Dynamics

**Table 1. Approach to Intracranial Pathology**

<table>
<thead>
<tr>
<th>Issue</th>
<th>Time Frame</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Sudden</td>
<td>No headache → occlusive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headache → hemorrhagic</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hours to days</td>
<td>Affects entire CNS</td>
</tr>
<tr>
<td>Infectious</td>
<td>Days to weeks</td>
<td>Often a source of infection on history</td>
</tr>
<tr>
<td>Tumour</td>
<td>Months</td>
<td>Increased ICP:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initially → Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Constant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Progressive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Worse in morning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>As ICP increases:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blurry vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Projectile vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severely raised ICP:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cushing’s reflex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bradycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypertension</td>
</tr>
</tbody>
</table>

Note: SAH - Subarachnoid Hemorrhage, ICH - Intracerebral Hemorrhage, IVH - Intraventricular Hemorrhage, AVM - Arteriovenous Malformation, ID20 - Infectious Disease 2014.
Table 2. Consequences of Common Brain Lesions

<table>
<thead>
<tr>
<th>Location of lesion</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe</td>
<td>1. Disinhibition</td>
</tr>
<tr>
<td></td>
<td>2. Concentration deficits</td>
</tr>
<tr>
<td></td>
<td>3. Orientation deficits</td>
</tr>
<tr>
<td></td>
<td>4. Judgement deficits</td>
</tr>
<tr>
<td></td>
<td>5. Primitive reflex re-emergence</td>
</tr>
<tr>
<td>Right parietal lobe</td>
<td>Spacial neglect syndrome</td>
</tr>
<tr>
<td></td>
<td>1. Rest tremor</td>
</tr>
<tr>
<td></td>
<td>2. Chorea</td>
</tr>
<tr>
<td></td>
<td>3. Athetosis</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>Contralateral hemiballismus</td>
</tr>
<tr>
<td>Subthalamnic nucleus</td>
<td>Kluver-Bucy syndrome*</td>
</tr>
<tr>
<td></td>
<td>1. Hyperorality</td>
</tr>
<tr>
<td></td>
<td>2. Hypersxuality</td>
</tr>
<tr>
<td></td>
<td>3. Disinhibition</td>
</tr>
<tr>
<td>Amygdala (bilateral)</td>
<td>Wemicke-Korsakoff syndrome</td>
</tr>
<tr>
<td></td>
<td>1. Wemicke</td>
</tr>
<tr>
<td></td>
<td>1. Confusion</td>
</tr>
<tr>
<td></td>
<td>2. Ophalmoplegia</td>
</tr>
<tr>
<td></td>
<td>3. Ataxia</td>
</tr>
<tr>
<td></td>
<td>2. Korsakoff</td>
</tr>
<tr>
<td></td>
<td>1. Memory loss</td>
</tr>
<tr>
<td></td>
<td>2. Confabulation</td>
</tr>
<tr>
<td></td>
<td>3. Personality changes</td>
</tr>
<tr>
<td>Mammillary bodies (bilateral)</td>
<td>Anterograde amnesia</td>
</tr>
<tr>
<td></td>
<td>1. Intention tremor</td>
</tr>
<tr>
<td></td>
<td>2. Limb ataxia</td>
</tr>
<tr>
<td></td>
<td>3. Fall towards side of lesion</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Reduc levels of arousal and wakefulness</td>
</tr>
<tr>
<td>Reticular activating system (midbrain)</td>
<td>Eyes look away from lesion</td>
</tr>
<tr>
<td>PPRF</td>
<td>Eyes look toward lesion</td>
</tr>
<tr>
<td>Frontal eye fields</td>
<td>Anterograde amnesia</td>
</tr>
<tr>
<td>Cerebellar hemisphere</td>
<td>1. Intention tremor</td>
</tr>
<tr>
<td></td>
<td>2. Limb ataxia</td>
</tr>
<tr>
<td></td>
<td>3. Fall towards side of lesion</td>
</tr>
<tr>
<td>Cerebellar vermis</td>
<td>Anterograde amnesia</td>
</tr>
<tr>
<td></td>
<td>1. Trancal ataxia</td>
</tr>
<tr>
<td></td>
<td>2. Dysarthria</td>
</tr>
</tbody>
</table>

ICP/Volume Relationship

- adult skull is rigid with a constant intracranial volume
- contents (CSF, blood, brain) are incompressible
- increase in one constituent/space-occupying lesion = increase in ICP
- however, ICP does not rise initially due to compensatory mechanisms (autoregulation):
  - immediate: displacement of CSF to lumbar theca, displacement of blood from venous sinuses
  - delayed: displacement of ECF or ICF, displacement of brain tissue into compartments under less pressure (herniation)
- once compensation is exhausted, ICP rises exponentially

Cerebral Blood Flow (CBF)

- CBF depends on cerebral perfusion pressure (CPP) and cerebral vascular resistance (CVR)
- normal CPP >50 mmHg in adults
- cerebral autoregulation maintains constant CBF by compensating for changes in CPP, unless:
  - high ICP such that CPP <60 mmHg
  - MAP >150 mmHg or MAP <50 mmHg
  - brain injury: e.g. SAH, severe trauma
ICP Measurement

- normal ICP <15 mmHg (8-18 cm H₂O) for adult, 3-7 mmHg (4-9.5 cm H₂O) for child; varies with patient position
  - moderate elevation: increase in mean pressure >20 mmHg
  - severe elevation: increase in mean pressure >40 mmHg
- waveform: comprised of respiratory and cardiac pulsations (Traube-Hering waves); the amplitude increases with ICP
  - β-waves: coarse, variably increased amplitude, frequency ½-2/min, often related to respiration
  - plateau waves: elevation of ICP over 50 mmHg lasting 5-20 min, precursor of further deterioration

Acute Monitoring
- lumbar puncture (LP) (see sidebar)
- intraventricular catheter/ventriculostomy/external ventricular drain (EVD) (“gold standard”, also permits therapeutic drainage of CSF to decrease ICP)

Chronic Monitoring
- fibre optic monitor (intraventricular, intraparenchymal, subdural), subarachnoid bolt (Richmond screw), and epidural monitor

Elevated ICP

Etiology
- intracranial space-occupying lesion:
  - tumour
  - pus
  - blood [trauma → hematoma (most common), subarachnoid hemorrhage]
  - depressed skull fracture
  - foreign body
- increased intracranial blood volume
  - vasodilatation (increased pCO₂/decreased pO₂/decreased extracellular pH, e.g. hypoventilation)
  - venous outflow obstruction (venous sinus thrombosis, superior vena cava syndrome, space occupying lesion)
  - cranial dependency
- cerebral edema
  - vasogenic (vessel damage, e.g. hypertensive encephalopathy, tumour)
  - cytotoxic (tissue/cell death, e.g. hypoxia, brain injury)
  - osmotic (acute hyponatremia, hepatic encephalopathy)
- impaired autoregulation (hypotension, hypertension, brain injury)
- hydrocephalus (obstructive, non-obstructive)
- tension pneumocephalus (gas within the cranial cavity)
- pseudotumour cerebri (idiopathic intracranial hypertension)
- status epilepticus (chronic seizure resulting in brain edema)

Clinical Features
1. Acute Elevated ICP
   - headache (H/A): worse in the morning, aggravated by stooping and bending
   - nausea and vomiting (N/V)
   - decreased level of consciousness (LOC) if ICP = diastolic BP, or midbrain compressed
   - drop in GCS = best index to monitor progress and predict outcome of acute intracranial process (see Neurotrauma, NS30)
   - papilledema ± retinal hemorrhages (may take 24-48 h to develop)
   - abnormal extra-ocular movements (EOM):
     - CN VI palsy: often falsely localizing (causative mass may be remote from nerve)
     - upward gaze palsy (especially in children with obstructive hydrocephalus)
   - herniation syndromes (see Herniation Syndromes, NS7)
   - focal signs/symptoms due to lesion

2. Chronic Elevated ICP
   - H/A
     - postural: worsened by coughing, straining, bending over
     - morning/evening H/A → vasodilatation due to increased CO₂ with recumbency

Blood Brain Barrier
- Infarction/neoplasm → destroy tight junctions → vasogenic edema
- Cushing’s Triad of Acute Raised ICP (full triad seen in 1/3 of cases)
  - Hypertension
  - Bradycardia (late finding)
  - Irregular respiratory pattern

Lumbar puncture is contraindicated with known/suspected intracranial mass.
visual changes
- due to papilledema
- enlarged blind spot, if advanced → episodic constrictions of visual fields (“grey-outs”)
- optic atrophy/blindness
- differentiate from papillitis (usually unilateral with decreased visual acuity)
- decreased level of consciousness

**Investigations**
- patients with suspected elevated ICP require an urgent CT/MRI
- ICP monitoring where appropriate

### Table 3. Herniation Syndromes

<table>
<thead>
<tr>
<th>Herniation Syndrome</th>
<th>Definition</th>
<th>Etiology</th>
<th>Clinical Features</th>
</tr>
</thead>
</table>
| 1. Subfalcine       | Cingulate gyrus herniates under falx | Lateral supratentorial lesion | Usually asymptomatic
|                     |            |          | Wors of impending transentorial herniation |
|                     |            |          | Risk of ACA compression |
| 2. Central Tentorial (Axial) | Displacement of diencephalon through tentorial notch | Supratentorial midline lesion | Small pupils, moderately dilated, fixed (rostral to caudal deterioration), sequential failure of diencephalon, medulla |
|                     |            | Diffuse cerebral swelling | Decreased LOC (midbrain compression) EOM/ upward gaze impairment (“sunset eyes”): compression of pretectum and superior colliculi |
|                     |            | Late uncal herniation | Brainstem hernorrhage (“Duret’s” = secondary to shearing of basilar artery perforating vessels) |
|                     |            |          | Diabetes insipidus (traction on pituitary stalk and hypothalamus), end-stage sign |
| 3. Lateral Tentorial (Uncal) | Uncus of temporal lobe herniates down through tentorial notch | Lateral supratentorial lesion (often rapidly expanding traumatic hematoma) | Ipsilateral non-reactive dilated pupil (earliest, most reliable sign) → ipsilateral EOM paralysis, ptosis (CN III compression) |
|                     |            |          | Decreased LOC (midbrain compression) |
|                     |            |          | Contralateral hemiplegia ± extensor (upgoing) plantar response ± ipsilateral hemiplegia (“Kernohan’s notch” – a false localizing sign resulting from pressure from the edge of the tentorium on the contralateral cerebral peduncle) |
| 4. Upward           | Cerebellar vermis herniates through tentorial incisura | Large posterior fossa mass (common after VP shunting) | Cerebellar infarct (superior cerebellar artery (SCA) compression) |
|                     |            |          | Hydrocephalus (cerebral aqueduct compression) |
| 5. Tonsillar        | Cerebellar tonsils herniate through foramen magnum | Infratentorial lesion | Neck stiffness and head tilt (tonsillar impaction) |
|                     |            | Following central tentorial herniation | Decreased LOC (midbrain compression) |
|                     |            | Following LP in presence of intracranial mass lesion | Flaccid paralysis |
|                     |            |          | Respiratory irregularities, respiratory arrest (compression of medullary respiratory centres) |
|                     |            |          | Blood pressure instability (compression of medullary cardiovascular centres) |

**Treatment of Elevated ICP**
- CT or MRI to identify etiology, assess for midline shift/herniation
- treat primary cause (i.e. remove mass lesions, ensure adequate ventilation)
- if elevated ICP persists following treatment of primary cause, consider therapy when ICP >20 mmHg
- goals: keep ICP <20 mmHg, CPP >65 mmHg, MAP >90 mmHg

**Conservative Measures**
- elevate head of bed at 30°, maintain neck in neutral position → increases intracranial venous outflow with minimal effect on arterial pressure
- prevent hypotension with fluid and vaspressors, dopamine, norepinephrine prn
- ventilate to normocarbia (pCO₂ 35-40 mmHg) → prevents vasodilatation
- oxygen to maintain pO₂ >60 mmHg → prevents hypoxic brain injury
- osmolar diuresis (mannitol 20% IV solution 1-1.5 g/kg, then 0.25 g/kg q6h to serum osmolarity of 315-320)
  - can give rapidly, acts in 15-30 min, must maintain sBP >90 mmHg
- corticosteroids → decrease edema over subsequent days around brain tumour, abscess, blood
  - no proven value in head injury or stroke
**Aggressive Measures**
- sedation ("light" e.g. barbiturates/codeine → "heavy" e.g. fentanyl/MgSO4)
- paralysis with vecuronium → reduces sympathetic tone, reduces HTN induced by muscle contraction
- hyperventilate to pCO$_2$ 30-35 mmHg
  - use for brief periods only – also results in decreased cerebral blood flow
- drain 3-5 mL CSF via ventricles, assess each situation independently
- insert EVD (if acute) or shunt
- barbiturate-induced coma induced with pentobarbital to reduce cerebral blood flow and metabolism (10 mg/kg over 30 min, then 1 mg/kg q1h continuous infusion)
  - decreases mortality, but no improvement in neurological outcome
- decompressive craniectomy is a last resort
- no role for the use of hypothermia in head injury

---

**Hydrocephalus**

- hydrocephalus in children, see *Pediatric Neurosurgery, NS36*

**Definition**
- increased CSF volume

**Etiology**
- obstruction to CSF flow
- decreased CSF absorption
- increased CSF production (rarely) – e.g. choroid plexus papilloma (0.4-1% of intracranial tumours)

**Epidemiology**
- estimated prevalence 1-1.5%; incidence of congenital hydrocephalus ~1-2/1000 live births

**Classification**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Definition</th>
<th>Etiology</th>
<th>Findings on CT/MRI</th>
</tr>
</thead>
</table>
| Obstructive (Non-Communicating) Hydrocephalus | Circulation blocked within ventricular system proximal to the arachnoid granulations | Acquired
  - Aqueductal stenosis (adhesions following infection, hemorrhage)
  - Intraventricular lesions (tumours e.g. 3rd ventricle colloid cyst, hematomas)
  - Mass causing tentorial herniation, aqueduct/4th ventricle compression
  - Others: neurosarcoïdosis, abscess/granulomas, arachnoid cysts | Ventricular enlargement proximal to block
  - Periventricular hypodensity (transpensional migration of CSF forced into extracellular space)
  - Sulcal effacement |
| Congenital | Aqueductal stenosis, Dandy-Walker malformation, Chiari malformation (see *Pediatric Neurosurgery, NS37*) | | |
| Non-Obstructive (Communicating) Hydrocephalus | CSF absorption blocked at extraventricular site = arachnoid granulations | Post-infectious (#1 cause)
  - meningitis, cysticercosis
  - Post-hemorrhagic (#2 cause) → SAH, IVH, traumatic
  - Choroid plexus papilloma (rare, causes increased CSF production)
  - Idiopathic → normal pressure hydrocephalus | All ventricles dilated |
| Normal Pressure Hydrocephalus (NPH) | Persistent ventricular dilatation in the context of normal CSF pressure | Idiopathic (50%)
  - Others: subarachnoid hemorrhage, meningitis, trauma, radiation-induced | Enlarged ventricles without increased prominence of cerebral sulci |
| Hydrocephalus Ex Vacuo | Ventricular enlargement resulting from atrophy of surrounding brain tissue | Normal aging
  - Alzheimer’s, Creutzfeldt-Jacob Disease | Enlarged ventricles and sulci
  - Cerebral atrophy |

**Figure 8. The flow of CSF**

CSF produced by choroid plexus, flows to: ventricles → foramina of Luschka (lateral) and Magendie (medial) → subarachnoid space → absorbed by arachnoid villi/granulations into venous sinuses.

CSF production = CSF reabsorption = $-500$ mL/d in normal adults

Normal CSF volume = 150 mL (50% spinal, 50% intracranial = 25 mL intraventricular, 50 mL subarachnoid)
Clinical Features
- acute hydrocephalus
  - signs and symptoms of acute elevated ICP (see Elevated ICP, NS6)
  - impaired upward gaze (“sunset eyes”) and/or CN VI palsy
- chronic/gradual onset hydrocephalus (i.e. NPH)
  - gradual onset of classic triad developing over weeks or months
    - pressure of ventricle on LE motor fibres → gait disturbance (ataxia and apraxia usually initial symptoms)
    - pressure on cortical bowel/bladder centre → urinary incontinence
    - pressure on frontal lobes → dementia
  - CSF pressure can be measured within clinically “normal” range

Investigations
- CT/MRI (periventricular lucency suggests raised CSF pressure)
- ultrasound (through anterior fontanelle in infants)
- ICP monitoring (e.g. LP) may be used to investigate NPH, test response to shunting (lumbar tap test)
- radionuclide cisternography can test CSF flow and absorption rate (unreliable)
- β-2 transferrin assay to test for the presence of CSF leak

Treatment
- ventricular drainage
  - surgical removal of obstruction (if possible) or excision of choroid plexus papilloma
- shunts
  - ventriculoperitoneal (VP): most common
  - ventriculopleural
  - ventriculo-atrial (VA): relatively increased risk of infections, shunt emboli
  - lumboperitoneal: for communicating hydrocephalus and pseudotumour cerebri
- third ventriculostomy (for obstructive hydrocephalus) via ventriculoscopy
- LPs for transient hydrocephalus (e.g. SAH), IVH in premature infants, etc.

Shunt Complications

<table>
<thead>
<tr>
<th>Table 5. Shunt Complications</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstruction (most common)</td>
<td></td>
<td>Acute hydrocephalus</td>
<td>“Shunt series” (plain x-rays of entire shunt that only rule-out disconnection, break, tip migration)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased ICP</td>
<td>CT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Radionuclide “shuntogram”</td>
</tr>
<tr>
<td>Infection (3-6%)</td>
<td>S. epidermidis</td>
<td>Fever, N/V, anorexia, irritability</td>
<td>CBC</td>
</tr>
<tr>
<td></td>
<td>S. aureus</td>
<td>Meningitis</td>
<td>Blood culture</td>
</tr>
<tr>
<td></td>
<td>P. acnes</td>
<td>Peritonitis</td>
<td>Tap shunt for C&amp;S (LP usually NOT recommended)</td>
</tr>
<tr>
<td></td>
<td>Gram-negative bacilli</td>
<td>Signs and symptoms of shunt obstruction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shunt nephritis (VA shunt)</td>
<td></td>
</tr>
<tr>
<td>Overshunting (10% over 6.5 yr)</td>
<td>Subdural hematoma</td>
<td>Chronic or recurring headaches often relieved when lying down</td>
<td>CT/MRI</td>
</tr>
<tr>
<td></td>
<td>Collapsing brain tears bridging veins (especially common in NPH patients)</td>
<td>Asymptomatic</td>
<td>CT</td>
</tr>
<tr>
<td></td>
<td>Secondary craniosynostosis (children): apposition and overlapping of the cranial sutures in an infant following decompression of hydrocephalus</td>
<td>Abnormal head shape</td>
<td>Clinical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CT</td>
</tr>
<tr>
<td>Seizures (5.5% risk in 1st yr, 1.1% after 3rd yr)</td>
<td>Increased intrapitoneal pressure/fluid results in hernia becoming apparent</td>
<td>EEG</td>
<td></td>
</tr>
<tr>
<td>Inguinal Hernia (17% incidence with VP shunt inserted in infancy) ± skin breakdown over hardware</td>
<td>Inguinal swelling, discomfort</td>
<td>U/S</td>
<td></td>
</tr>
</tbody>
</table>
**Idiopathic Intracranial Hypertension (Pseudotumour Cerebri)**

**Definition**
- raised intracranial pressure and papilledema without evidence of any mass lesion, hydrocephalus, infection, or hypertensive encephalopathy (diagnosis of exclusion)

**Etiology**
- unknown (majority), but associated with:
  - lateral venous sinus thrombosis
  - habitus/diet: obesity, hyper/hypovitaminosis A
  - endocrine: reproductive age, menstrual irregularities, Addison’s/Cushing’s disease, thyroid irregularities
  - hematological: iron deficiency anemia, polycythemia vera
  - drugs: steroid administration or withdrawal, tetracycline, nalidixic acid, etc.
- risk factors overlap with those of venous sinus thrombosis; similar to those for gallstones (“fat, female, fertile, forties”)

**Epidemiology**
- incidence ~0.5/100,000 per year
- usually in 3rd and 4th decade (F>M)

**Clinical Features**
- symptoms and signs of raised ICP (H/A in >90%, pulsatile intracranial noise), but no LOC or diplopia
- decreased visual acuity, papilledema, visual field defect, optic atrophy (key morbidity)
- usually self-limited, recurrence is common, chronic in some patients
- risk of blindness is not reliably correlated to symptoms or clinical course

**Investigations**
- CT: normal
- CSF studies: normal
- MRI: must look for venous sinus thrombosis

**Treatment**
- rule out conditions that cause intracranial hypertension (especially sinus thrombosis)
- discontinue offending medications, encourage weight loss, fluid/salt restriction
- pharmacotherapy: acetazolamide (decreases CSF production), thiazide diuretic or furosemide
- if above fail: serial LPs, shunt
- optic nerve sheath decompression (if progressive impairment of visual acuity)
- 2-yr follow-up with imaging to rule out occult tumour, ophthalmology follow-up

**Tumours**

**Ventricular:** colloid cyst, choroid plexus papilloma, ependymoma, germinoma, teratoma, meningioma

**Supratentorial extra-axial:** meningioma, cysts

**Supratentorial intra-axial:** astrocytoma, glioblastoma, oligodendroglioma, ganglioma, lymphoma, metastases

**Posterior fossa intra-axial:** schwannoma, meningioma, cysts, metastases

**Posterior fossa extra-axial:** schwannoma, meningioma, cyst, metastases

**Skull base:** carcinoma, chordoma, glomus jugulare, estoma

**Sellar or suprasellar:** pituitary edema, craniohypophyseoma, optic nerve glioma, cyst

**Important Features to Note on CT and MRI (≥ contrast enhancement)**
- Lesions (= edema, necrosis, hemorrhage)
- Midline shifts and herniations
- Effacement of ventricles and sulci (often ipsilateral), basal cisterns
- Single or multiple (multiple implies metastasis)

**DDx for Ring Enhancing Lesion on CT with Contrast**

**MAGICAL DR**
- Metastases*
- Abscess*
- Glioblastoma (high grade astrocytoma)*
- Infarct
- Contusion
- AIDS (toxoplasmosis)
- Lymphoma
- Demyelination
- Resolving hematoma
- (*) 3 most common Dxs

**Primary Sources of Metastatic Brain Tumours**
- Lung 44%
- Breast 10%
- Kidney (RCC) 7%
- GI 6%
- Melanoma 3%
Classification
- primary vs. metastatic, intra-axial (parenchymal) vs. extra-axial, supratentorial vs. infratentorial, adult vs. pediatric
- benign: non-invasive, devastating due to expansion of mass in fixed volume of skull (mass effect)
- malignant: implies rapid growth, invasiveness, but rarely extracranial metastasis
- types of intracranial tumours (* = most common)
  - neuroepithelial tissue
    - astrocytic tumours: astrocytoma, glioblastoma
    - oligodendrogial tumours
    - oligoastrocytic tumours
    - neuronal and mixed neuronal-glial tumours: gangliocytoma, ganglioglioma, neurocytoma, neuroblastoma
    - embryonal tumours: medulloblastoma, neuroectodermal
    - other: pineal, ependymal, and choroid plexus tumours
  - meningial: meningiomas*, mesenchymal, hemangioblastomas
  - cranial and parasellar nerves: schwannoma, neurofibroma
  - lymphomas and hematopoietic neoplasms
  - germ cell: germinomas, teratomas
  - pituitary adenomas*
  - sellar region: craniopharyngiomas, spindle cell oncocytoma
  - cysts: epidermoid/dermoid cysts, colloid cysts
  - local extension: chordomas, glomus jugulare tumours
  - metastatic tumours

Clinical Features
- progressive neurological deficit (70%): usually motor weakness, ± CN deficits, sensory, cognitive, personality, endocrine deficits (these may localize lesion)
- H/A (50%) ± symptoms of elevated ICP (see Elevated ICP, NS6)
- N/V (40%)
- seizures (25%)
- papilledema, vision changes
- symptoms suggestive of TIA (ictal, post-ictal, or ischemic 2o to “steal phenomenon”)
- rarely presents with hemorrhage
- familial syndromes associated with CNS tumours
  - von Hippel-Lindau (hemangioma)
  - tuberous sclerosis (astrocytoma)
  - neurofibromatosis type 1 and 2 (astrocytoma, acoustic neuroma respectively)
  - Li-Fraumeni (astrocytoma)
  - Turcot syndrome (glioblastoma multiforme)
  - multiple endocrine neoplasia type 1 (MEN-1) (pituitary adenoma)

Investigations
- CT, MRI, stereotactic biopsy (tissue diagnosis), metastatic work-up

Treatment
- conservative: serial Hx, Px, imaging for slow growing/benign lesions
- medical: corticosteroids to reduce cytotoxic cerebral edema, pharmacological conservative: serial Hx, Px, imaging for slow growing/benign lesions
- surgical: total or partial excision (decompressive, palliative), shunt if hydrocephalus
- radiotherapy: conventional fractionated radiotherapy (XRT), stereotactic radiosurgery (e.g. Gamma Knife*)
- chemotherapy: e.g. alkylating agents (temozolomide)

Table 6. Tumour Types: Age, Location

<table>
<thead>
<tr>
<th>Age</th>
<th>Supratentorial</th>
<th>Infratentorial (posterior fossa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15 yr</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
  - Incidence: 2.5-100,000/yr
  - 60% infratentorial
  - Astrocytoma (all grades) (50%) | Medulloblastoma (15-20%)
  - Cerebellar astrocytoma (15%) |
  - Others: pineal region tumours, choroid plexus tumours, ganglioglioma, DNET | Ependymoma (9%)
  - Brainstem astrocytoma |
| >15 yr |
  - 80% supratentorial
  - High grade astrocytoma (12-15%, e.g. GBM) | Metastasis
  - Metastasis (15-30%, includes infratentorial)
  - Meningioma (15-20%) |
  - Low grade astrocytoma (8%) | Acoustic neuroma (schwannoma) (5-10%)
  - Pituitary adenoma (5-8%)
  - Oligodendroglioma (5%)
  - Other: colloid cyst, CNS lymphoma, dermoid/epidermoid cysts | Hemangioblastoma (2%)
  - Meningioma |

Primary Brain Tumours
- Rarely undergo metastasis
- Adults = mostly supratentorial
- Children = mostly infratentorial

Brain Metastasis
- 1/3 of all adult brain tumours
- Well circumscribed, often at grey-white matter junction

Management of Single Brain Metastasis: A Practice Guideline

Carr Oncol 2007;14:131-143

Background: In Ontario the benefits of surgical resection ± adjuvant whole-brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) in confirmed single brain metastasis are summarized in this manuscript.

Methods: Medline, Cancerlit, Embase and Cochrane Library databases as well as abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1997-2005) and American Society for Therapeutic Radiology and Oncology (1998-2004) were systematically searched for relevant evidence. Outcomes were compared in terms of survival, local control of disease, quality of life, and adverse effects. The final review of these works was condensed into a practice guideline approved by the Neuro-oncology DSG and Ontario practitioners (through an electronic survey).

Results: Two of three RCTs reported a significant survival benefit for patients with single brain metastasis who underwent surgical resection as compared with those who received WBRT alone. The RCT that compared surgical resection plus WBRT with surgical resection alone reported no significant difference in overall survival or length of functional independence; however, tumour recurrence at the site of the metastasis and anywhere in the brain was less frequent in patients who received WBRT as compared with patients in the observation group. In addition, patients who received WBRT were less likely to die from neurologic causes. Results of the RCT that compared WBRT and SRS with WBRT alone indicated a significant improvement in median survival in patients who received SRS.

Conclusions: Surgical excision should be considered for patients with good performance status, minimal or no evidence of extracranial disease, and a surgically accessible single brain metastasis amenable to complete excision. Furthermore, to reduce the risk of tumour recurrence postoperative WBRT should be considered. As an alternative to surgical resection, WBRT followed by SRS boost should be considered, however, the evidence is insufficient to recommend SRS alone as a single-modality therapy.
### Table 7. Unique Presentations of Brain Tumours

<table>
<thead>
<tr>
<th>Tumour Features</th>
<th>Diagnosis</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumours at the base of the frontal lobe</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foster-Kennedy Syndrome</td>
<td>CT</td>
<td></td>
</tr>
<tr>
<td>1. Inappropriate behaviour</td>
<td>MRI (better)</td>
<td></td>
</tr>
<tr>
<td>2. Ipsilateral optic nerve atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Contralateral papilledema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Anosmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Youngsters</td>
<td>X-ray: calcified lesion above sella</td>
<td></td>
</tr>
<tr>
<td>2. Short for age</td>
<td>MRI</td>
<td></td>
</tr>
<tr>
<td>3. Bitemporal hemianopsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactinomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Young women</td>
<td>β-hCG → ± pregnancy</td>
<td></td>
</tr>
<tr>
<td>2. Amenorrhea</td>
<td>TSH, T4 → ± hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>3. Galactorrhea</td>
<td>Prolactin level</td>
<td></td>
</tr>
<tr>
<td>4. MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acromegaly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Enlarged hands, feet, tongue</td>
<td>Somatomedin C level</td>
<td></td>
</tr>
<tr>
<td>2. HTN</td>
<td>MRI</td>
<td></td>
</tr>
<tr>
<td>3. DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Sweaty hands</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. History of wedding bands/hats not fitting anymore</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary apoplexy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleed into tumour → destroy pituitary gland</td>
<td>1. CT</td>
<td></td>
</tr>
<tr>
<td>1. Pituitary tumour</td>
<td>2. MRI (better)</td>
<td>Must</td>
</tr>
<tr>
<td>• Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Visual loss</td>
<td>1. Replace steroid hormones</td>
<td></td>
</tr>
<tr>
<td>• Endocrine issues</td>
<td>2. Eventually replace other hormones</td>
<td></td>
</tr>
<tr>
<td>2. Episodic severe headaches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Increased compression of nearby structures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Decreased visual acuity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bilateral pallor of optic nerves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Pituitary destruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Stupor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pineal gland tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Loss of upper gaze</td>
<td>1. CT</td>
<td></td>
</tr>
<tr>
<td>2. “Sunset eyes” (Parinaud syndrome)</td>
<td>2. MRI (better)</td>
<td></td>
</tr>
<tr>
<td>Brain tumours in children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often posterior fossa tumours</td>
<td>1. CT</td>
<td></td>
</tr>
<tr>
<td>1. Cerebellar symptoms</td>
<td>2. MRI (better)</td>
<td></td>
</tr>
<tr>
<td>• Stumbling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Truncal ataxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. “Knee-chest” position to relieve headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain abscess</td>
<td>Similar symptoms as brain tumours</td>
<td>1. CT</td>
</tr>
<tr>
<td>+ fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ nearby infection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Metastatic Tumours

- most common brain tumour seen clinically
- 15-30% of cancer patients present with cerebral metastatic tumours
  - most common sources: lungs, breast
  - other sources: kidney, thyroid, stomach, prostate, testis, melanoma
- hematogenous spread most common

### Location

- 80% are hemispheric, often at grey-white matter junction or junction of temporal-parietal-occipital lobes (likely emboli spreading to terminal MCA branches)

### Investigations

- identify primary tumour
  - metastatic work-up (CXR, CT chest/abdo, abdominal U/S, bone scan, mammogram)
  - CT with contrast → round, well-circumscribed, often ring enhancing, ++ edema, often multiple
  - MRI more sensitive, especially for posterior fossa
  - consider biopsy in unusual cases, or if no primary identified

### Treatment

- medical
  - phenytoin (or levetiracetam) for seizure prophylaxis if patient presents with seizure
  - dexamethasone to reduce edema given with ranitidine
  - chemotherapy (e.g. small cell lung cancer)

---

![Figure 10. Multiple brain metastases (see arrows)](image-url)
• radiation
  ▪ stereotactic radiosurgery: for discrete, deep-seated/inoperable tumours
  ▪ multiple lesions: use whole brain radiation therapy (WBRT); consider stereotactic
  radiosurgery if <3 lesions
  ▪ post-op WBRT is commonly used
• surgical
  ▪ single/solitary lesions: use surgery + radiation

**Prognosis**
• median survival without treatment once symptomatic is ~1 mo, with optimal treatment
  6-9 mo but varies depending on primary tumour type

## Astrocytoma

• most common primary intra-axial brain tumour, common in 4-6th decades

### Table 8. Astrocytoma Grading System

<table>
<thead>
<tr>
<th>World Health Organization (WHO)</th>
<th>Typical CT/MRI Findings</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I – Pilocytic astrocytoma</td>
<td>± mass effect, ± enhancement</td>
<td>&gt;10 yr, cure if gross total resection</td>
</tr>
<tr>
<td>II – Low grade/diffuse</td>
<td>Mass effect, no enhancement</td>
<td>5 yr</td>
</tr>
<tr>
<td>III – Anaplastic</td>
<td>Complex enhancement</td>
<td>1.5-2 yr</td>
</tr>
<tr>
<td>IV – Glioblastoma multiforme (GBM)</td>
<td>Necrosis (ring enhancement)</td>
<td>12 mo, 10% at 2 yr</td>
</tr>
</tbody>
</table>

### Clinical Features
• sites: cerebral hemispheres >> cerebellum, brainstem, spinal cord
• symptoms: recent onset of new/worsening H/A, N/V, seizure, ± focal deficits or symptoms of increased ICP

### Investigations
• CT/MRI with contrast: variable appearance depending on grade (see Table 8)
• tissue biopsy: WHO grade and histology correlates with prognosis, but 25% chance of sampling error due to tumour heterogeneity

### Treatment
• low grade diffuse astrocytoma
  ▪ close follow-up, radiation, chemotherapy, surgery all valid options
  ▪ surgery: not curative, trend towards better outcomes
  ▪ radiotherapy alone or post-op prolongs survival (retrospective evidence)
  ▪ chemotherapy: usually reserved for tumour progression
• high grade astrocytomas (anaplastic astrocytoma and GBM)
  ▪ surgery
    ▪ gross total resection: maximal safe resection + fractionated radiation with 2 cm margin +
      concomitant and adjuvant temozolomide
      ▪ except: extensive dominant lobe GBM, significant bilateral involvement, end of life
        near, extensive brainstem involvement
    ▪ stereotactic biopsy if resection not possible, followed by fractionated radiation with 2 cm
      margin
  ▪ expectant (based on functional impairment – Karnofsky score <70; patient’s/family’s wishes)
  ▪ aim to prolong “quality” survival
  ▪ chemotherapy: ~20% response rate, temozolomide (agent of choice); better response to
temozolomide predicted by MGMT gene hypermethylation
• multiple gliomas: WBRT ± chemotherapy

## Meningioma

• mostly benign (1-2% anaplastic), slow-growing, extra-axial, circumscribed (non-infiltrative),
arise from arachnoid membrane
• often calcified, cause hyperostosis of adjacent bone
• classically see Psammoma bodies on histology
• common locations: parasagittal convexity or falx (70%), sphenoid wing, tuberculum sellae,
  foramen magnum, olfactory groove

### Clinical Features
• middle aged, slight female preponderance (M:F = 2:3), high progesterone receptors (increase in
  size with pregnancy), symptoms of increased ICP, focal deficits, usually solitary (10% multiple,
  likely with loss of NF2 gene/22q12 deletion)
Investigations
- CT with contrast: homogeneous, densely enhancing, along dural border ("dural tail"), well circumscribed (Figure 12)
- contrast enhanced MRI provides better detail
- angiography
  - most are supplied by external carotid feeders (meningeal vessels)
  - also assesses venous sinus involvement, "tumour blush" commonly seen (prolonged contrast image)
- octreotide scintigraphy: to establish if expression of somatostatin receptor

Treatment
- conservative management for non-progressive, asymptomatic lesions
- surgery is treatment of choice if symptomatic or progression on sequential imaging (curative if complete resection)
- SRS may be an option for lesions <3 cm
- endovascular embolization to facilitate surgery
- SRS or XRT for recurrent atypical/malignant meningiomas

Prognosis
- >90% 5-yr survival, recurrence rate variable (often ~10-20%)
- depends on extent of resection (Simpson’s classification)

Vestibular Schwannoma (Acoustic Neuroma)
- slow-growing (average of 1 mm/yr), benign posterior fossa tumour
- arises from vestibular component of CN VIII in internal auditory canal, expanding into bony canal and cerebello-pontine angle (CPA)
- if bilateral, diagnostic of neurofibromatosis type II
- epidemiology: all age groups affected, peaks at 4th-6th decades

Clinical Features
- compression of structures in CPA, often CN VIII (hearing loss 98%, tinnitus, dysequilibrium), followed by CN V and VII
- ataxia and raised ICP are late features

Investigations
- MRI with gadolinium or T2 FIESTA sequence (>98% sensitive/specific), CT with contrast 2nd choice
- audiogram, brainstem auditory evoked potentials, caloric tests

Treatment
- conservative: serial imaging
- radiation: stereotactic radiosurgery or fractionated radiotherapy
- surgery if: lesion >3 cm, brainstem compression, edema, hydrocephalus
  - curable if complete resection (almost always possible)
  - operative complications: CN VII, VIII dysfunction (only significant disability if bilateral), CSF leak

Pituitary Adenoma
- primarily from anterior pituitary, 3rd-4th decades, M=F
- incidence in autopsy studies approximately 20%
- classification
  - microadenoma <1 cm; macroadenoma ≥1 cm
  - endocrine active (functional/secretory) vs. inactive (non-functional)
- differential: parasellar tumours (e.g. craniopharyngioma, tuberculum sellae meningioma), carotid aneurysm

Clinical Features
- mass effects
  - H/A
  - bitemporal hemianopsia (compression of optic chiasm) (see Neurology, N12 for details of visual field deficit)
  - CN III, IV, V<sub>1</sub>, V<sub>2</sub>, VI palsy (compression of cavernous sinus)
- endocrine effects
  - hyperprolactinemia (prolactinoma): infertility, amenorrhea, galactorrhea, decreased libido
  - ACTH production: Cushing’s disease, hyperpigmentation
  - GH production: acromegaly/gigantism
  - panhypopituitarism (hypothyroidism, hypoadrenalism, hypogonadism)
  - associated MEN-1 syndrome
  - diabetes insipidus
- pituitary apoplexy (sudden expansion of mass due to hemorrhage or necrosis)
  - abrupt onset H/A, visual disturbances, ophthalmoplegia, reduced mental status, and panhypopituitarism
  - CSF rhinorrhea and seizures (rare)
  - signs and symptoms of subarachnoid hemorrhage (rare)

Investigations
- formal visual fields, CN testing
- endocrine tests (prolactin level, TSH, 8 AM cortisol, fasting glucose, FSH/LH, IGF-1), electrolytes, urine electrolytes, and osmolarity
- imaging (MRI with and without contrast)

Treatment
- medical
  - for apoplexy: rapid corticosteroid administration ± surgical decompression
  - for prolactinoma: dopamine agonists (e.g. bromocriptine)
  - for Cushing’s: serotonin antagonist (cyproheptadine), inhibition of cortisol production (ketoconazole)
  - for acromegaly: somatostatin analogue (octreotide) ± bromocriptine
  - endocrine replacement therapy
- surgical
  - trans-sphenoidal, trans-ethmoidal, trans-cranial approaches for non-secreting adenomas causing mass effect and Cushing/acromegaly (50% cure rate)

Pus

Sources of Pus/Infection
- four routes of microbial access to CNS
  1. hematogenous spread (most common): arterial and retrograde venous
     - adults: chest is #1 source (lung abscess, bronchiectasis, empyema)
     - children: congenital cyanotic heart disease with R to L shunt
     - immunosuppression (AIDS – toxoplasmosis)
  2. direct implantation (dural disruption)
     - trauma
     - iatrogenic (e.g. following LP post-op)
     - congenital defect (e.g. dermal sinus)
  3. contiguous spread (adjacent infection): from air sinus, naso/oropharynx, surgical site (e.g. otitis media, mastoiditis, sinusitis, osteomyelitis, dental abscess)
  4. spread from PNS (e.g. viruses: rabies, herpes zoster)
- common examples
  - epidural abscess: in cranial and spinal epidural space, associated with osteomyelitis
  - treatment: immediate drainage and antibiotics, surgical emergency if cord compression
  - subdural empyema: bacterial/fungal infection, due to contiguous spread from bone or air sinus, progresses rapidly
  - treatment: surgical drainage and antibiotics, 20% mortality
  - meningitis, encephalitis (see Infectious Diseases, ID19, ID20)
  - cerebral abscess (see Cerebral Abscess, below)

Cerebral Abscess

Definition
- pus in brain substance, surrounded by tissue reaction (capsule formation)

Etiology
- modes of spread (see above): 10-60% of patients have no cause identified
- pathogens
  - Streptococcus (most common), often anaerobic or microaerophilic
  - Staphylococcus (penetrating injury)
  - Gram-negatives, anaerobes (Bacteroides, Fusobacterium)
  - in neonates: Proteus and Citrobacter (exclusively)
  - immunocompromised: fungi and protozoa (Toxoplasma, Nocardia, Candida albicans, Listeria monocytogenes, Mycobacterium and Aspergillus)
**Risk Factors**
- lung abnormalities [infection, AV fistulas; especially Osler-Weber-Rendu syndrome (aka hereditary hemorrhagic telangiectasia)]
- congenital coronary heart disease: R-to-L shunt bypasses pulmonary filtration of micro-organisms
- bacterial endocarditis
- penetrating head trauma
- immunosuppression (e.g. AIDS)
- dental abscess

**Clinical Features**
- focal neurological signs and symptoms
  - H/A, decreased LOC; hemiparesis and seizures in 50%
- mass effect, increased ICP and sequelae (cranial enlargement in children)
- hemiparesis and seizures in 50%
- ± signs and symptoms of systemic infection (low-grade fever, leukocytosis)

**Complications**
- with abscess rupture: ventriculitis, meningitis, venous sinus thrombosis
- CSF obstruction
- transtentorial herniation

**Investigations**
- CT scan often first test in emergency department (see Figure 14)
- MRI
  - imaging of choice
  - apparent diffusion coefficient (ADC) used to differentiate abscess (black) from tumour (white)
- WBC/ESR may be normal, blood cultures rarely helpful and LP contraindicated if large mass
- CSF: non-specific (high ICP, high WBC, high protein, normal carbohydrate), rarely helpful, usually negative culture

**Treatment**
- aspiration ± excision and send for Gram stain, acid fast bacillus (AFB), C&S, fungal culture
- excision preferable if location suitable
- antibiotics
  - empirically: vancomycin + ceftriaxone + metronidazole or chloramphenicol or rifampin
  - 6-8 wk therapy
  - revise antibiotics when C&S known
- anti-convulsants (1-2 yr)
- follow up CT is critical (do weekly initially, more frequent if condition deteriorates)

**Prognosis**
- mortality with appropriate therapy ~10%, permanent deficits in ~50%

---

**Table 9. Comparison of Epidemiology and Etiology of Intracranial Bleeds**

<table>
<thead>
<tr>
<th>Types of Hematoma/Hemorrhage</th>
<th>Etiology</th>
<th>Epidemiology</th>
<th>Clinical Features</th>
<th>CT Features</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidual Hematoma</td>
<td>Skull fracture causing middle meningeal bleed</td>
<td>M&gt;F (4:1), associated with trauma</td>
<td>Lucid interval before LOC</td>
<td>Hyperdense lenticular mass with sharp margins, usually limited by suture lines</td>
<td>Craniotomy</td>
<td>Good with prompt management (Note: respiratory arrest can occur from uncal herniation)</td>
</tr>
<tr>
<td>Acute SDH</td>
<td>Ruptured subarachnoid bridging vessels</td>
<td>Age &gt;50, associated with trauma</td>
<td>No lucid interval, hemiparesis, pupillary changes</td>
<td>Hyperdense crescentic mass, crossing sutures lines</td>
<td>Craniotomy if bleed &gt;1 cm thick</td>
<td>Poor</td>
</tr>
<tr>
<td>Chronic SDH</td>
<td>Ruptured subarachnoid bridging vessels</td>
<td>Age &gt;50, ETOH abusers, anti-coagulated</td>
<td>Often asymptomatic, minor H/A, confusion, signs of increased ICP</td>
<td>Hyperdense crescentic mass, crossing suture lines</td>
<td>Burr hole to drain; craniotomy if recurs</td>
<td>Good</td>
</tr>
<tr>
<td>SAH</td>
<td>Trauma, spontaneous (aneurysms, idiopathic, AVM)</td>
<td>Age 55-60 20% cases under age 45</td>
<td>Sudden onset thunderclap headache, signs of increased ICP</td>
<td>Hyperdense blood in cisterns/lissures (sensitivity decreases over time)</td>
<td>Conservative: NPO, IV NS, ECG, Foley, BP 120-150, vasospasm prophylaxis (nimodipine); open vs. endovascular surgery to repair if rebleed</td>
<td>Poor: 50% mortality 30% of survivors have moderate to severe disability</td>
</tr>
<tr>
<td>ICH</td>
<td>HTN, vascular abnormality, tumours, infections, coagulopathy</td>
<td>Age &gt;55, male, drug use (cocaine, EtOH, amphetamine)</td>
<td>TIA-like symptoms, signs of increased ICP</td>
<td>Hyperdense intraparenchymal collection</td>
<td>Medical: decrease BP, control ICP Surgical: craniotomy</td>
<td>Poor: 44% mortality due to cerebral herniation</td>
</tr>
</tbody>
</table>
Extradural (“Epidural”) Hematoma

Etiology
- temporal-parietal skull fracture: 85% are due to ruptured middle meningeal artery; remainder of cases are due to bleeding from middle meningeal vein, dural sinus, or bone/diploic veins

Epidemiology
- young adult, male > female = 4:1; rare before age of 2 or after age 60

Clinical Features
- classic sequence (seen in <30%): post-traumatic reduced LOC, a lucid interval of several hours, then obtundation, hemiparesis, ipsilateral pupillary dilatation, and coma
- signs and symptoms depend on severity but can include H/A, N/V, amnesia, altered LOC, HTN and respiratory distress
- deterioration can take hours to days

Investigations
- CT without contrast: “lenticular-shaped” usually limited by suture lines (see Figure 15)

Treatment
- admission, observation with serial CT indicated if all of the following are present:
  - small volume clot, minimal midline shift (MLS < 5 mm), GCS > 8, no focal deficit
  - otherwise, craniotomy to evacuate clot, follow up CT
  - mannitol pre-op if elevated ICP/brain herniation

Prognosis
- good with prompt management, as the brain is often not damaged
- worse prognosis if bilateral Babinski or decerebration pre-op
- death is usually due to respiratory arrest from uncal herniation (injury to the midbrain)

Subdural Hematoma (SDH)

ACUTE SUBDURAL HEMATOMA

Etiology
- rupture of vessels that bridge the subarachnoid space (e.g. cortical artery, large vein, venous sinus) or cerebral laceration

Risk Factors
- trauma, acceleration-deceleration injury, anti-coagulants, alcohol, cerebral atrophy, infant head trauma (see Pediatrics, P86)

Clinical Features
- no lucid period, signs and symptoms can include altered LOC, pupillary irregularity, hemiparesis

Investigations
- CT: hyperdense concave “crescentic” mass, crossing suture lines (see Figure 16)

Treatment
- craniotomy if clinically symptomatic, if hematoma > 1 cm thick, or if MLS > 5 mm (optimal if surgery < 4 h from onset); otherwise observe with serial imaging

Prognosis
- poor overall since the brain parenchyma is often injured (mortality range is 50%-90%, due largely to underlying brain injury)
- prognostic factors: initial GCS and neurologic status, post-op ICP

CHRONIC SUBDURAL HEMATOMA

Etiology
- many start out as acute SDH
- blood within the subdural space evokes an inflammatory response:
  - fibroblast invasion of clot and formation of neomembranes within days → growth of neocapillaries → fibrinolysis and liquefaction of blood clot
  - course is determined by the balance of rebleeding from neomembranes and resorption of fluid
Risk Factors
• older, alcoholics, patients with CSF shunts, anti-coagulants, coagulopathies

Clinical Features
• often due to minor injuries or no history of injury
• may present with minor H/A, confusion, language difficulties, TIA-like symptoms, symptoms of raised ICP ± seizures, progressive dementia, gait problem
• obtundation disproportionate to focal deficit; “the great imitator” of dementia, tumours

Investigations
• CT: hypodense (liquefied clot), crescentic mass (see Figure 16)

Treatment
• seizure prophylaxis only if post-traumatic seizure
• reverse coagulopathies
• burr hole drainage of liquefied clot indicated if symptomatic or thickness >1 cm; craniotomy if recurs more than twice

Prognosis
• good overall as brain usually undamaged, but may require repeat drainage

Cerebrovascular Disease

Ischemic Cerebral Infarction (80%)
• embolic, thrombosis of intracerebral arteries, vasculitis, hypercoagulability, etc.
(see Neurology, N43)

Intracranial Hemorrhage (20%)
• subarachnoid hemorrhage (SAH), spontaneous intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH)

Subarachnoid Hemorrhage (SAH)

Definition
• bleeding into subarachnoid space (intracranial vessel between arachnoid and pia)

Etiology
• trauma (most common)
• spontaneous
  ▪ ruptured aneurysms (75-80%)
  ▪ idiopathic (14-22%)
  ▪ AVMs (4-5%)
• coagulopathies (iatrogenic or primary), vasculitides, tumours, cerebral artery dissections (<5%)

Epidemiology
• ~10-28/100,000 population/yr
• peak age 55-60, 20% of cases occur under age 45

Risk Factors
• hypertension
• pregnancy/parturition in patients with pre-existing AVMs, eclampsia
• oral contraceptive pill
• substance abuse (cigarette smoking, cocaine, alcohol)
• conditions associated with high incidence of aneurysms (see Intracranial Aneurysms, NS21)

Clinical Features of Spontaneous SAH
• sudden onset (seconds) of severe “thunderclap” headache usually following exertion and described as the “worst headache of my life” (up to 97% sensitive, 12-25% specific)
• nausea/vomiting, photophobia
• meningismus (neck pain/stiffness, positive Kernig’s and Brudzinski’s sign)
• decreased LOC (due to either raised ICP, ischemia, seizure)
• focal deficits: cranial nerve palsies (CN III, IV), hemiparesis
• ocular hemorrhage in 20-40% (due to sudden raised ICP compressing central retinal vein)
• reactive hypertension

Fisher Grade (SAH on CT scan)
Grade | Finding
--- | ---
1 | Normal scan
2 | <1 mm thick blood
3 | >1 mm thick blood
4 | SAH + ICH or IVH

Hunt and Hess Grade (clinical grading scale for SAH)
Grade | Description
--- | ---
1 | No Sx or mild H/A and/or mild meningismus
2 | Grade 1 + CN palsy
3 | Confusion/betargy, mild hemiparesis or aphasia
4 | GCS <15 but >8, moderate-severe hemiparesis, mild rigidity
5 | Coma (GCS <9), decerebrate, moribund appearance

Mortality of Grade 1-2 20%, increased with grade
• sentinel bleeds
  • represents undiagnosed SAH
  • SAH-like symptoms lasting <1 d (“thunderclap H/A”)
  • may have blood on CT or LP
  • ~30-60% of patients with full blown SAH give history suggestive of sentinel bleed within past 3 wk
• differential diagnosis: sentinel bleed, dissection/thrombosis of aneurysm, venous sinus thrombosis, benign cerebral vasculitis, benign exertional H/A

Investigations
• non-contrast CT (Figure 17) – for diagnosis of SAH
  • 98% sensitive within 12 h, 93% within 24 h; 100% specificity
  • may be negative if small bleed or presentation delayed several days
  • acute hydrocephalus, IVH, ICH, infarct or large aneurysm may be visible
• lumbar puncture (highly sensitive) – for diagnosis of SAH if CT negative but high suspicion:
  • bloody initially, xanthochromic supernatant with centrifugation ("yellow") by ~12 h, lasts 2 wk
  • RBC count usually >100,000/mm³ without significant drop from first to last tube (in contrast to traumatic tap)
  • elevated protein due to blood breakdown products
• four vessel cerebral angiography (“gold standard” for aneurysms)
  • demonstrates source of SAH in 80-85% of cases
  • angiogram negative SAH: repeat angiogram in 7-14 d, if negative → “perimesencephalic SAH”
• MRA and CTA: sensitivity up to 95% for aneurysms, CTA>MRA for smaller aneurysms and delineating adjacent bony anatomy

![Figure 17. Diagnosis of SAH](image)

**World Federation of Neurological Surgeons Grading of SAH**

<table>
<thead>
<tr>
<th>WFNS Grade</th>
<th>GCS Score</th>
<th>Aphasia, Hemiparesis, or Hemiplegia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0*</td>
<td>15</td>
<td>–</td>
</tr>
<tr>
<td>1</td>
<td>13-14</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>13-14</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>7-12</td>
<td>+ or –</td>
</tr>
<tr>
<td>4</td>
<td>3-6</td>
<td>+ or –</td>
</tr>
</tbody>
</table>

*Intact aneurysm

![Figure 18. Approach to SAH](image)

**Background:** Two rules for SAH diagnosis exist. A clinical prediction rule states that patients with acute severe headache but without the clinical variables age ≥ 40 yr, neck pain, loss of consciousness, or onset of headache with exertion are at low risk for SAH. An imaging prediction rule bases diagnosis on non-contrast cranial CT for patients within 6 h of headache onset.

**Methods:** Matched case-control study of 55 patients at 21 emergency departments between 2000 and 2011, and diagnoses were verified by lumbar puncture.

**Results:** The clinical prediction rule for diagnosis of SAH was 97.1% sensitive, 22.7% specific, and had a negative likelihood ratio of 0.13. Using the imaging prediction rule resulted in a false negative rate of 20%.

**Conclusions:** Performing the clinical and imaging rules together has the potential for maximizing sensitivity of prediction and reducing rates of lumbar puncture, but using imaging alone can result in missed cases.
Treatment
- admit to ICU or NICU
- oxygen/ventilation prn
- NPO, bed rest, elevate head of bed 30°, minimal external stimulation, neurological vitals q1h
- aim to maintain sBP = 120-150 (balance of vasospasm prophylaxis, risk of re-bleed, risk of hypotension since CBF autoregulation impaired by SAH)
- cardiac rhythm monitor, Foley prn, strict monitoring of ins and outs
- medications:
  - IV NS with 20 mmol KCl/L at 125-150 cc/h
  - nimodipine 60 mg PO/NG q4h x 21 d for vasospasm neuroprotection; may discontinue earlier if patient is clinically well
  - seizure prophylaxis: levetiracetam (Keppra®) 500 mg PO/IV q12h x 1 wk
  - mild sedation prn

Complications
- vasospasm: vasoconstriction and permanent pathological vascular changes in response to vessel irritation by blood
  - onset: 4-14 d post-SAH, peak at 6-8 d; most commonly due to SAH, rarely due to ICH/IVH
  - clinical features (delayed ischemic deficit): confusion, decreased LOC, focal deficit (speech or motor)
  - risk factors: large amount of blood on CT (high Fisher grade), smoking, increased age, HTN
  - “symptomatic” vasospasm in 20-30% of SAH patients
  - “radiographic” vasospasm in 30-70% of arteriograms performed 7 d following SAH
  - diagnosed clinically, and/or with transcranial Doppler (increased velocity of blood flow)
  - risk of cerebral infarct and death
- treatment
  - hyperdynamic (“triple H” – see sidebar) therapy using fluids and pressors, usually after ruptured aneurysm has been clipped/coiled
  - direct vasodilation via angioplasty or intraarterial verapamil for refractory cases
  - hydrocephalus (15-20%): due to blood obstructing CSF drainage
  - can be acute or chronic, requires extraventricular drain (EVD) or shunt, respectively
  - neurogenic pulmonary edema
  - hyponatremia: due to cerebral salt wasting (increased renal sodium loss and ECFV loss), not SIADH
  - diabetes insipidus
  - cardiac: arrhythmia (>50% have ECG changes), MI, CHF

Prognosis
- 10-15% mortality before reaching hospital, overall 50% mortality (majority within first 2-3 wk)
- 30% of survivors have moderate to severe disability
- a major cause of mortality is rebleeding, for aneurysms:
  - risk of rebleed: 4% on first day, 15-20% within 2 wk, 50% by 6 mo
  - if no rebleed by 6 mo, risk decreases to same incidence as unruptured aneurysm (2%)
  - only prevention is early clipping or coiling of “cold” aneurysm
  - rebleed risk for “perimesencephalic SAH” is approximately same as for general population

Intracerebral Hemorrhage (ICH)

Definition
- hemorrhage within brain parenchyma, accounts for ~10% of strokes
- can dissect into ventricular system (IVH) or through cortical surface (SAH)

Etiology
- HTN (usually causes bleeds at putamen, thalamus, pons and cerebellum)
- hemorrhagic transformation (reperfusion post stroke, surgery, strenuous exercise, etc.)
- NPO, bed rest, elevate head of bed 30°, minimal external stimulation, neurological vitals q1h
- venous sinus thrombosis
- arteriopathies (cerebral amyloid angiopathy, lipohyalinosis, vasculitis)
- tumors (1%): often malignant (e.g. GBM, lymphoma, metastases)
- drugs (amphetamine, cocaine, alcohol, anticoagulants, etc.)
- coagulopathy (iatrogenic, leukemia, TTP, aplastic anemia)
- CNS infections (fungal, granulomas, herpes simplex encephalitis)
- post trauma (immediate or delayed, frontal and temporal lobes most commonly injured via coup-contrecoup mechanism)
- eclampsia
- post-operative (post-carotid endarterectomy cerebral reperfusion, craniotomy)
- idiopathic
Epidemiology
• 12-15 cases/100,000 population/yr

Risk Factors
• increasing age (mainly >55 yr)
• male gender
• HTN
• Black/Asian > Caucasian
• previous CVA of any type (23x risk)
• both acute and chronic heavy alcohol use; cocaine, amphetamines
• liver disease
• anticoagulants

Clinical Features
• TIA-like symptoms often precede ICH, can localize to site of impending hemorrhage
• location: basal ganglia/internal capsule (50%), thalamus (15%), cerebral white matter (15%), cerebellum/brainstem – usually pons (15%)
• gradual onset of symptoms over minutes-hours, usually during activity
• H/A, N/V, and decreased LOC are common
• specific symptoms/deficits depend on location of ICH

Investigations
• hyperdense blood on non-contrast CT
• CTA routine, if spot sign demonstrated there is high likelihood of clot growth

Treatment
• medical
  ▪ decrease MAP to pre-morbid level or by ~20% (target BP 140/90)
  ▪ check PT/INR, and correct coagulopathy
  ▪ control raised ICP (see Intracranial Pressure Dynamics, NS4)
  ▪ levetiracetam/phenytoin for seizure prophylaxis
  ▪ follow electrolytes (SIADH common)
  ▪ angiogram to r/o vascular lesion unless >45 yr, known HTN, and putamen/thalamic/posterior fossa ICH (yield ~0%)
• surgical
  ▪ craniotomy with evacuation of clot, treatment of source of ICH (i.e. AVM, tumour, cavernoma), ventriculostomy to treat hydrocephalus
  ▪ indications
    ▪ symptoms of raised ICP or mass effect
    ▪ rapid deterioration (especially if signs of brainstem compression)
    ▪ favourable location (e.g. cerebellar, non-dominant hemisphere)
    ▪ young patient (<50 yr)
    ▪ if tumour, AVM, aneurysm, or cavernoma suspected (resection or clip to decrease risk of rebleed)
  ▪ contraindications
    ▪ small bleed: minimal symptoms, GCS >10
    ▪ poor prognosis: massive hemorrhage (especially dominant lobe), low GCS/coma, lost brainstem function
    ▪ medical reasons [e.g. very elderly, severe coagulopathy, difficult location (e.g. basal ganglia, thalamus)]

Prognosis
• 30-d mortality rate 44%, mostly due to cerebral herniation
• rebleed rate 2-6%, higher if HTN poorly controlled

Intracranial Aneurysms

Epidemiology
• prevalence 1-4% (20% have multiple)
• female > male; age 35-65 yr

Risk Factors
• autosomal dominant polycystic kidney disease (15%)
• fibromuscular dysplasia (7-21%)
• AVMs
• connective tissue diseases (Ehlers-Danlos, Marfan)
• family history
• bacterial endocarditis
• Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia)
• atherosclerosis and HTN
• trauma
Types (for location, see Figure 4, NS3)
- saccular (berry)
  - most common type
  - located at branch points of major cerebral arteries (Circle of Willis)
  - 85-95% in carotid system, 5-15% in vertebralbasilar circulation
- fusiform
- atherosclerotic
- more common in vertebralbasilar system, rarely rupture
- infectious
  - secondary to any infection of vessel wall, 20% multiple
  - 60% Streptococcus and Staphylococcus
  - 3-15% of patients with bacterial endocarditis

Clinical Presentation
- rupture (90%), most often SAH, but 30% ICH, 20% IVH, 3% subdural bleed
- sentinel hemorrhage ("thunderclap H/A") \rightarrow requires urgent clipping/coiling to prevent catastrophic bleed
- mass effect (giant aneurysms)
  - internal carotid or anterior communicating aneurysm may compress:
    - the pituitary stalk or hypothalamus causing hypopituitarism
    - the optic nerve or chiasm producing a visual field defect
    - basilar artery aneurysm may compress midbrain, pons (limb weakness), or CN III
  - posterior communicating artery aneurysm may produce CN III palsy
  - intracavernous aneurysms (CN III, IV, V1, V2, VI)
  - distal embolization (e.g. amaurosis fugax)
  - seizures
  - headache (without hemorrhage)
  - incidental CT or angiography finding (asymptomatic)

Investigations
- CT angiogram (CTA), magnetic resonance angiography (MRA), cerebral angiogram

Treatment
- ruptured aneurysms
  - overall trend towards better outcome with early surgery or coiling (48-96 h after SAH)
  - treatment options: surgical placement of clip across aneurysm neck, trapping (clipping of proximal and distal vessels), thrombosing using Guglielmi detachable coils (coiling), wrapping (last resort)
  - choice of surgery vs. coiling not yet well defined, consider location, size, shape, and tortuosity of the aneurysm, patient comorbidities, age, and neurological condition. In general:
    - clipping: posterior > anterior circulation, deep/eloquent location, basilar artery bifurcation/apex, older age, presence of comorbidities, presence of vasospasm
    - coiling: superficial > deep, broad aneurysmal base, branching arteries at the aneurysm base, tortuosity/atherosclerosis of afferent vessels, dissection, hematoma, acute brainstem compression
- unruptured aneurysms
  - average 1% annual risk of rupture: risk dependent on size and location of aneurysm
  - no clear evidence on when to operate: need to weigh life expectancy
  - risk of morbidity/mortality of SAH (20%-50%) vs. surgical risk (2%-5%)
  - generally treat unruptured aneurysms >10 mm
  - consider treating when aneurysm 7-9 mm in middle-aged, younger patients or patients with a family history of aneurysms
  - follow smaller aneurysms with serial angiography

Table 10. 5-year Cumulative Rupture Risk in Unruptured Aneurysms Based on Size and Location

<table>
<thead>
<tr>
<th>Size</th>
<th>Cavernous Carotid</th>
<th>AC/MC/IC</th>
<th>Vertebralbasil/PC/PComm</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7 mm</td>
<td>0%</td>
<td>0%</td>
<td>2.5%</td>
</tr>
<tr>
<td>7-12 mm</td>
<td>0%</td>
<td>2.6%</td>
<td>14.5%</td>
</tr>
<tr>
<td>13-24 mm</td>
<td>3%</td>
<td>14.5%</td>
<td>18.4%</td>
</tr>
<tr>
<td>≥24 mm</td>
<td>6.4%</td>
<td>40%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Clinical Presentation
- rupture (90%), most often SAH, but 30% ICH, 20% IVH, 3% subdural bleed
- sentinel hemorrhage ("thunderclap H/A") \rightarrow requires urgent clipping/coiling to prevent catastrophic bleed
- mass effect (giant aneurysms)
  - internal carotid or anterior communicating aneurysm may compress:
    - the pituitary stalk or hypothalamus causing hypopituitarism
    - the optic nerve or chiasm producing a visual field defect
    - basilar artery aneurysm may compress midbrain, pons (limb weakness), or CN III
  - posterior communicating artery aneurysm may produce CN III palsy
  - intracavernous aneurysms (CN III, IV, V1, V2, VI)
  - distal embolization (e.g. amaurosis fugax)
  - seizures
  - headache (without hemorrhage)
  - incidental CT or angiography finding (asymptomatic)

Investigations
- CT angiogram (CTA), magnetic resonance angiography (MRA), cerebral angiogram

Treatment
- ruptured aneurysms
  - overall trend towards better outcome with early surgery or coiling (48-96 h after SAH)
  - treatment options: surgical placement of clip across aneurysm neck, trapping (clipping of proximal and distal vessels), thrombosing using Guglielmi detachable coils (coiling), wrapping (last resort)
  - choice of surgery vs. coiling not yet well defined, consider location, size, shape, and tortuosity of the aneurysm, patient comorbidities, age, and neurological condition. In general:
    - clipping: posterior > anterior circulation, deep/eloquent location, basilar artery bifurcation/apex, older age, presence of comorbidities, presence of vasospasm
    - coiling: superficial > deep, broad aneurysmal base, branching arteries at the aneurysm base, tortuosity/atherosclerosis of afferent vessels, dissection, hematoma, acute brainstem compression
- unruptured aneurysms
  - average 1% annual risk of rupture: risk dependent on size and location of aneurysm
  - no clear evidence on when to operate: need to weigh life expectancy
  - risk of morbidity/mortality of SAH (20%-50%) vs. surgical risk (2%-5%)
  - generally treat unruptured aneurysms >10 mm
  - consider treating when aneurysm 7-9 mm in middle-aged, younger patients or patients with a family history of aneurysms
  - follow smaller aneurysms with serial angiography

Table 10. 5-year Cumulative Rupture Risk in Unruptured Aneurysms Based on Size and Location

<table>
<thead>
<tr>
<th>Size</th>
<th>Cavernous Carotid</th>
<th>AC/MC/IC</th>
<th>Vertebralbasil/PC/PComm</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7 mm</td>
<td>0%</td>
<td>0%</td>
<td>2.5%</td>
</tr>
<tr>
<td>7-12 mm</td>
<td>0%</td>
<td>2.6%</td>
<td>14.5%</td>
</tr>
<tr>
<td>13-24 mm</td>
<td>3%</td>
<td>14.5%</td>
<td>18.4%</td>
</tr>
<tr>
<td>≥24 mm</td>
<td>6.4%</td>
<td>40%</td>
<td>50%</td>
</tr>
</tbody>
</table>
Carotid Stenosis

Definition
- narrowing of the internal carotid artery lumen due to atherosclerotic plaque formation, usually near common carotid bifurcation into internal and external carotids

Risk Factors
- for atherosclerosis: HTN, smoking, DM, CVD or CAD, dyslipidemia

Clinical Features
- may be asymptomatic
- symptomatic stenosis may present as TIA, reversible ischemic neurologic deficit (RIND), or stroke
- retinal insufficiency or infarct permanently or temporarily (amaurosis fugax), (see Ophthalmology, OP37)
- middle cerebral artery (MCA) occlusive symptoms

Investigations
- CBC, PTT/INR (hypercoagulable states)
- fundoscopy: cholesterol emboli in retinal vessels (Hollenhorst plaques)
- auscultation over carotid bifurcation for bruits (do not correlate with degree of stenosis)
- carotid duplex: determines severity of disease (mild/moderate/severe stenosis of occlusion)
- angiogram: “gold standard” but invasive and 1/200 risk of stroke (not for screening)
- MRA: safer than angiogram, may overestimate stenosis

Treatment
- control of HTN, lipids, diabetes
- antiplatelet agents (ASA ± dipyridamole, clopidogrel) ~25% relative risk reduction
- carotid endarterectomy (generally if symptomatic and >70% stenosis, see Tables 11 and 12)
- endovascular angioplasty ± stenting

Prognosis

Table 11. Symptomatic Carotid Stenosis: North American Symptomatic Carotid Endarterectomy Trial (NASCET)

<table>
<thead>
<tr>
<th>% Stenosis on Angiogram</th>
<th>Medical Rx</th>
<th>Medical + Surgical Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-99%</td>
<td>26% over 2 yr</td>
<td>9% over 2 yr</td>
</tr>
<tr>
<td>50-69%</td>
<td>22% over 5 yr</td>
<td>16% over 5 yr</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>Surgery has no benefit with 5% complication rate</td>
<td></td>
</tr>
</tbody>
</table>

Table 12. Asymptomatic Carotid Stenosis: Asymptomatic Carotid Atherosclerosis Study (ACAS) and Asymptomatic Carotid Surgery Trial (ACST)

<table>
<thead>
<tr>
<th>% Stenosis on Angiogram</th>
<th>Medical Rx</th>
<th>Medical + Surgical Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-99%</td>
<td>11% over 5 yr</td>
<td>5.1% over 5 yr (ACAS)</td>
</tr>
<tr>
<td>50-69%</td>
<td>11.8% over 5 yr</td>
<td>6.4% over 5 yr (ACST)</td>
</tr>
</tbody>
</table>

Vascular Malformations

Types
- arteriovenous malformations (AVMs)
- cavernous malformations (= cavernomas, cavernous hemangiomas/angiomas)
- venous angioma
- capillary telangiectasias
- arterio-venous fistula (AVF) (carotid-cavernous fistula, dural AVF; vein of Galen aneurysm)
- “angiographically occult vascular malformations” (any type, 10% of malformations)

Arteriovenous Malformations (AVMs)

Definition
- tangle of abnormal vessels/arteriovenous shunts, with no intervening capillary beds or brain parenchyma, usually congenital

Epidemiology
- prevalence ~0.14%, male:female = 2:1, average age at diagnosis = 33 yr
- 15-20% of patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) will have cerebral AVMs

Spetzler-Martin AVM Grading Scale

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td></td>
</tr>
<tr>
<td>0-2 cm</td>
<td>1</td>
</tr>
<tr>
<td>3.1-6.0 cm</td>
<td>2</td>
</tr>
<tr>
<td>&gt;6 cm</td>
<td>3</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Noneloquent</td>
<td>0</td>
</tr>
<tr>
<td>Eloquent</td>
<td>1</td>
</tr>
<tr>
<td>Deep venous drainage</td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
</tbody>
</table>

AVM grades calculated by adding the 3 individual Spetzler-Martin Scale scores from the above table. e.g. a 2 cm tumour in noneloquent location without deep venous drainage = Grade I
Clinical Features

- hemorrhage (40-60%): small AVMs are more likely to bleed due to direct high pressure AV connections
- seizures (50%): more common with larger AVMs
- mass effect
- focal neurological signs secondary to ischemia (high flow → "steal phenomena")
- localized headache, increased ICP
- bruit (especially with dural AVMs)
- may be asymptomatic ("silent")

Investigations

- MRI (flow void), MRA
- angiography (7% will also have one or more associated aneurysms)

Treatment

- decreases risk of future hemorrhage and seizure
  - surgical excision is treatment of choice
  - SRS is preferred for small (<3 cm) or very deep lesions
  - endovascular embolization (glue, balloon) can facilitate surgery or SRS for larger lesions
  - conservative (e.g. palliative embolization, seizure control if necessary)

Prognosis

- 10% mortality, 30-50% morbidity (serious neurological deficit) per bleed
- risk of major bleed in untreated AVMs: 2-4% per year

Cavernous Malformations

- benign vascular hamartoma consisting of irregular sinusoidal vascular channels located within the brain without intervening neural tissue or associated large arteries/veins
- several genes now described: CCM1, CCM2, CCM3
- prevalence of 0.1-0.2%, both sporadic and hereditary forms described

Clinical Features

- seizures (60%), progressive neurological deficit (50%), hemorrhage (20%), H/A
- often an incidental finding
- hemorrhage risk less than AVM, usually minor bleeds

Investigations

- T2WI MRI (non-enhancing; see Figure 19) gradient echo sequencing (best for diagnosis)

Treatment

- surgical excision
  - only appropriate for symptomatic lesions that are surgically accessible (supratentorial lesions are less likely to bleed than infratentorial lesions)

EXTRACRANIAL PATHOLOGY

Approach to Limb/Back Pain

- see Orthopedics, OR21

Extradural Lesions

Root Compression

Differential Diagnosis

- herniated disc
- neoplasm (neurofibroma, schwannoma)
- synovial cyst, abscess
- hypertrophic bone/spur

Cervical Disc Syndrome

Etiology

- nucleus pulposus herniates through annulus fibrosus and impinges upon nerve root, most commonly at C6-C7 (C7 root)
Clinical Features
- pain down arm in nerve root distribution, worse with neck extension, ipsilateral rotation and lateral flexion (all compress the ipsilateral neural foramen)
- LMN signs and symptoms
- central cervical disc protrusion causes myelopathy as well as nerve root deficits

Investigations
- if red flags: C-spine x-ray, CT, MRI (imaging of choice)
- only consider EMG, nerve conduction studies if diagnosis uncertain and presenting more as peripheral nerve issue.

Treatment
- conservative
  - no bedrest unless severe radicular symptoms
  - activity modification, patient education (reduce sitting, lifting)
  - physiotherapy, exercise programs focus on strengthening core muscles
  - analgesics, NSAIDs are more efficacious
  - avoid cervical manipulation, like traction
- surgical indications
  - intractable pain despite adequate conservative treatment for >3 mo
  - progressive neurologic deficit
  - anterior cervical discectomy is usual surgical choice

Prognosis
- 95% improve spontaneously in 4-8 wk

Table 13. Lateral Cervical Disc Syndromes

<table>
<thead>
<tr>
<th>Root Involved</th>
<th>C4-5</th>
<th>C5-6</th>
<th>C6-7</th>
<th>C7-T1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>2%</td>
<td>19%</td>
<td>69%</td>
<td>10%</td>
</tr>
<tr>
<td>Sensory</td>
<td>Shoulder</td>
<td>Thumb</td>
<td>Middle finger</td>
<td>Ring finger, 5th finger</td>
</tr>
<tr>
<td>Motor</td>
<td>Deltoid, biceps, supraspinatus</td>
<td>Biceps</td>
<td>Triceps</td>
<td>Digital flexors, intrinsic</td>
</tr>
<tr>
<td>Reflex</td>
<td>No change</td>
<td>Biceps, brachioradialis</td>
<td>Triceps</td>
<td>Finger jerk (Hoffmann’s sign)</td>
</tr>
</tbody>
</table>

Cervical Stenosis (Cervical Spondylosis)

Definition
- cervical spondylosis is chronic disc degeneration and associated facet arthropathy
- resultant syndromes include mechanical neck pain, radiculopathy (root compression), myelopathy (spinal cord compression), and combinations

Epidemiology
- typically begins at age 40-50, male > female, most commonly at the C5-C6 > C6-C7 levels

Pathogenesis
- cervical stenosis leading to spinal cord compression and myelopathy is a serious and common issue
- pathophysiology includes static compression, dynamic compression and vascular compromise

Clinical Features
- insidious onset of mechanical neck pain exacerbated by excess vertebral motion (particularly rotation and lateral bending with a vertical compressive force – Spurling’s test)
- occipital headache is common
- radiculopathy may involve 1 or more roots, and symptoms include neck, shoulder and arm pain, paresthesias and numbness
- cervical myelopathy may be characterized by weakness (upper > lower extremity), decreased dexterity, and sensory changes
- UMN findings such as hyperreflexia, clonus and Babinski reflex may be present
- most worrisome complaint is lower extremity weakness (corticospinal tracts)
- myelopathy may be associated with funicular pain, characterized by burning and stinging ± Lhermitte’s sign (lightning-like sensation down the back with neck flexion)

Investigations
- x-ray of cervical spine ± flexion/extension (alignment, fractures)
- MRI most useful for determination of compression of the neural element
- CT is only used for better determination of bony anatomy (i.e. OPLL)
- EMG/nerve conduction studies reserved for peripheral nerve investigation

Treatment
- decompression and stabilization need to be included in the management
- NSAIDs, moist heat, strengthening and range of motion exercises, analgesics, cervical collar, cervical traction
- surgical indications: myelopathy with motor impairment, progressive neurologic impairment, intractable pain

Disc herniations impinge the nerve root at the level below the interspace (i.e. C5-6 disc affects the C6 nerve root).

Figure 20A. Axial section of cervical spine with vascular and functional territories

Figure 20B. Axial section of thoracic spine with vascular and functional territories

Figure 20C. Axial section of lumbar spine with vascular and functional territories
Lumbar Disc Syndrome

Etiology
• posterolaterally herniated disc compressed nerve root exiting BELOW the level of the disc or the traversing nerve root
• far lateral disc herniation compressed nerve root AT the level of the disc or the exiting nerve root
• central herniation causes cauda equina or lumbar stenosis (neurogenic claudication)

Clinical Features
• initially back pain, then leg pain > back pain
• limited back movement (especially forward flexion) due to pain
• motor weakness, dermatomal sensory changes, decreased reflexes
• exacerbation with coughing, sneezing or straining. Relief with flexing the knee or thigh
• nerve root tension signs
  - straight leg raise (SLR: Lasegue’s test) or crossed SLR (pain should occur at less than 60 degrees) suggests L5, S1 root involvement
  - femoral stretch test suggests L2, L3 or L4 root involvement

Investigations
• MRI is modality of choice
• x-ray spine (only to rule out other lesions), CT (bony anatomy)
• myelogram and post-myelogram CT (only if MRI is contraindicated)

Treatment
• conservative (same as cervical disc disease)
• surgical indications
  - same as cervical disc + cauda equina syndrome

Prognosis
• 95% improve spontaneously within 4 to 8 wk
• do not follow patients with serial MRIs. Clinical status is more important at guiding management

Table 14. Lateral Lumbar Disc Syndromes

<table>
<thead>
<tr>
<th>L3-4</th>
<th>L4-5</th>
<th>L5-S1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root Involved</td>
<td>L4</td>
<td>L5</td>
</tr>
<tr>
<td>Incidence</td>
<td>&lt;10%</td>
<td>45%</td>
</tr>
<tr>
<td>Pain</td>
<td>Femoral pattern</td>
<td>Sciatic pattern</td>
</tr>
<tr>
<td>Sensory</td>
<td>Medial leg</td>
<td>Dorsal foot to hallux</td>
</tr>
<tr>
<td>Motor</td>
<td>Tibialis anterior (dorsiflexion)</td>
<td>Extensor hallucis longus (hallux extension)</td>
</tr>
<tr>
<td>Reflex</td>
<td>Knee jerk</td>
<td>Medial hamstrings</td>
</tr>
</tbody>
</table>

Table 15. Differentiating Conus Medullaris Syndrome from Cauda Equina Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Conus Medullaris Syndrome</th>
<th>Cauda Equina Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Sudden, bilateral</td>
<td>Gradual, unilateral</td>
</tr>
<tr>
<td>Spontaneous Pain</td>
<td>Rare, if present usually bilateral, symmetric in perineum or thighs</td>
<td>Severe, radicular type: in perineum, thighs, legs, back, or bladder</td>
</tr>
<tr>
<td>Sensory Deficit</td>
<td>Saddle; bilateral and symmetric; sensory dissociation</td>
<td>Saddle; no sensory dissociation; may be unilateral and asymmetric</td>
</tr>
<tr>
<td>Motor Deficit</td>
<td>Symmetric; paresis less marked; fasciculations may be present</td>
<td>Asymmetric; paresis more marked; atrophy may be present; fasciculations rare</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Only ankle jerk absent (preserved knee jerk)</td>
<td>Knee and ankle jerk may be absent</td>
</tr>
<tr>
<td>Autonomic Symptoms (bladder dysfunction, impotence, etc.)</td>
<td>Urinary retention and atomic anal sphincter prominent early; impotence frequent</td>
<td>Sphincter dysfunction presents late; impotence less frequent</td>
</tr>
</tbody>
</table>

Cauda Equina Syndrome

Etiology
• compression or irritation of lumbosacral nerve roots below conus medullaris (below L2 level)
• decreased space in the vertebral canal below L2
• common causes: herniated disc ± spinal stenosis, vertebral fracture, and tumour
Clinical Features
- usually acute (develops in less than 24 h); rarely subacute or chronic
- motor (LMN signs)
  - weakness/paraparesis in multiple root distribution
  - reduced deep tendon reflexes (knee or ankle)
- autonomic
  - urinary retention (or overflow incontinence) and/or fecal incontinence due to loss of anal sphincter tone
- sensory
  - low back pain radiating to legs (sciatica) aggravated by Valsalva maneuver and by sitting; relieved by lying down
  - bilateral sensory loss or pain; depends on the level affected
  - saddle area (S2-S5) anesthesia
  - sexual dysfunction (late finding)

Investigations
- urgent MRI to confirm compression of S2-3-4 nerve root by a large disc herniation
- post-void residual very helpful to determine if true retention is present. Volumes controversial but anything over 250 cc in a healthy individual is cause for concerns

Treatment
- surgical decompression (<48 h) to preserve bowel, bladder and sexual function, and/or to prevent progression to paraplegia

Prognosis
- markedly improves with surgical decompression
- recovery correlates with function at initial presentation: if patient is ambulatory, likely to continue to be ambulatory; if unable to walk, unlikely to walk after surgery

Lumbar Spinal Stenosis

Etiology
- congenital narrowing of spinal canal combined with degenerative changes (herniated disc, hypertrophied facet joints, and ligamentum flavum)

Clinical Features
- gradually progressive back and leg pain with standing and walking that is relieved by sitting or lying down (neurogenic claudication – 60% sensitive)
- neurologic exam may be normal, including straight leg raise test

Investigations
- MRI is the optimal investigation to confirm and localize the level of stenosis. Unlike nerve root compression which can be localized with clinical exam this is more difficult and requires imaging

Treatment
- conservative: NSAIDs, analgesia
- surgical: laminectomy with root decompression (the role of fusion may need to be considered if the amount of bone removed with the laminectomy results in de-stabilization)

Neurogenic Claudication

Etiology
- ischemia of lumbosacral nerve roots secondary to vascular compromise and increased demand from exertion, often associated with lumbar stenosis

Clinical Features
- dermatomal pain/paresthesia/weakness of buttock, hip, thigh, or leg initiated by standing or walking
- slow relief with postural changes (sitting >30 min), NOT simply exertion cessation
- induced by variable degrees of exercise or standing
- may be elicited with lumbar extension, but may not have any other neurological findings, no signs of vascular compromise (e.g. ulcers, poor capillary refill, etc.)

Investigations
- bicycle test may help distinguish neurogenic claudication (NC) from vascular claudication (the waist-flexed individuals on the bicycle with NC can last longer)

Treatment
- same as for lumbar spinal stenosis
Intradural Intramedullary Lesions

Syringomyelia (Syrinx)

Definition
- cystic cavitation of the spinal cord
- presentation is highly variable, usually progresses over months to years
- initially pain, weakness; later atrophy and loss of pain and temperature sensation

Etiology
- 70% are associated with Chiari I malformation, 10 % with basilar invagination
- post-traumatic
- tumour
- tethered cord

Clinical Features
- nonspecific features for any intramedullary spinal cord pathology:
  - initially pain, weakness, atrophy, loss of pain and temperature in upper extremities (central syrinx) with progressive myelopathy over years
  - sensory loss with preserved touch and joint position sense in a band-like distribution at the level of cervical syrinx
  - sensory loss: suspended dissociated sensory loss may result in painless ulcerations and/or burns
  - dysesthetic pain often occurs in the distribution of the sensory loss
  - LMN arm/hand weakness or wasting
  - painless neuropathic arthropathies (Charcot’s joints), especially in the shoulder and neck due to loss of pain and temperature sensation (seen in less than 5%)

Investigations
- MRI is best method, myelogram with delayed CT

Treatment
- treat underlying cause (e.g. posterior fossa decompression for Chiari I, surgical removal of tumour if causing a syrinx)
- rarely does the syrinx need to be shunted, only when progressive and size allows for insertion of tube

Spinal Cord Syndromes

- see Neurology, N4, for spinal cord anatomy
- Spinal cord injury impairment classified according to ASIA score
  - ASIA A: complete, no motor/sensory below neurological level including S4/5
  - ASIA B: incomplete, sensory but not motor function preserved below neurological level including S4/5
  - ASIA C: incomplete, motor function preserved below neurological level and more than half of the key muscles below neurological level have a muscle grade <3
  - ASIA D: incomplete, motor function preserved below neurological level and more than half of the key muscles below neurological level have a muscle grade 3 or more
  - ASIA E: normal motor and sensory function

Complete Spinal Cord Lesion
- bilateral loss of motor/sensory and autonomic function at ≥4 segments below lesion/injury, with UMN signs
- about 3% of patients with complete injuries will develop some recovery within 24 h, beyond 24 h, no distal function will recover

Incomplete Spinal Cord Lesion
- any residual function at ≥4 segments below lesion
- signs include sensory/motor function in lower limbs and “sacral sparing” (perianal sensation, voluntary rectal sphincter contraction)
Table 16. Comparison between Incomplete Spinal Cord Lesion Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Etiology</th>
<th>Motor</th>
<th>Sensory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown-Séquard</td>
<td>Hemisection of cord</td>
<td>Ipsilateral LMN weakness at the lesion</td>
<td>Ipsilateral loss of vibration and proprioception</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ipsilateral UMN weakness below the lesion</td>
<td>Contralateral loss of pain and temperature</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urinary retention</td>
<td>Preserved light touch</td>
</tr>
<tr>
<td>Anterior Cord</td>
<td>Anterior spinal artery compression or occlusion</td>
<td>Bilateral LMN weakness at the lesion</td>
<td>Preserved vibration and proprioception</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bilateral UMN weakness below the lesion</td>
<td>Bilateral loss of pain and temperature</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urinary retention</td>
<td>Preserved light touch</td>
</tr>
<tr>
<td>Central Cord</td>
<td>Syringomyelia, tumours, spinal hyperextension injury</td>
<td>Bilateral motor weakness: Upper limb weakness (LMN lesion) greater than Lower limb weakness (UMN lesion)</td>
<td>Variable bilateral suspended sensory loss</td>
</tr>
<tr>
<td>(most common)</td>
<td></td>
<td>Urinary retention</td>
<td>Loss of pain and temperature greater than loss of vibration and proprioception</td>
</tr>
<tr>
<td>Posterior Cord</td>
<td>Posterior spinal artery infarction, trauma</td>
<td>Preserved</td>
<td>Bilateral loss of vibration, proprioception, light touch at and below the lesion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Preserved pain and temperature</td>
</tr>
</tbody>
</table>

Peripheral Nerves

- see Neurology, N31 and Plastic Surgery, PL28

 Seddon's Classification of Peripheral Nerve Injury

- class I: neurapraxia – axon structurally intact but fails to function; recovery within hours to months (average 6-8 wk)
- class II: axonotmesis – axon and myelin sheath disrupted but endoneurium and supporting structures intact → Wallerian degeneration of axon segment distal to injury → spontaneous axonal recovery at 1 mm/d, max at 1-2 yr
- class III: neurotmesis – nerve completely transected, need surgical repair for possibility of recovery
- etiologies: ischemia, nerve entrapment – nerve compressed by nearby anatomic structures, often secondary to localized, repetitive mechanical trauma with additional vascular injury to nerve

Investigations

- neurological exam (power, sensation, reflexes), localization via Tinel’s sign (paresthesias elicited by tapping along the course of a nerve)
- electrophysiological studies (EMG, nerve conduction study) may be helpful in assessing nerve integrity and monitoring recovery, not helpful until 2-3 wk post-injury
- labs: bloodwork, CSF
- imaging: C-spine, chest/bone x-rays, myelogram, CT, magnetic resonance neurography; identify etiology
- angiogram if vascular damage is suspected

Treatment

- early neurosurgical consultation if injury is suspected
- entrapment
  - conservative: prevent repeated stress/injury, physiotherapy, NSAIDs, local anaesthesia/steroid injection
  - surgical: nerve decompression ± transposition for progressive deficits, muscle weakness/atrophy, failure of medical management
- stretch/contusion
  - follow-up clinically for recovery; exploration if no recovery in 3 mo
- axonotmesis
  - if no evidence of recovery, resect damaged segment
  - prompt physical therapy and rehabilitation to increase muscle function, maintain joint range of motion, and maximize return of useful function
  - recovery usually incomplete
- neurotmesis
  - surgical repair of nerve sheath unless known to be intact [suture nerve sheaths directly if ends approximate or nerve graft (usually sural nerve)]
  - clean laceration: early exploration and repair
  - contamination or associated injuries: tag initially with nonabsorbable suture, reapproach within 10 d

Complications

- neuropathic pain: with neuroma formation
- complex regional pain syndrome: with sympathetic nervous system involvement
SPECIALTY TOPICS

Neurotrauma

Trauma Management (see also Emergency Medicine, ER6)

Indications for Intubation in Trauma
1. depressed LOC (patient cannot protect airway): usually GCS ≤8
2. need for hyperventilation
3. severe maxillofacial trauma: patency of airway is doubtful
4. need for pharmacologic paralysis for evaluation or management
   • if basal skull fracture suspected, use orotracheal instead of nasotracheal intubation
   • note: intubation prevents patient’s ability to verbalize for determining GCS

Trauma Assessment

INITIAL MANAGEMENT

ABCs of Trauma Management
• see Emergency Medicine, ER8

NEUROLOGICAL ASSESSMENT

Mini-History
• period of LOC, post-traumatic amnesia, loss of sensation/function, type of injury/accident

Neurological Exam
• Glasgow Coma Scale (GCS)
• head and neck (lacerations, bruises, basal skull fracture signs, facial fractures, foreign bodies)
• spine (palpable deformity, midline pain/tenderness)
• eyes (pupillary size and reactivity)
• brainstem (breathing pattern, CN palsies)
• cranial nerve exam
• motor exam, sensory exam (only if GCS is 15), reflexes
• sphincter tone
• record and repeat neurological exam at regular intervals

Investigations
• spinal injury precautions (cervical collar) are continued until C-spine is cleared
• C, T, L-spine x-rays
  • AP, lateral, odontoid views for C-spine (must see from C1 to T1; swimmer’s view if necessary) or CT
  • rarely done: oblique views looking for pars interarticularis fracture (“Scottie dog” sign)
• CT head and upper C-spine (whole C-spine if patient unconscious) look for fractures, loss of massoid or sinus air spaces, blood in cisterns, pneumocephalus
• cross and type, ABG, CBC, drug screen (especially alcohol)
• chest and pelvic x-ray as indicated

TREATMENT

Treatment for Minor Head Injury
• observation over 24-48 h
• wake every hour
• judicious use of sedatives or pain killers during monitoring period

Treatment for Severe Head Injury (GCS ≤8)
• clear airway and ensure breathing (if GCS ≤8, intubate)
• secure C-spine
• maintain adequate BP
• monitor for clinical deterioration
• monitor and manage increased ICP if present (see Herniation Syndromes, NS7)

Admission required if:
• skull fracture (indirect signs of basal skull fracture, see Head Injury, NS31)
• confusion, impaired consciousness, concussion with >5 min amnesia
• focal neurological signs, extreme headache, vomiting, seizures
• unstable spine
• use of alcohol
• poor social support

Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Eye Response</th>
<th>Verbal Response</th>
<th>Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 spontaneous</td>
<td>5 oriented</td>
<td>6 obeyed commands</td>
</tr>
<tr>
<td>3 opens eyes to voice</td>
<td>4 confused</td>
<td>5 localize pain</td>
</tr>
<tr>
<td>2 opens eyes to pain</td>
<td>3 inappropriate verbal sounds</td>
<td>4 withdraws from pain</td>
</tr>
<tr>
<td>1 no eye opening</td>
<td>2 incomprehensible sounds</td>
<td>3 flexion to pain (decorticate posturing)</td>
</tr>
<tr>
<td>1 no response</td>
<td>2 extension to pain (decorticate posturing)</td>
<td></td>
</tr>
<tr>
<td>1 intubated</td>
<td>1 no response</td>
<td></td>
</tr>
</tbody>
</table>

Best response for each component recorded individually (e.g. E3V3M5)

Assessment of Spine CT/X-ray (parasagittal view)

ABCDS
• Alignment (Columns: anterior vertebral line, posterior vertebral line, spinolaminar line, posterior spinous line)
• Bone (vertebral bodies, facets, spinous processes)
• Cartilage
• Disc (disc space and interspinous space)
• Soft tissues

The Canadian CT Head Rule for Patients with Minor Head Injury
The Lancet 2001;357:1381-1396

CT Head is only required for patients with minor head injuries with any one of the following:

High risk (for neurological intervention)
• GCS score <15 at 2 h after injury
• Suspected open or depressed skull fracture
• Any sign of basal skull fracture (hemotympanum, “raccoon” eyes, cerebrospinal fluid otorrhea/ rhinorrhea, Battle’s sign)
• Hematoma ≥2 episodes
• Age >65 yr

Medium risk (for brain injury on CT)
• Amnesia after impact >30 min
• Dangerous mechanism (pedestrian struck by motor vehicle, occupant ejected from motor vehicle, fall from height >3 feet or five stairs)

Minor head injury is defined as witnessed loss of consciousness, definite amnesia, or witnessed disorientation in a patient with a GCS score of 13-15.

• Never do lumbar puncture in head injury unless increased ICP has been ruled out
• All patients with head injury have C-spine injury until proven otherwise
• Suspect hematoma in alcoholic-related injuries
• Low BP after head injury means injury elsewhere
• Must clear spine both radiologically AND clinically
Head Injury

Epidemiology
- male to female: 2-3:1

Pathogenesis
- acceleration/deceleration: contusions, subdural hematoma, axon and vessel shearing/ mesencephalic hematoma
- impact: skull fracture, concussion, epidural hematoma
- penetrating: worse with high velocity and/or high missile mass
  - low velocity: highest damage to structures on entry/exit path
  - high velocity: highest damage away from missile tract

Scalp Injury
- rich blood supply
- considerable blood loss (vessels contract poorly when ruptured)
- minimal risk of infection due to rich vascularity

Skull Fractures
- depressed fractures: double density on skull x-ray (outer table of depressed segment below inner table of skull), CT with bone window is gold standard
- simple fractures (closed injury): no need for antibiotics, no surgery
- compound fractures (open injury): increased risk of infection, surgical debridement within 24 h is necessary
- internal fractures into sinus may lead to meningitis, pneumocephalus
- risk of operative bleed may limit treatment to antibiotics
- basal skull fractures: not readily seen on x-ray, rely on clinical signs
  - retroauricular ecchymoses (Battle's sign)
  - periorbital ecchymoses (raccoon eyes)
  - hemotympanum
  - CSF rhinorrhea, otorrhea (suspect CSF if halo or target sign present); suspect with Lefort II/III midface fracture

Cranial Nerve Injury
- most traumatic causes of cranial nerve injury do not warrant surgical intervention
- surgical intervention
  - CN II: local eye/orbit injury
  - CN III, IV, VI: if herniation secondary to mass
  - CN VII: repair of ossicles
- CN injuries that improve
  - CN I: recovery may occur in a few months; most do not improve
  - CN III, IV, VI: majority recover
  - CN VII: recovery with delayed lesions
- CN VIII: vestibular symptoms improve over weeks, deafness usually permanent (except when resulting from hemotympanum)

Arterial Injury
- e.g. carotid-cavernous (C-C) fistula, carotid/vertebral artery dissection

Intracranial Bleeding
- see Blood, NS16 and Cerebrovascular Disease, NS18

Brain Injury

Primary Impact Injury
- mechanism of injury determines pathology: penetrating injuries, direct impact
  - low velocity: local damage
  - high velocity: distant damage possible (due to wave of compression), concussion
- concussion: a trauma-induced alteration in mental status
  - American Academy of Neurology (AAN) Classification (see sidebar)
  - no parenchymal abnormalities on CT
- coup (damage at site of blow) and contrecoup (damage at opposite site of blow) (see Figure 25)
  - acute decompression causes cavitation followed by a wave of acute compression
- contusion (hemorrhagic)
  - high density areas on CT ± mass effect
  - commonly occurs with brain impact on bony prominences (inferior frontal lobe, pole of temporal lobe)
- diffuse axonal injury/shearing
  - wide variety of damage results
  - may tear blood vessels (hemorrhagic foci)
  - often the cause of decreased LOC if no space occupying lesion on CT

A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury
NEJM 2012;367:2471-2481
Background: ICP monitoring is frequently used to monitor severe traumatic brain injury, but controversy exists over whether it is beneficial.
Methods: Study sample (n=324 patients, aged 13 yr or older) consisted of those who had severe traumatic brain injury and were being treated in ICU in Bolivia or Ecuador. Patients were randomly assigned to one management group:
1. ICP-monitoring based management or
2. management based on imaging and clinical examination.
Results: No significant difference between management groups based on primary outcome, 6-mo mortality, median length of ICU stay, or occurrence of serious adverse events. However, duration of brain-specific treatments (e.g., use of hyperosmolar fluids or hyperventilation) higher in the imaging-clinical examination group (4.8 d vs. 3.4 d, p=0.002).
Conclusion: Maintaining monitored ICP at 20 mmHg or less is not superior to care based on imaging and clinical examination.

AAN Classification
Grade 1: altered mental status < 15 min
Grade 2: altered mental status > 15 min
Grade 3: any loss of consciousness
See sidebar on NS32 for management by classification
Secondary Pathologic Processes
- same subsequent biochemical pathways for each traumatic etiology
- delayed and progressive injury to the brain due to
  - high glutamate release \(\rightarrow\) NMDA \(\rightarrow\) cytotoxic cascade
  - cerebral edema
  - intracranial hemorrhages
  - ischemia/infarction
  - raised ICP, intracranial HTN
  - hydrocephalus

Extracranial Conditions
- hypoxemia
  - due to trauma to the chest, upper airway, brainstem
  - extremely damaging to vulnerable brain cells
  - leads to ischemia, raised ICP
- hypercarbia
  - leads to raised ICP (secondary to vasodilation)
- systemic hypotension
  - caused by blood loss (e.g., ruptured spleen)
  - loss of cerebral autoregulation leads to decreased CPP, ischemia
- hyperpyrexia
  - leads to increased brain metabolic demands \(\rightarrow\) ischemia
- fluid and electrolyte imbalance
  - iatrogenic (most common)
  - SIADH caused by head injury
  - diabetes insipidus (DI)
  - may lead to cerebral edema and raised ICP
- coagulopathy

Intracranial Conditions
- raised ICP due to traumatic cerebral edema OR traumatic intracranial hemorrhage

Brain Injury Outcomes
- mildly traumatic (GCS 13–15): post-concussive symptoms: H/A, fatigue, dizziness nausea, blurred vision, diplopia, memory impairment, tinnitus, irritability, low concentration; 50% at 6 wk, 14% at 1 yr
- moderately traumatic (GCS 9–12): proportional to age (>40) and CT findings; 60% good recovery, 26% moderately disabled, 7% severely disabled, 7% vegetative/dead
- severe (GCS ≤8): difficult to predict, correlates with post-resuscitation GCS (especially motor) and age

Late Complications of Head/Brain Injury
- seizures: 5% of head injury patients develop seizures
  - incidence related to severity and location of injury (increased with local brain damage or intracranial hemorrhage)
  - post-traumatic seizure may be immediate, early, or late
  - presence of early (within first wk) post-traumatic seizure raises incidence of late seizures
- menigitis: associated with CSF leak from nose or ear
- hydrocephalus: acute hydrocephalus or delayed normal pressure hydrocephalus (NPH)

Spinal Cord Injury (SCI)
- see Orthopedics, OR21 and Emergency Medicine, ER9

Neurogenic and Spinal Shock
1. neurogenic shock: hypotension that follows SCI (sBP usually ≤80 mmHg) caused by:
   - interruption of sympathectics (unopposed parasympathetics) below the level of injury
   - loss of muscle tone due to skeletal muscle paralysis below level of injury \(\rightarrow\) venous pooling
   - relative hypovolemia
   - blood loss from associated wounds (true hypovolemia)
2. spinal shock: transient loss of all neurologic function below the level of the spinal cord injury, causing flaccid paralysis and areflexia for variable periods

Whiplash-Associated Disorders
- definition: traumatic injury to the soft tissue structures in the region of the cervical spine due to hyperflexion, hyperextension, or rotational injury to the neck
Initial Management of SCI
• major causes of death in SCI are aspiration and shock
• the following patients should be treated as having a SCI until proven otherwise:
  ▪ all victims of significant trauma
  ▪ minor trauma patients with decreased LOC or complaints of neck or back pain, weakness, abdominal breathing, numbness/tingling, or priapism

Stabilization and Initial Evaluation in the Hospital
1. ABCs, immobilization (backboard/head strap), oxygenation, foley catheter to urometer, temperature regulation
2. hypotension: maintain sBP >90 mmHg with pressors (dopamine), hydration, and atropine
   ▪ DVT prophylaxis
3. monitor CBC/electrolytes
4. focused history (see Trauma Assessment, NS30)
5. spine palpation: point tenderness or deformity
6. motor level assessment (including rectal exam for voluntary anal sphincter contraction)
7. sensory level assessment: pinprick, light touch, and proprioception
8. evaluation of reflexes
9. signs of autonomic dysfunction: altered level of perspiration, bowel or bladder incontinence, priapism
10. radiographic evaluation
   ▪ 3 views C-spine x-rays (AP, lateral, and odontoid) to adequately visualize C1 to C7-T1 junction
   ▪ flexion-extension views to disclose occult instability
   ▪ CT scan (bony injuries) typically most trauma centre use the CT as the modality of choice for looking at fractures, very sensitive with the high resolution scanners.
   ▪ MRI mandatory if neurological deficits (soft tissue injuries)

Medical Management Specific to SCI
• option: methylprednisolone (given within 8 h of injury) this is controversial and you need to confer with Neurosurgery service
• ± decompression in acute, non-penetrating SCI

Fractures of the Spine
FRAC TURES AND FR AC TURE-DISLOCATIONS OF THE TH ORACIC AND LUMBAR SPINE
• assess ligamentous instability using flexion/extension x-ray views of C-spine ± MRI
• thoracolumbar spine unstable if 4/6 segments disrupted (3 columns divided into left and right)
  ▪ anterior column: anterior half of vertebral body, disc, and anterior longitudinal ligament
  ▪ middle column: posterior half of vertebral body, disc, and posterior longitudinal ligament
  ▪ posterior column: posterior arch, facet joints, pedicle, lamina and supraspinous, interspinous and ligamentum ligaments

Types of Injury (Denis Classification)
• compression fracture (58%)
  ▪ produced by flexion
  ▪ posterior ligament complex (supraspinous and interspinous ligaments, ligamentum flavum and intervertebral joint capsules) remain intact
  ▪ fractures are stable but lead to kyphotic deformity
• burst fracture (17%)
  ▪ stable: anterior and middle columns parted with bone retropulsed nearby
    ▪ hallmark is pedicle widening on AP X-ray
    ▪ spinal cord (seen on x-ray and CT); posterior column is uninjured
  ▪ unstable: same as the stable but with posterior column disruption (usually ligamentous)
• flexion distraction injury (6%)
  ▪ hyperflexion and distraction of posterior elements
  ▪ middle and posterior columns fail in distraction
  ▪ classic: Chance = horizontal fracture through posterior arch, pedicles, posterior vertebral body
  ▪ can be purely ligamentous, i.e. through PLL and disc
• fracture-dislocation (6%)
  ▪ anterior and cranial dislocation of superior vertebral body ➔ 3 column failure
  ▪ three types:
    ▪ flexion-rotation
    ▪ flexion-distraction
    ▪ shear/hyperextension (rare)

Management of Thoracolumbar Injury
• severity and management based on TLICS classification (see sidebar)
FRACTURES OF THE CERVICAL SPINE

Types of Injury
- C1 vertebral fracture (Jefferson fracture)
  - vertical compression forces the occipital condyles of the skull down on the C1 vertebra (atlas), pushing the lateral masses of the atlas outward and disrupting the ring of the atlas
  - also can cause an occipital condylar fracture
- odontoid process fracture (see Figure 26)
  - causes C1 and odontoid of C2 to move independently of C2 body
  - this occurs because
    - normally C1 vertebra and odontoid of C2 are a single functional unit
    - alar and transverse ligaments on posterior aspect of odontoid most commonly remain intact following injury
  - patients often report a feeling of instability and present holding their head with their hands
- C2 vertebral fracture (hangman fracture, traumatic spondylolisthesis of axis):
  - bilateral fracture through the pars interarticularis of C2 with subluxation of C2 on C3
  - usually neurologically intact
- Clay-Shoveler fracture
  - avulsion of spinous process, usually C6 or C7

Imaging
- AP spine x-ray (open-mouth and lateral view), CT

Treatment
- immobilization in cervical collar or halo vest until healing occurs (usually 2-3 mo)
- Type II and III odontoid fractures
  - consider surgical fixation for comminution, displacement or inability to maintain alignment with external immobilization
  - confirm stability after recovery with flexion-extension x-rays

Neurologically Determined Death

Definition
- irreversible and diffuse brain injury resulting in absence of clinical brain function
- cardiovascular activity may persist for up to 2 wk

Criteria of Diagnosis
- prerequisites: no CNS depressant drugs/neuromuscular blocking agents, no drug intoxication/poisoning, temperature >32°C, no electrolyte/acid-base/endocrine disturbance
- absent brainstem reflexes:
  - absent pupillary light reflex
  - absent corneal reflexes
  - absent oculocephalic response
  - absent caloric responses (e.g. no deviation of eyes to irrigation of each ear with 50 cc of ice water – allow 1 min after injection, 5 min between sides)
  - absent pharyngeal and tracheal reflexes
  - absent cough with tracheal suctioning
  - absent respiratory drive at PaCO2 >60 mmHg or >20 mmHg above baseline (apnea test)
- 2 evaluations separated by time, usually performed by two specialists (e.g. anesthetist, neurologist, neurosurgeon)
- confirmatory testing: flat EEG, absent perfusion assessed with cerebral angiogram

Coma

Definition
- an unrousable state in which patients show no meaningful response to environmental stimuli

Pathophysiology
- lesions affecting the cerebral cortex bilaterally, the reticular activating system (RAS) or their connecting fibres
- focal supratentorial lesions do not alter consciousness except by herniation (compression on the brainstem or on the contralateral hemisphere) or by precipitating seizures
Classification
- structural lesions (tumour, pus, blood, infarction, CSF): 1/3 of comas
  - supratentorial mass lesion: leads to herniation
  - infratentorial lesion: compression of or direct damage to the RAS or its projections
- metabolic disorders/diffuse hemispheric damage: 2/3 of comas
  - deficiency of essential substrates (e.g. oxygen, glucose, vitamin B₁₂)
  - exogenous toxins (e.g. drugs, heavy metals, solvents)
  - endogenous toxins/systemic metabolic diseases (e.g. uremia, hepatic encephalopathy, electrolyte imbalances, thyroid storm)
  - infections (meningitis, encephalitis)
  - trauma (concussion, diffuse shear axonal damage)

Investigations and Management
- ABCs
- labs: electrolytes, extended electrolytes, TSH, LFTs, Cr, BUN, toxin screen, glucose
- CT/MRI, LP, EEG

**Persistent Vegetative State**

Definition
- a condition of complete unawareness of the self and the environment accompanied by sleep-wake cycles with either complete or partial preservation of hypothalamic and brainstem autonomic function
- “awake but not aware”
- follows comatose state

Etiology/Prognosis
- most commonly caused by cardiac arrest or head injury
- due to irreversible loss of cerebral cortical function but intact brainstem function
- average life expectancy is 2-5 yr

**Pediatric Neurosurgery**

**Spinal Dysraphism**

**SPINA BIFIDA OCCULTA**

Definition
- congenital absence of a spinous process and a variable amount of lamina
- no visible exposure of meninges or neural tissue

Epidemiology
- 15-20% of the general population; most common at L5 or S1

Etiology
- failure of fusion of the posterior neural arch

Clinical Features
- no obvious clinical signs
- presence of lumbosacral cutaneous abnormalities (dimple, sinus, port-wine stain, or hair tuft) should increase suspicion of an underlying anomaly (lipoma, dermoid, diastematomyelia)

Investigations
- plain film: absence of the spinous process along with minor amounts of the neural arch
- U/S, MRI to exclude spinal anomalies

Treatment
- requires no treatment

Figure 27. Spina bifida occulta
MENINGOCELE (SPINA BIFIDA APERTA)

Definition
• herniation of meningeal tissue and CSF through a defect in the spine, without associated herniation of neural tissue

Etiology
• primary failure of neural tube closure

Clinical Features
• most common in lumbosacral area
• usually no disability, low incidence of associated anomalies and hydrocephalus

Investigations
• plain films, CT, MRI, U/S, echo, genitourinary (GU) investigations

Treatment
• surgical excision and tissue repair (excellent results)

MYELOMENINGOCELE (SPINA BIFIDA APERTA)

Definition
• herniation of meningeal and CNS tissue through a defect in the spine

Etiology
• same as meningocele

Clinical Features
• sensory and motor changes distal to anatomic level producing varying degrees of weakness
• urinary and fecal incontinence
• 65-85% of patients with myelomeningocele have hydrocephalus
• most have Type II Chiari malformation (see Chiari Malformations, NS37)

Investigations
• plain films, CT, MRI, U/S, echo, GU investigations

Treatment
• surgical closure to preserve neurologic status and prevent CNS infections
• closure in-utero shown to decrease hydrocephalus and improve post natal motor scores

Prognosis
• operative mortality close to 0%, 95% 2-yr survival
• 80% have IQ >80 (but most are 80-95), 40-85% ambulatory, 3-10% have normal urinary continence
• early mortality usually due to Chiari malformation complications (respiratory arrest and aspiration), whereas late mortality is due to shunt malfunction

Intraventricular Hemorrhage (IVH)

• see Pediatrics, P73

Hydrocephalus in Pediatrics

Etiology
• congenital
  • aqueductal anomalies, primary aqueductal stenosis in infancy
  • secondary gliosis due to intrauterine viral infections (mumps, varicella, TORCH)
  • Dandy-Walker malformation (2-4%)
  • Chiari malformation, especially Type II
  • myelomeningocele
• acquired
  • post meningitis
  • post hemorrhage (SAH, IVH)
  • masses (vascular malformation, neoplastic)

Clinical Features
• symptoms and signs of hydrocephalus are age related in pediatrics
• increased head circumference (HC), bulging anterior fontanelle, widened cranial sutures
• irritability, lethargy, poor feeding and vomiting
• “cracked pot” sound on cranial percussion
• scalp vein dilation (increased collateral venous drainage)
• sunset sign – forced downward deviation of eyes
• episodic bradycardia and apnea

Investigations
• skull x-ray, U/S, CT, MRI, ICP monitoring

Treatment
• similar to adults (see Hydrocephalus, NS8)

Dandy-Walker Malformation

Definition
• atresia of foramina of Magendie and Luschka, resulting in:
  • complete or incomplete agenesis of the cerebellar vermis with widely separated, hypoplastic
cerebellar hemispheres
  • posterior fossa cyst, enlarged posterior fossa
  • dilatation of 4th ventricle (also 3rd and lateral ventricles)
• associated anomalies
  • hydrocephalus (90%)
  • agenesis of corpus callosum (17%)
  • occipital encephalocele (7%)

Epidemiology
• 2-4% of pediatric hydrocephalus

Clinical Features
• 20% are asymptomatic, seizures occur in 15%
• symptoms and signs of hydrocephalus combined with a prominent occiput in infancy
• ataxia, spasticity, poor fine motor control common in childhood

Investigations
• ultrasound, CT, MRI

Treatment
• asymptomatic patients require no treatment
• associated hydrocephalus requires surgical treatment
  • e.g. ventriculoperitoneal (VP) shunt, cystoperitoneal (CP) shunt, limboperitonal (LP) shunt,
ventriculoatrial (VA) shunt, lumbar drain

Prognosis
• 75-100% survival, 50% have normal IQ

Chiari Malformations

Definition
• malformations at the medullary-spinal junction

Etiology
• unclear, likely maldevelopment/dysgenesis during fetal life

Categories
• Type I (cerebellar ectopia)
  • definition: cerebellar tonsils lie below the level of the foramen magnum
  • epidemiology: average age at presentation 15 yr
  • clinical features:
    • many are asymptomatic
    • scoliosis
    • brain compression
    • central cord syndrome (65%)
    • syringomyelia (50%)
    • foramen magnum compression syndrome (22%)
    • cerebellar syndrome (11%)
    • hydrocephalus (10%)
• Type II
  • definition: part of cerebellar vermis, medulla, and 4th ventricle extend through the foramen
magnum often to midcervical region
  • almost always associated with a myelomingocele
  • epidemiology: present in infancy
  • clinical features: findings due to brainstem and lower cranial nerve dysfunction
  • syringomyelia, hydrocephalus in >80%
Investigations
- MRI

Treatment
- indications for surgical decompression
  - Type I: symptomatic patients (early surgery recommended; <2 yr post symptom onset) → suboccipital craniectomy, duraplasty
  - Type II: neurogenic dysphagia, stridor, apneic spells → cervical laminectomy, duraplasty

Craniosynostosis

Definition
- premature closure of the cranial suture(s)

Classification
- sagittal (most common): long narrow head with ridging sagittal suture (scaphocephaly)
- coronal: expansion in superior and lateral direction (brachiocephaly)
- metopic (trigonocephaly)
- lambdoid: least common

Epidemiology
- 0.6/1000 live births, most cases are sporadic; familial incidence is 2% of sagittal and 8% of coronal synostosis

Clinical Features
- skull deformity, raised ICP ± hydrocephalus
- ophthalmologic problems due to increased ICP or bony abnormalities of the orbit
- must differentiate between positional plagiocephaly (secondary to back sleeping)

Investigations
- plain radiographs, CT scan

Treatment
- parental counseling about nature of deformity, associated neurological symptoms
- surgery for cosmetic purposes, except in cases of elevated ICP (≥2 sutures involved)

Pediatric Brain Tumours

- see also Tumours, NS10

Epidemiology
- 20% of all pediatric cancers (second only to leukemia)
- 60% of pediatric brain tumours are infratentorial
- pediatric brain tumours arise from various cellular lineages
  - glia: low-grade astrocytoma (supra- or infratentorial), anaplastic astrocytoma, glioblastoma multiforme (largely supratentorial) (see Astrocytoma, NS13 for details)
  - primitive nerve cells: supratentorial [primitive neuroectodermal tumour (PNET)]
  - 90% of neonatal brain tumours, infratentorial (medulloblastoma), pineal gland (pineoblastoma)
  - non-neuronal cells: germ cell tumour, craniopharyngioma, dermoid, meningioma, neurinoma (schwanoma), pituitary adenoma, others

Clinical Features
- vomiting, seizure, macrocrania, hydrocephalus
- developmental delay, poor feeding, failure to thrive
- often initially escapes diagnosis due to expansile cranium and neural plasticity in children

Table 17. Overview of Childhood Primary Brain Tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocytic (low grade)</td>
<td>40</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>(23)</td>
</tr>
<tr>
<td>Supratentorial</td>
<td>(17)</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>20</td>
</tr>
<tr>
<td>Brainstem glioma</td>
<td>8</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>8</td>
</tr>
<tr>
<td>Malignant glioma</td>
<td>6</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>6</td>
</tr>
<tr>
<td>Pineal, germ cell tumour</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
</tr>
</tbody>
</table>

Relative Frequency of Pediatric Brain Tumours

- Reprinted with permission from Elsevier.
## Functional Neurosurgery

### Movement Disorders

- see Tremor, Parkinson's Disease, Dystonia, and Multiple Sclerosis sections in Neurology, N25, N26, N27, N46, respectively

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Indications</th>
<th>Procedures</th>
<th>Outcomes</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson's Disease</td>
<td>Intractable contralateral bradykinesia/tremor</td>
<td>Simultaneous, bilateral surgery/</td>
<td>39-48% improvement in Unified Parkinson's Disease Rating Scale (UPDRS) scores</td>
<td>Intracerebral hemorrhage, infection, seizure (1%-4%)</td>
</tr>
<tr>
<td></td>
<td>Failure of medical management (advanced disease)</td>
<td>stimulation is most common</td>
<td>Reduced dosage of medications (STN)</td>
<td>Parkinson's disease vs. depression</td>
</tr>
<tr>
<td></td>
<td>Drug-induced dyskinesias (see dystonia, below)</td>
<td>Other targets: stereotactic ablation (pallidotomy)/stimulation of posteroventral globus pallidus pars interna (GPi)</td>
<td>More effective than medical management in advanced PD</td>
<td>involuntary movements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caudal zona incerta</td>
<td>Early intervention may reduce severity, course, and progression of disease</td>
<td>Cognitive functioning: decreased lexical fluency, impaired executive function (STN &gt; GPi)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parkinsonian tremor: stereotactic ablation (thalamotomy)/stimulation of ventral intermediate (Vim) nucleus of thalamus</td>
<td>Of little benefit for patients with atypical presentations</td>
<td>Psychiatric: depression, mania, anxiety, apathy (STN &gt; GPi)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simultaneous, bilateral surgery/</td>
<td>39-48% improvement in Unified Parkinson's Disease Rating Scale (UPDRS) scores</td>
<td>Intracerebral hemorrhage, infection, seizure (1%-4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>stimulation is most common</td>
<td>Reduced dosage of medications (STN)</td>
<td>Parkinson's disease vs. depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other targets: stereotactic ablation (pallidotomy)/stimulation of posteroventral globus pallidus pars interna (GPi)</td>
<td>More effective than medical management in advanced PD</td>
<td>involuntary movements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caudal zona incerta</td>
<td>Early intervention may reduce severity, course, and progression of disease</td>
<td>Cognitive functioning: decreased lexical fluency, impaired executive function (STN &gt; GPi)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parkinsonian tremor: stereotactic ablation (thalamotomy)/stimulation of ventral intermediate (Vim) nucleus of thalamus</td>
<td>Of little benefit for patients with atypical presentations</td>
<td>Psychiatric: depression, mania, anxiety, apathy (STN &gt; GPi)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simultaneous, bilateral surgery/</td>
<td>39-48% improvement in Unified Parkinson's Disease Rating Scale (UPDRS) scores</td>
<td>Intracerebral hemorrhage, infection, seizure (1%-4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>stimulation is most common</td>
<td>Reduced dosage of medications (STN)</td>
<td>Parkinson's disease vs. depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other targets: stereotactic ablation (pallidotomy)/stimulation of posteroventral globus pallidus pars interna (GPi)</td>
<td>More effective than medical management in advanced PD</td>
<td>involuntary movements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caudal zona incerta</td>
<td>Early intervention may reduce severity, course, and progression of disease</td>
<td>Cognitive functioning: decreased lexical fluency, impaired executive function (STN &gt; GPi)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parkinsonian tremor: stereotactic ablation (thalamotomy)/stimulation of ventral intermediate (Vim) nucleus of thalamus</td>
<td>Of little benefit for patients with atypical presentations</td>
<td>Psychiatric: depression, mania, anxiety, apathy (STN &gt; GPi)</td>
</tr>
</tbody>
</table>

### Neuropsychiatric Disorders

- see Tourette's Syndrome, Obsessive Compulsive Disorder and Depression sections in Neurology, N28 and Psychiatry, PS16, PS10

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Indications</th>
<th>Procedures</th>
<th>Outcomes</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessive Compulsive Disorder (OCD)</td>
<td>Severe symptoms refractory to medical management</td>
<td>Anterior capsulotomy/stimulation of the anterior limb of the internal capsule (IC)</td>
<td>Currently under investigation Reportedly 25-75% response rate</td>
<td>Intracerebral hemorrhages (1%-2%) Mild effects on cognitive functioning Anxiety ± panic disorder (case report)</td>
</tr>
<tr>
<td>Tourette's Syndrome</td>
<td>Severe symptoms refractory to medical management</td>
<td>Stimulation of midline intralaminar nuclei of the thalamus</td>
<td>Currently under investigation Reportedly &gt;70% reduction in vocal or motor tics + urge</td>
<td>Intracerebral hemorrhages (1%-2%) Mild sexual dysfunction</td>
</tr>
<tr>
<td>Major Depressive Disorder (MDD)</td>
<td>Severe depression refractory to medical management and ECT</td>
<td>Stimulation of the subgenual cingulate cortex</td>
<td>Currently under investigation Reportedly 60% response rate; 35% remission rate</td>
<td>Intracerebral hemorrhages (1%-2%) Pain, headache Worsening mood, irritability</td>
</tr>
</tbody>
</table>
### Chronic Pain

**Table 20. Surgical Targets for Chronic Pain**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Indications</th>
<th>Procedures</th>
<th>Outcomes</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic Pain</td>
<td>Severe, intractable, organic neuropathic pain (e.g. post-stroke pain, phantom limb pain, trigeminal neuralgia, chronic low-back pain, complex regional pain syndrome)</td>
<td>Preferred target: stimulation of the contralateral VPL VPM thalamic nuclei ± periventricular/periaqueductal grey matter (PVG/PAG) Other targets: stimulation of the contralateral IC Stimulation of the contralateral motor cortex</td>
<td>47% improvement in perception of pain intensity Less favourable results in central pain syndromes and poorly localized pain</td>
<td>Intracerebral hemorrhages (1%-2%) Paraesthesia Anxiety ± panic disorder</td>
</tr>
<tr>
<td>Nociceptive Pain</td>
<td>Severe, intractable, organic nociceptive pain</td>
<td>Bilateral (most common) stimulation of the PVG/PAG</td>
<td>Reportedly 63% improvement in perception of pain intensity</td>
<td>Intracerebral hemorrhages (1%-2%) Paraesthesia Anxiety ± panic disorder</td>
</tr>
</tbody>
</table>

### Surgical Management of Epilepsy

- see Neurology, N16 for the medical treatment of epilepsy

**Indications**
- medically refractory seizures, usually defined as seizures resistant to two first line anti-seizure medications used in succession
- identification of a distinct epileptogenic region through clinical history, EEG, MRI, and neuropsychological testing. Other localizing investigations include magnetoencephalography, SPECT, and PET
- if a distinct epileptogenic region cannot be identified, the patient may be a candidate for a palliative procedure such as corpus callosotomy

**Procedure**
- adults: resection of the hippocampus and parahippocampal gyrus for mesial temporal lobe epilepsy arising from mesial temporal sclerosis
- children: resection of an epileptogenic space-occupying lesion
- hemispherectomy and corpus callosotomy are less common

**Outcomes**
- 41-79% of adult patients are seizure free for 5 yr after temporal lobe resection
- 58-78% of children are seizure free after surgery
- surgery is associated with improvements in preexisting psychiatric conditions such as depression and anxiety, as well as improvement in quality of life measures

**Morbidity**
- 0.4-4% of surgical patients will have partial hemianopsia, aphasia, motor deficit, sensory deficit, or cranial nerve palsy following anteromedial temporal lobectomies
- most patients will have some decline in verbal memory following dominant temporal lobectomy and in visuospatial memory in non-dominant temporal resection
- the degree of memory decline stabilizes after 1-2 yr

**Predictors**
- positive predictive factors for seizure freedom following anteromedial temporal lobectomy
  - hippocampal sclerosis (unilateral)
  - focal localization of interictal epileptiform discharges
  - absence of preoperative generalized seizures
  - tumoural cause
  - complete resection of the lesion

---

**A Randomized, Controlled Trial of Surgery for Temporal Lobe Epilepsy**

*NEJM* 2001;345:311-318

**Introduction**: This RCT evaluates the efficacy and safety of neurosurgery for temporal lobe epilepsy. Methods: 80 patients with poorly controlled temporal lobe epilepsy were randomized for surgery (n=40) or for continued treatment with antiepileptic drugs (n=40). The primary outcome was freedom from seizures that impair awareness of self and surroundings during the period of 1 yr. Secondary outcomes included frequency and severity of seizures, quality of life, disability and death.

**Results**: The surgical group had higher cumulative proportion of patients without seizures impairing awareness compared to the medical group (p<0.01). The surgical group also had lower seizure frequency (p<0.001) and better quality of life (p<0.001). 4 patients in the surgical group had adverse effects (thalamic infarct, n = 1; wound infection, n = 1; verbal memory decline impairment occupation, n = 2). One patient in the medical group died; no patients died in the surgical group.

**Conclusions**: In patients with poorly controlled temporal-lobe epilepsy, surgery is superior to prolonged medical therapy.
Surgical Management for Trigeminal Neuralgia

- reserved for cases refractory to medical management; see Neurology, N36 for medical management

Surgical Options
- trigeminal nerve branch procedures
  - local blocks (phenol, alcohol)
  - neurectomy of the trigeminal branch
- nerve branches
  - V1: block at the supraorbital, supratrochlear nerves
  - V2: block at the foramen rotundum or infraorbital nerves
  - V3: block at the foramen ovale
- percutaneous trigeminal rhizotomy
  - glycerol injection
  - mechanotrauma via catheter balloon
- radiofrequency thermocoagulation
- Gamma Knife® radiosurgery
- microvascular decompression
  - posterior fossa craniotomy with microsurgical exploration of the root entry zone, displacement of the vessel impinging on the nerve with placement of non-absorbable Teflon® felt

Common Medications

Table 21. Common Medications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Common Interactions</th>
<th>Contraindications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>lorazepam</td>
<td>4 mg IV over 2 min, q10-15min (do not exceed 8 mg/12h)</td>
<td>Status epilepticus</td>
<td>Drowsiness, sedation</td>
<td>Other CNS depressants, digoxin (increases digoxin levels)</td>
<td>Start phenytoin loading simultaneously</td>
<td></td>
</tr>
<tr>
<td>carbamazepine</td>
<td>Trigeminal neuralgia (tic douloureux): 100 mg PO bid, increase by 200 mg/d up to a maximum of 1200 mg/d Seizures: 200 mg PO bid, increase by 200 mg (inpatient: q3hd; outpatient: q7d) until therapeutic level achieved (usual optimum dosage: 800-1200 mg/d; range: 600-2000 mg/d)</td>
<td>Seizures</td>
<td>Worsening of seizures, heart failure, arrhythmias, AV block, aplastic anemia, agranulocytosis, thrombocytopenia, hepatitis, erythema multiforme, Stevens-Johnson syndrome</td>
<td>Lithium (increases lithium toxicity), MAOI Other meds may increase carbamazepine levels or have decreased effects</td>
<td>Hypersensitivity to TCAs, previous bone marrow suppression, MAOI in past 14 d Monitor CBC (potential hematological toxicity)</td>
<td></td>
</tr>
<tr>
<td>phenytoin</td>
<td>Seizures: Loading dose: 18 mg/kg slow IV or 300-600 mg PO/d divided bid/tid Maintenance: 200-500 mg IV/d (max rate: &lt;40-50 mg/min or 300 mg PO q4h); average maintenance dose: 300 mg/d PO Status epilepticus: 200 mg IV over 30 min (~ 20 mg/kg; if not taking regularly), or 500 mg IV over 10 min (if already on phenytoin)</td>
<td>Seizures Status epilepticus</td>
<td>Thrombocytopenia, leukopenia, agranulocytosis, pancytopenia, toxic hepatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis</td>
<td>Other meds may increase phenytoin levels and toxicity or have decreased effects</td>
<td>Bradyarrhythmias, heart block Important to give over time to prevent causing a cardiac arrest</td>
<td></td>
</tr>
<tr>
<td>dexamethasone</td>
<td>Loading dose: 10-20 mg IV Maintenance: 4-6 mg IV/d divided qid (may be PO)</td>
<td>Cerebral edema (e.g. secondary to tumour, head injury, pseudotumour cerebri) Preoperative preparation for patients with increased ICP secondary to brain neoplasms</td>
<td>Pseudotumour cerebri, seizures, heart failure, arrhythmias, thromboembolism, pancreatitis, acute adrenal insufficiency; avoid abrupt withdrawal</td>
<td>Aminoglutethimide, anti-diabetics, ASA, NSAIDs, barbituates, phenytoin, rifampin, cardiac glycosides, cyclosporine, ephedrine, oral anticoagulants, potassium-depleting drugs, salicylates, skin-testing antigens, toxoids, vaccines</td>
<td>Systemic fungal infections, immunosuppressive dose with live virus vaccines No longer used in acute spinal cord injury</td>
<td></td>
</tr>
</tbody>
</table>
Table 21. Common Medications (continued)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Common Interactions</th>
<th>Contraindications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>mannitol</td>
<td>1-1.5 g/kg IV rapid infusion (350 mL of 20% solution) followed by 0.25 g/kg IV q6h</td>
<td>Raised ICP</td>
<td>Seizures, heart failure</td>
<td>Lithium (increases excretion of lithium)</td>
<td>Anuria, severe pulmonary congestion, frank pulmonary edema, severe heart failure, severe dehydrtation, metabolic edema, progressive renal disease or dysfunction, active intracranial bleeding except during craniotomy</td>
<td>Effect occurs in 1-5 min, maximal at 20-60 min Often alternated with furosemide 10-20 mg IV q6h Indwelling urinary catheter to measure ins and outs</td>
</tr>
</tbody>
</table>

nifedipine (Nimotop®) 60 mg PO/NG q4h x 21 d started within 96 h of SAH Vasospasm in SAH Decreased blood pressure, tachycardia, dyspnea Anti-hypertensives (may increase hypotensive effects), CCB (may increase effects), cimetidine (increases nimodipine bioavailability) None known Causes vasoocludion Only calcium channel blocker that crosses blood brain barrier Use half the normal dose for liver failure; monitor BP always

References

Textbooks
Acronyms ................................................. 2

Basic Anatomy Review ............................... 2

Pregnancy .................................................. 2
Diagnosis of Pregnancy
Maternal Physiology

Prenatal Care ............................................. 4
Preconception Counselling
Initial Prenatal Visit
Subsequent Prenatal Visits
Prenatal Screening and Diagnostic Tests

Counselling of the Pregnant Woman .......... 9
Nutrition
Lifestyle
Medications
Immunizations
Radiation

Termination of Pregnancy ......................... 11

Prenatal Fetal Monitoring ......................... 12
Fetal Movements

Medical Conditions in Pregnancy ............... 13
Iron and Folate Deficiency Anemia
Diabetes Mellitus (DM)
Hypertension in Pregnancy
Nausea and Vomiting
Hyperemesis Gravidarum
Jaundice in Pregnancy
Urinary Tract Infection (UTI)
Infections During Pregnancy
Venous Thromboembolism (VTE)

Bleeding in Pregnancy ................................. 22
First and Second Trimester Bleeding
Spontaneous Abortions

Ectopic Pregnancy ..................................... 23

Antepartum Hemorrhage ......................... 25
Placenta Previa
Abruption Placentae
Vasa Previa

Multiple Gestation .................................... 28
Twin-Twin Transfusion Syndrome

Growth Discrepancies ................................. 29
Intra-Uterine Growth Restriction
Macrosomia
Polyhydramnios/Oligohydramnios

Normal Labour and Delivery ....................... 31
Definition of Labour
The Cervix
The Fetus
Four Stages of Labour
The Cardinal Movements of the Fetus
during Delivery
Analgesic and Anesthetic Techniques
in Labour and Birth
Fetal Monitoring in Labour

Induction of Labour .................................. 36
Induction Methods
Augmentation of Labour

High Risk Labour and Delivery .................. 38
Preterm Labour
Premature Rupture of Membranes
Breech Presentation
Vaginal Birth After Cesarean (VBAC) aka Trial of
Labour After Cesarean (TOLAC)
Prolonged Pregnancy
Intrauterine Fetal Death

Complications of Labour and Delivery ........ 42
Meconium in Amniotic Fluid
Abnormal Progression of Labour (Dystocia)
Shoulder Dystocia
Umbilical Cord Prolapse
Uterine Rupture
Amniotic Fluid Embolus
Chorioamnionitis

Operative Obstetrics .................................. 46
Operative Vaginal Delivery
Forceps
Vacuum Extraction
Lacerations
Episiotomy
Cesarean Delivery

Puerperal Complications ......................... 48
Postpartum Hemorrhage
Retained Placenta
Uterine Inversion
Postpartum Pyrexia
Mastitis
Postpartum Mood Alterations

Postpartum Care ................................. 52
Breastfeeding and Drugs

Common Medications ............................... 53

References ................................................ 54
**Basic Anatomy Review**

**Fetal Circulation**
- Umbilical arteries (deoxygenated blood)
- Umbilical vein (oxygenated blood)
- Endometrial artery
- Endometrial vein
- Amnion
- Chorion (fetal)
- Decidua (maternal)
- Placenta
- Umbilical cord

**Maternal Circulation**
- Endometrial artery
- Endometrial vein

Figure 1. Placental blood flow

**Placenta**
- Site of fetal nutritive, respiratory, and excretory function
- Discoid mass composed of fetal (chorion frondosum) and maternal (decidua basalis) tissues divided by fissures into cotyledons (lobules) on the uterine side
- Produces hormones such as progesterone, placental lactogen, estrogen, relaxin, β-hCG and IGFs
- Poor implantation can lead to spontaneous abortion
- Abnormal location, implantation, or detachment can lead to antepartum hemorrhage
- (see Antepartum Hemorrhage, OB25)

**Pregnancy**

**Diagnosis of Pregnancy**

**History**
- Obstetrical and gynecological history
- Obtain the year, location, mode of delivery, duration of labour, sex, gestational age, birth weight and complications of every pregnancy; organize into GTPAL format:
  - Gravity (G)
    - G: total number of pregnancies of any gestation
    - Includes current pregnancy, abortions, ectopic pregnancies, and hydatidiform moles (multiple gestation = one pregnancy)
  - Parity (TPAL)
    - T: number of term infants delivered (>37 wk)
    - P: number of premature infants delivered (20-36+6 wk)
    - A: number of abortions (loss of intrauterine pregnancy prior to viability of fetus <20 wk and/or <500 g fetal weight)
      - Induced (therapeutic) and spontaneous (miscarriage)
    - L: number of living children
  - Symptoms: amenorrhea, nausea and/or vomiting, breast tenderness, urinary frequency, fatigue

**Physical Signs**
- Goodell's sign: softening of the cervix (4-6 wk)
- Chadwick's sign: bluish discolouration of the cervix and vagina due to pelvic vasculature engorgement (6 wk)
- Hegar's sign: softening of the cervical isthmus (6-8 wk)
- Uterine enlargement
- Breast engorgement

**Acronyms**

- ACOG: American Congress of Obstetricians and Gynecologists
- AFI: amniotic fluid index
- AEFP: acute fatty liver of pregnancy
- AFV: amniotic fluid volume
- ALPHA: antenatal psychosocial health assessment
- AP: anteposterior
- APS: antiphospholipid antibody syndrome
- BPP: biophysical profile
- C/S: Cesarean section
- CD: cervical dilation and curettage
- DIC: disseminated intravascular coagulation
- DVT: deep vein thrombosis
- D lying: external cephalic version
- EFM: electronic fetal monitoring
- EFW: estimated fetal weight
- FDP: fibrin degradation products
- FHR: fetal heart rate
- FL: femur length
- FM: fetal movement
- FPG: fasting plasma glucose
- FTS: first trimester screen
- GACOG: Group B Streptococcus
- GDM: gestational diabetes mellitus
- HC: head circumference
- HELLP: hemolysis, elevated liver enzymes, low platelets
- IGf: infant growth factors
- ILO: induction of labour
- IP: integrated prenatal screen
- IUFD: intrauterine fetal death
- IUGR: intrauterine growth restriction
- IVH: intraventricular hemorrhage
- LDP: left lateral decubitus position
- LMP: last menstrual period
- MSAFP: maternal serum α-fetoprotein
- MSX: maternal serum screen
- MTX: methotrexate
- NST: non-stress test
- NTd: neural tube defects
- NTUS: nuchal translucency ultrasound
- OA: occiput anterior
- OCCT: oral glucose challenge test
- ONTD: open neural tube defect
- OP: occiput posterior
- OT: occiput transverse
- PAPP-a: pregnancy-associated plasma protein A plasma glucose
- PPD: postpartum depression
- PPH: postpartum hemorrhage
- PROM: preterm premature rupture of membranes
- PROM: premature rupture of membranes
- PTL: preterm labour
- RDS: respiratory distress syndrome
- ROM: rupture of membranes
- SHF: symphysis fundal height
- SOCQ: Society ofObstetricians and Gynaecologists of Canada
- SUV: spontaneous vaginal delivery
- TENS: transcutaneous electrical neuro stimulation
- TPN: total parental nutrition
- UTI: urinary tract infection
- VBAC: vaginal birth after Cesarean

**Umbilical Vessels**
- Always check the umbilical cord for 2 arteries and 1 vein: approximately 1/3 of babies with a single uterine artery will have another anomaly.
Investigations

- **β-hCG**: peptide hormone composed of α and β subunits produced by placental trophoblastic cells – maintains the corpus luteum during pregnancy
  - positive in serum 9 d post-conception, positive in urine 28 d after first day of LMP
  - plasma levels double every 1-2 d, peak at 8-10 wk, then fall to a plateau until delivery
  - levels less than expected by dates suggest: ectopic pregnancy, abortion, or inaccurate dates
  - levels higher than expected suggest: multiple gestation, molar pregnancy, trisomy 21, or inaccurate dates

- **U/S**
  - transvaginal
    - 5 wk: gestational sac visible (β-hCG ≥1,200-1,500 mIU/mL)
    - 6 wk: fetal pole seen
    - 7-8 wk: fetal heart tones visible
  - transabdominal
    - 6-8 wk: intratube pregnancy visible (β-hCG ≥6,500 mIU/mL)

Maternal Physiology

Table 1. Physiologic Changes During Pregnancy

<table>
<thead>
<tr>
<th>Skin</th>
<th>Increased pigmentation of perineum and areola, chloasma (pigmentation changes under eyes and on bridge of nose), linea nigra (midline abdominal pigmentation) Other: spider angiomas, palmar erythema due to increased estrogen, striae gravidarum due to connective tissue changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Hyperdynamic circulation Increased CO, HR and blood volume Decreased BP due to decreased PVR Enlarging uterus compresses IVC and pelvic veins Decreased venous return leads to risk of hypotension Increased venous pressure leads to risk of varicose veins, hemorrhoids, leg edema</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Hemodilution causes physiologic anemia and apparent decrease in hemoglobin and hematocrit Increased leukocyte count but impaired function leads to improvement in autoimmune diseases Gestational thrombocytopenia: mild (platelets &gt;70,000/µL) and asymptomatic, normalizes within 2-12 wk following delivery Hypercoagulable state: increased risk of DVT and PE but also decreased bleeding at delivery</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Increased incidence of nasal congestion and epistaxis Increased O₂ consumption to meet increased metabolic requirements Elevated diaphragm i.e. patient appears more “barrel-chested” Increased minute ventilation leads to decreased CO₂, resulting in mild respiratory alkalosis that helps CO₂ diffuse across the placenta from fetal to maternal circulation No change in VC and FEV; Decreased TLC, FRC, and RV</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>GERD due to increased intra-abdominal pressure and progesterone (causing decreased sphincter tone and delayed gastric emptying) Increased gallstones due to progesterone causing increased gallbladder stasis Constipation and hemorrhoids due to progesterone causing decreased GI motility</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Increased urinary frequency due to increased total urinary output Increased incidence of UTI and pyelonephritis due to urinary stasis (see Urinary Tract Infection, OB20) Glycosuria that can be physiologic especially in the 3rd trimester; must test for GDM Ureters and renal pelvis dilation (R&gt;L) due to progesterone-induced smooth muscle relaxation and uterine enlargement Increased CO and thus increased GFR leads to decreased creatinine (normal in pregnancy 35-44 mmoL, uric acid, and BUN</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Increased incidence of carpal tunnel syndrome and Bell’s palsy</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Thyroid: moderate enlargement and increased basal metabolic rate Increased total thyroxine and thyroxine binding globulin (TBG) Free thyroxine index and TSH levels are normal Adrenal: maternal cortisol rises throughout pregnancy (total and free) Calcium: decreased total maternal Ca²⁺ due to decreased albumin Free ionized Ca²⁺ (i.e. active) proportion remains the same due to parathyroid hormone (PTH), results in increased bone resorption and gut absorption, increased bone turnover (but no loss of bone density due to estrogen inhibition)</td>
</tr>
</tbody>
</table>
Prenatal Care

- provided by obstetrician, family doctor, midwife, or multidisciplinary team (based on patient preference and risk factors)
- Antenatal Records (province specific)

Preconception Counselling

- 3-8 wk GA is a critical period of organogenesis, so early preparation is vital
- past medical history: optimize medical illnesses and necessary medications prior to pregnancy (see Medical Conditions in Pregnancy, OB13, and Medications in Pregnancy, OB10)

- supplementation
  - folic acid: encourage diet rich in folic acid and supplement 8-12 wk preconception until end of T1 to prevent NTDs
    - 0.4-1 mg daily in all women, 5 mg if previous NTD, anti-epileptic medications, diabetes mellitus or BMI >35 kg/m²
  - iron supplementation, prenatal vitamins

- risk modification
  - lifestyle: balanced nutrition and physical fitness
  - medications: patients with chronic diseases should discuss whether their medications may be teratogenic prior to conception so they may be adjusted. It is not advised to stop medications abruptly when becoming pregnant
  - infection screening: rubella, HBsAg, VDRL, Pap smear, gonorrhea/chlamydia, HIV
  - genetic testing as appropriate for high risk groups (see Prenatal Screening section, Table 2, OB5); consider genetics referral in known carriers, recurrent pregnancy loss/stillbirth, family members with developmental delay or birth anomalies
  - social: alcohol, smoking, drug use, domestic violence
    - use ALPHA form to screen for antenatal risk factors associated with poor postpartum family outcomes (woman abuse, child abuse, postpartum depression, marital dysfunction and increased physical illness)

Initial Prenatal Visit

- usually within 12 wk of the first day of LMP or earlier if <20 or >35 yr old or other risk factors are present
- Antenatal Records are filled out on the first prenatal visit

History

- gestational age by dates from the first day of the LMP
- if LMP unreliable, get a dating ultrasound (see below)
- EDC using Naegle's Rule:
  - 1st day of LMP + 7 d – 3 mo
  - e.g. LMP = 1 Apr 2013, EDC = 8 Jan 2014 (modify if cycle >28 d by adding number of d >28)
- history of present pregnancy (e.g. bleeding, nausea, vomiting)
- history of all previous pregnancies
- past medical history, past gynecological history
- prescription and non-prescription medications
- family history: genetic disease, birth defects, multiple gestation
- social history: smoking, alcohol, drug use, domestic violence (use ALPHA form), consanguinity

Physical Examination

- complete exam to obtain baseline patient information
- BP and weight important for interpreting subsequent changes
- pelvic exam

Investigations

- bloodwork
  - CBC, blood group and type, Rh antibodies, infection screening as per preconception counselling
  - urine R&M, C&S
  - screen for bacteriuria and proteinuria
- pelvic exam
  - Pap smear (unless done within last 6-12 mo), cervical culture for N. gonorrhoeae (GC) and C. trachomatis, vaginal swab for bacterial vaginosis (BV)
**Subsequent Prenatal Visits**

**Timing**
- for uncomplicated pregnancies, q4-6wk until 28 wk, q2wk from 28 to 36 wk and weekly from 36 wk until delivery

**Assess at Every Visit**
- record estimated GA
- history of present pregnancy: fetal movements, uterine bleeding, leaking, cramping
- physical exam: BP, weight gain, SFH, Leopold’s maneuvers (T3) for lie, position and presentation of fetus
- investigations: urinalysis for glucosuria, ketones, proteinuria; fetal heart rate starting at 12 wk using Doppler U/S

**Leopold’s Maneuvers**
- performed after 30-32 wk gestation
- first maneuver: to determine which fetal part is lying furthest away from the pelvic inlet
- second maneuver: to determine the location of the fetal back
- third maneuver: to determine which fetal part is lying above the pelvic inlet
- fourth maneuver: to locate the fetal brow

![Figure 2. Leopold’s maneuvers (T3)](https://example.com/leopolds-maneuvers)

Reprinted with permission from Essentials of Clinical Examination Handbook, 6th ed. Lincoln, McSheffrey, Tran, Wong

**Prenatal Screening and Diagnostic Tests**

**Screening Tests**
- testing should only occur following counselling and with the informed consent from the patient

<table>
<thead>
<tr>
<th>Disease [Inheritance]</th>
<th>Population(s) at Risk</th>
<th>Screening Test(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassemia [AR]</td>
<td>Mediterranean, South East Asian, Western Pacific, African, Middle Eastern, Caribbean, South American</td>
<td>CBC (MCV and MCH), Hb electrophoresis or HPLC</td>
</tr>
<tr>
<td>Sickle Cell [AR]</td>
<td>African, Caribbean, Mediterranean, Middle Eastern, Indian, South American</td>
<td>CBC (MCV and MCH), Hb electrophoresis or HPLC</td>
</tr>
<tr>
<td>Cystic Fibrosis (CF) [AR]</td>
<td>Mediterranean, Finnish, Caucasian, or FHx</td>
<td>CFTR gene DNA analysis</td>
</tr>
<tr>
<td>Tay Sachs Disease [AR]</td>
<td>Ashkenazi Jewish*, French Canadians, Cajun</td>
<td>Enzyme assay HEXA, or DNA analysis</td>
</tr>
<tr>
<td>Fragile X Syndrome [X-linked]</td>
<td>Family history – confirmed or suspected</td>
<td>DNA analysis: FMR-1 gene</td>
</tr>
</tbody>
</table>

*AR = autosomal recessive; HPLC = high performance liquid chromatography; HEXA = hexosaminidase A
*If both partners are Ashkenazi Jewish, test for Canavan disease and Familial Dysautonomia (FD), if family history of a specific condition, look for carrier status: e.g., Gaucher, CF, Bloom syndrome, Niemann-Pick disease, etc. In all cases, if both partners positive, refer for genetic counselling

**Symphysis Fundal Height (SFH)**
- 12 wk: Uterine fundus at pubic symphysis
- 20 wk: Fundus at umbilicus, SFH should be within 2 cm of GA between 20-36 wk
- 37 wk: Fundus at sternum

**Small for Dates**
- Date miscalculation
- IUGR
- Fetal demise
- Oligohydramnios

**Large for Dates**
- Date miscalculation
- Multiple gestation
- Polyhydramnios
- LGA (familial), diabetes

---

**Figure 2. Leopold’s maneuvers (T3)**

Reprinted with permission from Essentials of Clinical Examination Handbook, 6th ed. Lincoln, McSheffrey, Tran, Wong
Table 3. Gestation-Dependent Screening Investigations

<table>
<thead>
<tr>
<th>Gestational Age (wk)</th>
<th>Investigations</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-12</td>
<td>Dating U/S, initial Pap smear, chlamydia/gonorrhea cultures</td>
<td></td>
</tr>
<tr>
<td>10-12</td>
<td>CVS</td>
<td></td>
</tr>
<tr>
<td>11-14</td>
<td>FTS IPS Part 1</td>
<td>Measures: 1. Nuchal translucency on U/S 2. β-hCG 3. PAPP-A</td>
</tr>
<tr>
<td>11-14</td>
<td>Nuchal translucency U/S</td>
<td></td>
</tr>
<tr>
<td>15-18 to term</td>
<td>Amniocentesis</td>
<td></td>
</tr>
<tr>
<td>15-20</td>
<td>IPS Part 2</td>
<td>Measures: 1. MSAFP 2. β-hCG 3. Unconjugated estrogen (estriol or µE3) 4. Inhibin A</td>
</tr>
<tr>
<td>15-20</td>
<td>Maternal serum screen (MSS) (or MSAFP only for patients who did FTS earlier)</td>
<td>Measures: 1. MSAFP 2. β-hCG 3. Unconjugated estrogen (estriol or µE3)</td>
</tr>
<tr>
<td>18-20 to term</td>
<td>Fetal movements (quickening)</td>
<td></td>
</tr>
<tr>
<td>18-20</td>
<td>U/S for dates, fetal growth and anatomy assessment</td>
<td></td>
</tr>
<tr>
<td>24-28</td>
<td>50 g OGCT</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Repeat CBC, RhIG for all Rh negative women</td>
<td></td>
</tr>
<tr>
<td>35-37</td>
<td>GBS screen</td>
<td></td>
</tr>
<tr>
<td>6 wk postpartum</td>
<td>Discuss contraception, menses, breastfeeding, depression, mental health, support Physical exam: breast exam, pelvic exam including Pap smear (only if due as per provincial screening)</td>
<td></td>
</tr>
</tbody>
</table>

Maternal serum screen is also referred to as Triple Screen. If Inhibin A is also tested, it is referred to as Quadruple Screen. Ideally testing for MSS and IPS Part 2 occur between 15-18 wk to give women more time to make decisions and move ahead with diagnostic testing should the result screen be positive.

ULTRASOUND SCREENING
- dating ultrasound best done between 8-12 wk GA (most accurate form of pregnancy dating)
  - measurement of crown-rump length (margin of error ± 5 d)
  - change EDC to U/S date if >1 wk discrepancy from EDC based on LMP
- NTUS at 11-14 wk GA
  - measures the amount of fluid behind the neck of the fetus
  - early screen for Trisomy 21 (may also detect cardiac and other aneuploidies like Turner’s syndrome)
  - NT measurement is necessary for the FTS and IPS Part 1
- fetal growth and anatomy ultrasound routinely done at 18-20 wk GA (margin of error ± 7 d)
  (see Pediatrics, P41 for congenital anomalies)
- earlier or subsequent ultrasounds performed when medically indicated

Table 4. Comparison of FTS, MSS and IPS

<table>
<thead>
<tr>
<th>First Trimester Screen (FTS)</th>
<th>Maternal Serum Screen (MSS)</th>
<th>Integrated Prenatal Screen (IPS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-14 wk</td>
<td>15-20 wk</td>
<td>Nuchal translucency on 12 wk U/S FTS at 11-14 wk MSS + inhibin A at 15-20 wk</td>
</tr>
<tr>
<td>Risk estimate for 1. Down syndrome (Trisomy 21): increased NT, increased β-hCG, decreased PAPP-A</td>
<td>Risk estimate for 1. oNTD: increased MSAFP (sensitivity 80-90%) 2. Trisomy 21: decreased MSAFP, increased β-hCG, decreased µE3 (sensitivity 65%) 3. Trisomy 18: decreased MSAFP, decreased β-hCG, decreased µE3 (sensitivity 80%)</td>
<td>Risk estimate for oNTD, Trisomy 21, Trisomy 18 Sensitivity -- 85-90% 2% false positive rate Patients with positive screen should be offered U/S and/or amniocentesis</td>
</tr>
<tr>
<td>Note: does not measure risk of open neural tube defect (oNTD) and should be combined with MSAFP at 16 wk Useful where patient wants results within the first trimester More accurate estimate of Down syndrome risk than MSS, sensitivity ~85% (when combined with age) 9% false positive rate Patients with positive screen should be offered CVS or amniocentesis</td>
<td>Only offered alone if patient missed the time window for IPS or FTS 8% baseline false positive rate for Trisomy 21, lower for oNTD and Trisomy 18 Patients with positive screen should be offered U/S or amniocentesis</td>
<td></td>
</tr>
</tbody>
</table>

Note: In twins, FTS, MSS and IPS are not applicable; screen with NT for chromosomal abnormalities and MSAFP for oNTDs.
**DIAGNOSTIC TESTS**

**Indications**
- Maternal age >35 (increased risk of chromosomal anomalies)
- Risk factors in current pregnancy:
  - Abnormal U/S
  - Abnormal prenatal screen (IPS, FTS, or MSS)
- Past history/family history of:
  - Previous pregnancy with chromosomal anomaly or genetic disease
  - Either parent a known carrier of a genetic disorder or balanced translocation
  - Family history of chromosomal anomaly, genetic disorder, birth defect, or undiagnosed mental retardation
  - Consanguinity
  - Three or more spontaneous abortions

**AMNIOCENTESIS**
- U/S-guided transabdominal extraction of amniotic fluid

**Indications**
- Identification of genetic anomalies (15-16 wk gestation) as per indications above
- Assessment of fetal lung maturity (T3) via the L/S ratio (lecithin:sphingomyelin)
  - If >2:1, RDS is less likely to occur

**Advantages**
- Also screens for oNTD (acetylcholinesterase and amniotic AFP) - 96% accurate
- In women >35 yr, the risk of chromosomal anomaly (1/180) is greater than the risk of miscarriage from the procedure
- More accurate genetic testing than CVS

**Disadvantages**
- 1/400 – 1/500 risk of spontaneous abortion
- Results take 14-28 days; FISH can be done on chromosomes X, Y, 21, 13, 18 to give preliminary results in 48 h

**CHORIONIC VILLUS SAMPLING**
- Biopsy of fetal-derived chorion using a trans-abdominal needle or trans-cervical catheter at 10-12 wk

**Advantages**
- Enables pregnancy to be terminated earlier than with amniocentesis
- Rapid karyotyping and biochemical assay within 48 h, including FISH analysis
- High sensitivity and specificity

**Disadvantages**
- 1-2% risk of spontaneous abortion
- Does not screen for oNTD
- 1-2% incidence of genetic mosaicism “false negative” results

**ISOIMMUNIZATION SCREENING**

**Definition**
- Isoimmunization: antibodies (Ab) produced against a specific RBC antigen (Ag) as a result of antigentic stimulation with RBC of another individual

**Etiology**
- Maternal-fetal circulation normally separated by placental barrier, but sensitization can occur and can affect the current pregnancy, or more commonly, future pregnancies
- In pregnancy, anti-Rh Ab produced by a sensitized Rh-negative mother can lead to fetal hemolytic anemia
- Overall risk of isoimmunization of an Rh-negative mother with an Rh-positive ABO-compatible infant is 16%

**Sensitization routes**
- Incompatible blood transfusions
- Previous fetal-maternal transplacental hemorrhage (e.g. ectopic pregnancy)
- Invasive procedures in pregnancy (e.g. prenatal diagnosis, cerclage, D&C)
- Any type of abortion
- Labour and delivery
Investigations
- routine screening with indirect Coombs test at first visit for blood group, Rh status, and antibodies
- Kleihauer-Betke test used to determine extent of fetomaternal hemorrhage by estimating volume of fetal blood volume that entered maternal circulation.
- detailed U/S for hydrops fetalis

Prophylaxis
- exogenous Rh IgG (Rhogam® or WinRho®) binds to Rh antigens of fetal cells and prevents them from contacting maternal immune system
- Rhogam® (300 µg) given to all Rh negative and antibody screen negative women in the following scenarios:
  - routinely at 28 wk GA (provides protection for ~12 wk)
  - within 72 h of the birth of an Rh positive fetus
  - with a positive Kleihauer-Betke test
  - with any invasive procedure in pregnancy (CVS, amniocentesis)
  - in ectopic pregnancy
  - with miscarriage or therapeutic abortion (only 50 µg required)
  - with an antepartum hemorrhage
- if Rh negative and Ab screen positive, follow mother with serial monthly Ab titres throughout pregnancy ± serial amniocentesis as needed (Rhogam® has no benefit)

Investigations
- MCA dopplers are done to assess degree of fetal anemia or if not available bilirubin is measured by serial amniocentesis to assess the severity of hemolysis
- cordocentesis for fetal Hb should be used cautiously (not first line)

Treatment
- falling biliary pigment warrants no intervention (usually indicative of either unaffected or mildly affected fetus)
- intrauterine transfusion of O-negative pRBCs may be required for severely affected fetus or early delivery of the fetus for exchange transfusion

Complications
- anti-Rh IgG can cross the placenta and cause fetal RBC hemolysis resulting in fetal anemia, CHF, edema, ascites
- severe cases can lead to fetal hydrops (edema in at least two fetal compartments due to fetal heart failure secondary to anemia) or erythroblastosis fetalis (moderate to severe immune-mediated hemolytic anemia)

GROUP B STREPTOCOCCUS SCREEN

Epidemiology
- 15-40% vaginal carrier rate

Risk Factors (for neonatal disease)
- GBS bacteriuria during current pregnancy even if treated
- previous infant with invasive GBS infection
- preterm labour <37 wk
- ruptured membranes >18 h before delivery
- intrapartum maternal temperature ≥38°C
- positive GBS screen during current pregnancy

Clinical Features
- not harmful to mother
- risk of vertical transmission (neonatal sepsis, meningitis or pneumonia, and death)

Investigations
- offer screening to all women at 35-37 wk with vaginal and anorectal swabs for C&S

Treatment
- treatment of maternal GBS at delivery decreases neonatal morbidity and mortality
- indications for antibiotic prophylaxis: positive GBS screen or GBS status unknown and one of the risk factors (see above)
- antibiotics for GBS prophylaxis
  - penicillin G 5 million units IV then 2.5 million units IV q4h until delivery
  - penicillin allergic but not at risk for anaphylaxis: cefazolin 2 g IV then 1 g q8h
  - penicillin allergic and at risk for anaphylaxis: clindamycin 900 mg IV q8h or erythromycin 500 mg IV q6h
- if fever, broad spectrum antibiotic coverage is advised

Indications for Intrapartum Antibiotic GBS Prophylaxis
- • Previous infant with invasive GBS disease
- • GBS bacteriuria during any trimester of the current pregnancy
- • Positive GBS vaginal-rectal screening culture in late gestation during current pregnancy
- • Unknown GBS status at the onset of labour (culture not done, incomplete, or results unknown) and any of the following:
  - Delivery at <37 wk gestation
  - Amniotic membrane rupture ≥18 h
  - Intrapartum temperature ≥100.4°F (≥38.0°C)
  - Intrapartum nucleic-acid amplification test positive for GBS

Rh Antibody Titre
- A positive titre (≥1:16) indicates an increased risk of fetal hemolytic anemia.

Standard dose of 300 µg of Rhogam sufficient for 30 mL of fetal blood. Give additional 10 µg of Rhogam for every mL of fetal blood over 30 mL.
Counselling of the Pregnant Woman

Nutrition

- Canada’s Food Guide to Healthy Eating suggests:
  - 3–4 servings of milk products daily (greater if multiple gestation)
  - a daily caloric increase of ~100 cal/d in the 1st trimester, ~300 cal/d in the second and third trimesters and ~450 cal/d during lactation
  - daily multivitamin should be continued in the 2nd trimester for women who do not consume an adequate diet; otherwise routine vitamin supplementation is not necessary (avoid excess vitamin A)

- nutrients important during pregnancy
  - folate: 0.4 mg/d for first 12 wk (5 mg/d if high risk)
    - supports maternal increase in blood volume, growth of maternal and fetal tissue, decreases incidence of neural tube defects
    - foods rich in folic acid include: spinach, lentils, chick peas, asparagus, broccoli, peas, Brussels sprouts, corn and oranges
  - calcium: 1200-1500 mg/d
    - maintains integrity of maternal bones, skeletal development of fetus, breast milk production
  - vitamin D: 1000 IU
    - promotes calcium absorption
  - iron: 0.8 mg/d in T1, 4-5 mg/d in T2 and >6 mg/d in T3
    - supports maternal increase in blood cell mass, supports fetal and placental tissue
    - required amounts exceed normal body stores and typical intake, and therefore need supplemental iron
    - iron is the only known nutrient for which requirements during pregnancy cannot be met by diet alone (see Iron Deficiency Anemia, OB13)
  - essential fatty acids – supports fetal neural and visual development
    - contained in vegetable oils, margarines, peanuts, fatty fish

Caffeine

- diuretic and stimulant that readily crosses placenta
- less than 200 mg per day is not thought to contribute to miscarriage or preterm birth (ACOG)
- relationship between caffeine and IUGR is unknown (ACOG)
- SOCG states 1-2 cups/d are safe during pregnancy

Herbal Teas and Preparations

- not enough scientific information about safety of various herbs and herbal products to recommend their use during pregnancy
- some herbal teas can have toxic or pharmacological effects on the mother or fetus
- chamomiles have been reported to exhibit adverse effects on the uterus

Food Borne Illnesses

- microbiological contamination of food may occur through cross-contamination and/or improper food handling
  - listeriosis (Listeria monocytogenes) and toxoplasmosis (Toxoplasma gondii) are of concern during pregnancy
  - avoid consumption of raw meats, fish, poultry, raw eggs, and unpasteurized dairy products
  - avoid soft cheeses, deli meats, smoked salmon and pates as they may be sources of Listeria
- chemical contamination of food
  - current guideline for mercury of 0.5 ppm in fish is not considered harmful for the general population, including pregnant women
  - Health Canada advises pregnant women to limit consumption of top predator fish such as shark, swordfish, king mackerel, tilefish, and fresh/frozen tuna (not canned tuna) to one meal per month

Lifestyle

- exercise under physician guidance
- absolute contraindications
  - ruptured membranes, preterm labour, hypertensive disorders of pregnancy, incompetent cervix, IUGR, multiple gestations (>3), placenta previa after 28th wk, persistent 2nd or 3rd trimester bleeding, uncontrolled type 1 diabetes, uncontrolled thyroid disease, or other serious cardiovascular, respiratory or systemic disorder
- relative contraindications
  - previous preterm birth, mild/moderate cardiovascular or respiratory disorder, anemia (Hb ≤100 g/L), malnutrition or eating disorder, twin pregnancy after 28th wk, other significant medical conditions
- weight gain: optimal gain depends on pre-pregnancy weight (varies from 6.8-18.2 kg)
- work: strenuous work, extended hours and shift work during pregnancy may be associated with greater risk of low birth weight, prematurity, and spontaneous abortion
- travel: not harmful, but stress related to travel may be associated with preterm labour
  - air travel is acceptable in second trimester; airline cutoff for travel is 36-38 wk gestation depending on the airline to avoid giving birth on the plane
- smoking: assist/encourage to reduce or quit smoking
  - increased risk of: decreased birth weight, placenta previa/abruption, spontaneous abortion, preterm labour, stillbirth
- alcohol: no amount of alcohol is safe in pregnancy. Encourage abstinence from alcohol during pregnancy; alcohol increases incidence of abortion, stillbirth, and congenital anomalies
  - fetal alcohol syndrome (see Pediatrics, P24)
- cocaine: microcephaly, growth retardation, prematurity, abruptio placentae

### Medications

- most drugs cross the placenta to some extent
- very few drugs are teratogenic, but very few drugs have proven safety in pregnancy
- use any drug with caution and only if necessary
- analgesics: acetaminophen preferable to ASA or ibuprofen

#### Table 5. Documented Adverse Effects, Contraindicated

<table>
<thead>
<tr>
<th>Contraindicated Medication</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Fetal renal defects, IUGR, oligohydramnios</td>
</tr>
<tr>
<td>tetracycline</td>
<td>Stains infant’s teeth, may affect long bone development</td>
</tr>
<tr>
<td>retinoids (e.g. Accutane®)</td>
<td>CNS, craniofacial, cardiac, and thymic anomalies</td>
</tr>
<tr>
<td>DES (and other estrogenic or androgenic compounds)</td>
<td>Vaginal adenosin, adenocarcinoma, uterine malformation in females exposed to DES in utero</td>
</tr>
<tr>
<td>misoprostol</td>
<td>Mobius syndrome (congenital facial paralysis with or without limb defects, spontaneous abortion, preterm labour)</td>
</tr>
</tbody>
</table>

#### Table 6. Documented Adverse Effects, Weigh Benefits vs. Risks and Consider Medication Change

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenytoin</td>
<td>Fetal hydantoin syndrome in 5-10% (IUGR, mental retardation, facial dysmorphogenesis, congenital anomalies)</td>
</tr>
<tr>
<td>valproate</td>
<td>oNTD in 1%</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>oNTD in 1-2%</td>
</tr>
<tr>
<td>lithium</td>
<td>Ebstein’s cardiac anomaly, goitre, hyponatraemia</td>
</tr>
<tr>
<td>warfarin</td>
<td>Increased incidence of spontaneous abortion, stillbirth, prematurity, IUGR, fetal warfarin syndrome (nasal hypoplasia, epiphysical stippling, optic atrophy, mental retardation, intracranial hemorrhage)</td>
</tr>
<tr>
<td>erythromycin</td>
<td>Maternal liver damage (acute fatty liver)</td>
</tr>
<tr>
<td>sulpha drugs</td>
<td>Anti-folate properties, therefore theoretical risk in T1; risk of kernicterus in T3</td>
</tr>
<tr>
<td>chloramphenicol</td>
<td>Grey baby syndrome (fetal circulatory collapse 2° to toxic accumulation)</td>
</tr>
</tbody>
</table>

### Immunizations

#### Intrapartum

- administration is dependent on the risk of infection vs. risk of immunization complications
- safe: tetanus toxoid, diphtheria, influenza, hepatitis B
- avoid live vaccines (risk of placental and fetal infection): polio, measles/mumps/rubella, varicella
- contraindicated: rubella, oral typhoid

#### Postpartum

- rubella vaccine for all non-immune mothers
- hepatitis B vaccine should be given to infant within 12 h of birth if maternal status unknown or positive – follow-up doses at 1 and 6 mo
- human papillomavirus (HPV) vaccine – if meets criteria
Radiation

- Ionizing radiation exposure is considered teratogenic at high doses
  - If indicated for maternal health, should be done
- Imaging not involving direct abdominal/pelvic high dosage is not associated with adverse effects
  - Higher dosage to fetus: plain x-ray of lumbar spine/abdomen/pelvis, barium enema, CT abdomen, pelvis, lumbar spine
- Most investigations involve minimal radiation exposure (see Table 7)
- Radioactive isotopes of iodine are contraindicated
- No known adverse effects from US or MRI

**Table 7. Approximate Fetal Doses from Common Diagnostic Procedures**

<table>
<thead>
<tr>
<th>Examination</th>
<th>Estimated Fetal Dose (rad)</th>
<th>Number of Exams Safe in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plain Film</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>0-14</td>
<td>35</td>
</tr>
<tr>
<td>Pelvis</td>
<td>0-11</td>
<td>45</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0-17</td>
<td>29</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>0.009</td>
<td>555</td>
</tr>
<tr>
<td>Chest (2 views)</td>
<td>&lt;0.001</td>
<td>5000</td>
</tr>
<tr>
<td><strong>CT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>0-8</td>
<td>6</td>
</tr>
<tr>
<td>Pelvis</td>
<td>2-5</td>
<td>2</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0-24</td>
<td>20</td>
</tr>
<tr>
<td>Chest</td>
<td>0.006</td>
<td>833</td>
</tr>
</tbody>
</table>

Adapted from Cohen-Kerem, et al. 2005 and Valentin, 2000

Termination of Pregnancy

- See **Gynecology: GY9**

**Definition**

Active termination of a pregnancy before fetal viability (usually <500 g or 20 wk GA)

**Indications**

- Inability to carry a pregnancy to term due to medical or social reasons (including patient preference)

**Management**

- Medical
  - <9 wk: methotrexate + misoprostol
  - >12 wk: prostaglandins (intra- or extra-amniotically or IM) or misoprostol
- Surgical
  - <12 wk: dilatation + vacuum aspiration ± curettage
  - >12 wk: dilatation and evacuation, early induction of labour
  - Common complications: pain or discomfort
  - Less common complications: hemorrhage, perforation of uterus, laceration of cervix, risk of infertility, infection/endometritis, Asherman’s syndrome (adhesions within the endometrial cavity causing amenorrhea/infertility), retained products of conception
- Counselling
  - Supportive and counselling services
  - Future contraception and family planning services
  - Ensure follow-up

**CMA policy (1988)**

“Induced abortion should be uniformly available to all women in Canada” and “there should be no delay in the provision of abortion services.”

Terminations are generally done until the stage of viability (~23.5 wk), although this varies depending on the provider.

**Induced Abortion Statistics**

- Rate per 1,000 women (all ages): 13.7
- 31.4% of all abortion services are accessed by women aged 20-24

Adapted from Statistics Canada. Induced abortion statistics. 82-223-XWE, 2005/16
Prenatal Fetal Monitoring

Fetal Movements

- Patients will generally first notice fetal movement ("quickening") at 18-20 wk in primigravidas; can occur 1-2 wk earlier in multigravidas; can occur 1-2 wk later if placenta is implanted on the anterior wall of uterus.
- If the patient is concerned about decreased fetal movement, she is counselled to choose a time when the fetus is normally active to count movements (usually recommended after 28 wk).
  - If there is a subjective decrease in fetal movement, try drinking juice, eating, changing position or moving to a quiet room and count for 2 h. There should be ≥6 movements in 2 h.
  - If there are <6 movement counts in 2 h, patient should present to labour and delivery triage.

NON-STRESS TEST (NST)

Definition

- FHR tracing ≥20 min using an external Doppler to assess FHR and its relationship to fetal movement (see Fetal Monitoring in Labour, OB34).

Indication

- Any suggestion of uteroplacental insufficiency or suspected compromise in fetal well-being.

Table 8. Classification of Antepartum Non-Stress Test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal NST (Previously &quot;Reactive&quot;)</th>
<th>Atypical NST (Previously &quot;Non-Reactive&quot;)</th>
<th>Abnormal NST (Previously &quot;Non-Reactive&quot;)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>110-160 bpm</td>
<td>100-110 bpm or &gt;160 bpm for &lt;30 min</td>
<td>Bradycardia &lt;100 bpm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rising baseline</td>
<td>Tachycardia &gt;160 for &gt;30 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Erratic baseline</td>
</tr>
<tr>
<td><strong>Variability</strong></td>
<td>6-25 bpm (moderate)</td>
<td>≤5 (absent or minimal) for &lt;40 min</td>
<td>≤5 for 80 min</td>
</tr>
<tr>
<td></td>
<td>≤5 (absent or minimal) for</td>
<td></td>
<td>Sinusoidal</td>
</tr>
<tr>
<td></td>
<td>40-80 min</td>
<td></td>
<td>25 bpm for &gt;10 min</td>
</tr>
<tr>
<td><strong>Decelerations</strong></td>
<td>None or occasional variable &lt;30 s</td>
<td>Variable decelerations 30-60 s duration</td>
<td>Variable decelerations &gt;80 s</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Late deceleration(s)</td>
</tr>
<tr>
<td><strong>Accelerations in</strong></td>
<td>2 accelerations with acme of</td>
<td>2 accelerations with acme of</td>
<td>&lt;2 accelerations with acme of</td>
</tr>
<tr>
<td><strong>Term Fetus</strong></td>
<td>≥15 bpm, lasting 15 s over &lt;40 min</td>
<td>≥15 bpm, lasting 15 s in 40-80 min</td>
<td>≥15 bpm, lasting 15 s in &gt;80 min</td>
</tr>
<tr>
<td><strong>Accelerations in</strong></td>
<td>&gt;2 accelerations with acme of</td>
<td>&lt;2 accelerations with acme of</td>
<td>&lt;2 accelerations with acme of</td>
</tr>
<tr>
<td><strong>Preterm Fetus</strong></td>
<td>&gt;10 bpm, lasting 10 s in &lt;40 min</td>
<td>&gt;10 bpm, lasting 10 s in 40-80 min</td>
<td>&gt;10 bpm, lasting 10 s in &gt;80 min</td>
</tr>
<tr>
<td></td>
<td>&lt;2 accelerations with acme of &lt;40</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Action</strong></td>
<td>FURTHER ASSESSMENT OPTIONAL, based on total</td>
<td>FURTHER ASSESSMENT REQUIRED</td>
<td>URGENT ACTION REQUIRED</td>
</tr>
<tr>
<td></td>
<td>clinical picture</td>
<td></td>
<td>An overall assessment of the situation and further investigation with U/S or BPP is required. Some situations will require delivery</td>
</tr>
</tbody>
</table>

Adapted from SOGC, Fetal Health Surveillance: Antepartum and Intrapartum Consensus Guideline, September 2007

Operating Characteristics

- False positive rate depends on duration; false negative rate = 0.2-0.3%

Interpretation

- Normal: at least 2 accelerations of FHR >15 bpm from the baseline lasting >15 s, in 20 min.
- Abnormal: <2 accelerations of FHR in 40 min.
- If no observed accelerations or fetal movement in the first 20 min, stimulate fetus (fundal pressure, acoustic/vibratory stimulation) and continue monitoring for 30 min.
- If NST abnormal, then perform BPP.

BIOPHYSICAL PROFILE

Definition

- U/S assessment of the fetus ± NST

Indications

- Abnormal or atypical NST
- Post-term pregnancy
- Decreased fetal movement
- Any other suggestion of fetal distress or uteroplacental insufficiency
Operating Characteristics
• false positive rate ≤30%, false negative rate = 0.1%

Table 9. Scoring of the BPP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reassuring (2 points)</th>
<th>Non-Reassuring (0 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFV*</td>
<td>Fluid pocket of 2 cm in 2 axes</td>
<td>Oligohydramnios</td>
</tr>
<tr>
<td>Breathing</td>
<td>At least one episode of breathing lasting at least 30 s</td>
<td>No breathing</td>
</tr>
<tr>
<td>Limb Movement</td>
<td>Three discrete movements</td>
<td>Two or less</td>
</tr>
<tr>
<td>Fetal Tone</td>
<td>At least one episode of limb extension followed by flexion</td>
<td>No movement</td>
</tr>
</tbody>
</table>

*AFV is a marker of chronic hypoxia, all other parameters indicate acute hypoxia

Interpretation
• 8: perinatal mortality rate 1:1000; repeat BPP as clinically indicated
• 6: perinatal mortality 31:1000; repeat BPP in 24 h
• 0-4: perinatal mortality rate 200:1000; deliver fetus if benefits of delivery outweigh risks

Medical Conditions in Pregnancy

Iron and Folate Deficiency Anemia

Table 10. Iron Deficiency and Folate Deficiency Anemia

<table>
<thead>
<tr>
<th>Iron Deficiency Anemia</th>
<th>Folate Deficiency Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>See Hematology, H14</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Responsible for 80% of causes of non-physiologic anemia during pregnancy</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>See Hematology, H14</td>
</tr>
<tr>
<td>Investigations</td>
<td>See Hematology, H14</td>
</tr>
<tr>
<td>Management</td>
<td>Prevention (non-anemic): 30 mg elemental iron/d (met by most prenatal vitamins) Treatment (anemic): 30-120 mg elemental iron/d 325 mg ferrous fumarate = 106 mg elemental Fe²⁺; 325 mg ferrous sulfate = 65 mg elemental Fe²⁺; 325 mg ferrous gluconate = 36 mg elemental Fe²⁺</td>
</tr>
<tr>
<td>Complications</td>
<td>Maternal: angina, CHF, infection, slower recuperation, preterm labour Fetal: decreased oxygen carrying capacity leading to fetal distress, IUGR and low birth weight</td>
</tr>
<tr>
<td>Notes</td>
<td>Mother needs 1 g of elemental iron per fetus; this amount exceeds normal stores + dietary intake Iron requirements increase during pregnancy due to fetal/placental growth (500 mg), increased maternal RBC mass (500 mg) and losses (200 mg) – more needed for multiple gestations</td>
</tr>
</tbody>
</table>

Diabetes Mellitus (DM)

Classification of Diabetes Mellitus
• Type 1 and Type 2 DM (see Endocrinology, E6)
• GDM: onset of diabetes mellitus during pregnancy

Etiology
• Type 1 and Type 2 DM
• GDM: usually around 24-28 wk GA, anti-insulin factors produced by placenta and high maternal cortisol levels create increased peripheral insulin resistance → higher fasting glucose → leading to GDM and/or exacerbating pre-existing DM

Epidemiology
• 2-4% of pregnancies are complicated by DM
MANAGEMENT

A. TYPE 1 AND TYPE 2 DM

Preconception
- pre-plan and refer to high-risk clinic
- optimize glycemic control
- counsel patient re: potential risks and complications
- evaluate for diabetic retinopathy, neuropathy, coronary artery disease

Pregnancy
- if already on oral medication, generally switch to insulin therapy
  - continuing glyburide or metformin controversial
  - teratogenicity unknown for other oral anti-hyperglycemics
- tight glycemic control
  - insulin dosage may need to be adjusted in T2 due to increased demand and increased insulin resistance
- monitor as for normal pregnancy plus initial 24 h urine protein and creatinine clearance, retinal exam, HbA1c
  - HbA1c: >140% of pre-pregnancy value associated with increased risk of spontaneous abortion and congenital malformations
- increased fetal surveillance (BPP, NST)

Labour
- timing of delivery depends on fetal and maternal health and risk factors (i.e. must consider size of baby, lung maturity, maternal blood glucose and blood pressure control)
- can wait for spontaneous labour if blood glucose well-controlled and BPP normal
- induce by 40 wk
- type of delivery
  - increased risk of cephalopelvic disproportion (CPD) and shoulder dystocia with babies >4,000 g (8.8 lbs)
  - elective C/S for predicted birthweight >4,500 g (9.9 lbs) (controversial)
- monitoring
  - during labour monitor blood glucose q1h with patient on insulin and dextrose drip
  - aim for blood glucose between 3.5 to 6.5 mmol/L to reduce the risk of neonatal hypoglycemia

Postpartum
- insulin requirements dramatically drop with expulsion of placenta (source of insulin antagonists)
- no insulin is required for 48-72 h postpartum in most Type 1 DM
- monitor glucose q6h, restart insulin at two-thirds of pre-pregnancy dosage when glucose >8 mmol/L

B. GESTATIONAL DIABETES MELLITUS

Screening + Diagnosis
- at 24-28 wk GA
- pregnant females age >25 or age <25 yr with >1 risk factor (see sidebar)
- 1 h, 50 g Oral Glucose Challenge Test (OGCT): not fasting
  - PG <7.8 mmol/L = no GDM
  - PG ≥7.8-10.3 mmol/L = further investigation with OGTT
  - PG ≥10.3 mmol/L = GDM
- 2 h, 75 g Oral Glucose Tolerance Test (OGTT): fasting
  - FPG ≥5.3 mmol/L
  - PG 1 h ≥10.6 mmol/L
  - PG 2 h ≥8.9 mmol/L
  - 2/3 of the above = GDM
  - 1/3 of the above = impaired glucose tolerance (IGT)

Management
- treat both GDM and IGT
- first line is management through diet modification and increased physical activity
- tight glycemic control optimal as in Type 1 and Type 2 DM
- monitoring and timing of delivery as for Type 1 and Type 2 DM
- stop insulin and diabetic diet postpartum
- follow-up with 2 h, 75 g OGTT 6 wk-6 mo postpartum

Risk Factors for GDM:
- Age >25
- Obesity
- Ethnicity (Aboriginal, Hispanic, Asian, African)
- FHx of DM
- Previous history of GDM
- Previous child with birthweight >4.0 kg
- Polycystic ovarian syndrome
- Current use of glucocorticoids
- Essential hypertension or pregnancy-related hypertension

Postprandial blood glucose values seem to be the most effective at determining the likelihood of macrosomia or other adverse pregnancy outcomes.
Prognosis
• most maternal and fetal complications are related to hyperglycemia and its effects

Long Term Maternal Complications
• Type 1 and Type 2 DM: risk of progressive retinopathy and nephropathy
• GDM: 50% risk of developing Type 2 DM in next 20 yr

Table 11. Complications of DM in Pregnancy

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Fetal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obstetric</strong></td>
<td><strong>Growth Abnormalities</strong></td>
</tr>
<tr>
<td>Hypertension/preeclampsia (especially if pre-existing nephropathy/proteinuria): insulin resistance is implicated in etiology of hypertension</td>
<td>Macroamia: maternal hyperglycemia leads to fetal hyperinsulinemia resulting in accelerated anabolism</td>
</tr>
<tr>
<td>Polyhydramnios: maternal hyperglycemia leads to fetal hyperglycemia, which leads to fetal polyuria (a major source of amniotic fluid)</td>
<td>Intrauterine growth restriction (IUGR): due to placental vascular insufficiency</td>
</tr>
<tr>
<td><strong>Diabetic Emergencies</strong></td>
<td><strong>Delayed Organ Maturity</strong></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Fetal lung immaturity: hyperglycemia interferes with surfactant synthesis (respiratory distress syndrome)</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td><strong>Congenital Anomalies (occur in DM1 and DM2, not in GDM)</strong></td>
</tr>
<tr>
<td>Diabetic coma</td>
<td>• 2-7x increased risk of cardiac (VSD), NTD, GU (cystic kidneys), GI (anal atresia), and MSK (sacral agenesis) anomalies due to hyperglycemia</td>
</tr>
<tr>
<td><strong>End-organ Involvement or Deterioration</strong></td>
<td>• Note: Pregnancies complicated by GDM do not manifest an increased risk of congenital anomalies because GDM develops after the critical period of organogenesis (in T1)</td>
</tr>
<tr>
<td>(occur in DM1 and DM2, not in GDM)</td>
<td><strong>Labour and Delivery</strong></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>• Preterm labour/prematurity: most commonly in patients with hypertension/preeclampsia. Preterm labour is associated with poor glycemic control but the exact mechanism is unknown</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>• Increased incidence of stillbirth</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>• Birth trauma: due to macrosomia, can lead to difficult vaginal delivery and shoulder dystocia</td>
</tr>
<tr>
<td>Pyelonephritis/UTI: glucosuria provides a culture medium for E. coli and other bacteria</td>
<td><strong>Neonatal</strong></td>
</tr>
<tr>
<td>Increased incidence of spontaneous abortion (in DM1 and DM2, not in GDM): related to pre-conception glycemic control</td>
<td>• Hypoglycemia: due to pancreatic hyperplasia and excess insulin secretion in the neonate</td>
</tr>
<tr>
<td>• Hyperbilirubinemia and jaundice: due to prematurity and polycythemia</td>
<td><strong>Hypertension in Pregnancy</strong></td>
</tr>
<tr>
<td>• Hyponatremia: exact pathophysiology not understood, may be related to functional hypoparathyroidism</td>
<td>• Polycythemia: hyperglycemia stimulates fetal erythropoietin production</td>
</tr>
</tbody>
</table>

Labour and Delivery
• Preterm labour/prematurity: most commonly in patients with hypertension/preeclampsia. Preterm labour is associated with poor glycemic control but the exact mechanism is unknown
• Increased incidence of stillbirth
• Birth trauma: due to macrosomia, can lead to difficult vaginal delivery and shoulder dystocia

Neonatal
• Hypoglycemia: due to pancreatic hyperplasia and excess insulin secretion in the neonate
• Hyperbilirubinemia and jaundice: due to prematurity and polycythemia
• Hypocalcemia: exact pathophysiology not understood, may be related to functional hypoparathyroidism
• Polycythemia: hyperglycemia stimulates fetal erythropoietin production

**Hypertension in Pregnancy**

• hypertensive disorders of pregnancy are classified as either preexisting or gestational hypertension

**PRE-EXISTING HYPERTENSION**

Definition
• HTN (>140/90) prior to 20 wk GA, persisting >7 wk postpartum
• essential hypertension is associated with an increased risk of gestational HTN, abruptio placenta, IUGR and intrauterine fetal demise (IUFD)

**GESTATIONAL HYPERTENSION**

Definition
• sBP >140 or dBP >90 developing after 20th wk GA in a woman known to be normotensive before pregnancy

Risk Factors
• maternal factors
  • primigravida (80-90% of gestational HTN)
  • first conception with a new partner
  • PMHx or FHx of gestational HTN
  • DM, chronic HTN, or renal insufficiency
  • Antiphospholipid syndrome
  • extremes of maternal age (<18 or >35 yr)
• fetal factors
  • IUGR or oligohydramnios, GTN, multiple gestation, fetal hydrops
  • previous stillbirth or intrauterine fetal demise
Clinical Evaluation of Hypertension in Pregnancy

- in general, clinical evaluation should include the mother and fetus
- evaluation of mother:
  - body weight
  - central nervous system
    - presence and severity of headache
    - visual disturbances – blurring, scotomata
    - tremulousness, irritability, somnolence
    - hyperreflexia
  - hematologic
    - bleeding, petechiae
  - hepatic
    - RUQ or epigastric pain
    - severe nausea and vomiting
  - renal
    - urine output and colour
    - non-dependent edema (i.e. hands and face)
- evaluation of fetus:
  - fetal movement
  - fetal heart rate tracing – NST
  - ultrasound for growth
  - biophysical profile
  - Doppler flow studies

Laboratory Evaluation of Gestational Hypertension

- hemoglobin, platelets, blood film
- PTT, INR, fibrinogen, D-dimer – especially if surgery or regional anesthetics are planned
- ALT, AST, LDH, bilirubin
- proteinuria, creatinine, uric acid
- 24 h urine collection for total protein and creatinine clearance

Complications

- maternal
  - liver and renal dysfunction
  - seizure
  - abruptio placentae
  - left ventricular failure/pulmonary edema
  - DIC (release of placental thromboplastin consumptive coagulopathy)
  - HELLP syndrome (see Table 12, OB19)
  - treat with FFP infusion or plasma exchange
  - hemorrhagic stroke (50% of deaths)
- fetal (2° to placental insufficiency)
  - IUGR, prematurity, abruptio placentae, IUFD

Management

- for both preexisting and gestational hypertension, labetalol 100-300 mg PO bid/tid, nifedipine, 30-50 mg PO daily or α-methyldopa 250-500 mg PO tid/qid
- no ACE inhibitors, diuretics or propanolol (teratogens)
- preexisting HTN and gestational HTN without any deterioration can be followed until 37 wk then decide to induce shortly thereafter

PREECLAMPSIA

Definition

- pre-existing or gestational hypertension with new onset proteinuria or adverse conditions

Risk Factors

- nulliparity
- preeclampsia in a previous pregnancy
- age >40 yr or <18 yr
- FHx of preeclampsia
- chronic HTN
- chronic renal disease
- antiphospholipid antibody syndrome or inherited thrombophilia
- vascular or connective tissue disease
- diabetes mellitus (pregestational and gestational)
- high BMI
- hydrops fetalis


- For BP measurement, Korotkoff phase V should be used to designate the dBP
- For preeclampsia prevention among low-risk women with low dietary calcium intake (<600 mg/d), oral calcium supplementation of at least 1 g/d is recommended
- For preeclampsia prevention among increased risk women, low-dose Aspirin® (75-100 mg/d) is recommended until delivery
- Umbilical artery Doppler velocimetry should be part of the antenatal/fetal surveillance in preeclampsia
- Initial antihypertensive therapy for severe hypertension (sBP >160 mmHg or dBP ≥110) should be with labetalol, nifedipine, or hydralazine
- Initial antihypertensive therapy for non-severe hypertension (sBP 140-159/90-109 mmHg) should be with methyladopa, β-blockers, or calcium channel blockers
- Antenatal corticosteroids for fetal lung maturation should be considered for all women with preeclampsia before 34 wk gestation
- In a planned vaginal delivery with an unfavourable cervix, cervical ripening should be used
- Oxycin 5 units IV or 10 units IM should be used as part of the management during the third stage of labour
- MgSO₄ is the recommended first-line treatment for eclampsia
- MgSO₄ is the recommended eclampsia prophylaxis in severe preeclampsia

Hypertension in Pregnancy

Adverse Maternal Conditions

- sBP >160 mmHg
- dBP >100 mmHg
- HELLP
- Cerebral haemorrhage
- Renal dysfunction: oliguria <500 mL/d
- Left ventricular failure, pulmonary edema
- Abruption, DIC

Symptoms:

- Abdominal pain, nausea, vomiting
- Headaches, visual problems
- SOB, chest pain
- Eclampsia: convulsions

Adverse Fetal Conditions

- Intrauterine growth restriction
- Oligohydramnios
- Absent/reversed umbilical artery end diastolic flow

Can result in:

- Fetal disability and/or death
• unexplained fetal growth restriction
• abruptio placentae
• there is a potential for further deterioration to severe preeclampsia as defined above (see Figure 3)
• the adverse conditions are many and include both maternal and fetal issues (see sidebar, OB15)

Management
• management will depend on GA, possible threat of seizures (check reflexes)
• if stable and no adverse factors, may admit and follow, ± decide to deliver as approaching 34-36 wk (must weigh risks of fetal prematurity vs. risks of developing severe preeclampsia/eclampsia)
• for severe preeclampsia, stabilize and deliver
• if severe preeclampsia, during labour, increase maternal monitoring: hourly input and output, urine dip q12h, hourly neurological vitals, and increase fetal monitoring (continuous FHR monitoring)
• antihypertensive therapy
  ▪ lowering BP decreases the risk of stroke
  ▪ hydralazine 5-10 mg IV bolus over 5 min q15-30min as necessary
  ▪ labetalol 20-50 mg IV q10min
  ▪ 2nd line: nifedipine 10-20 mg PO q20-60min
• seizure prevention
  ▪ MgSO₄
  ▪ postpartum management
  ▪ risk of seizure highest in first 24 h postpartum – continue MgSO₄ for 12-24 h after delivery
  ▪ vitals q1h
  ▪ consider HELLP syndrome in toxic patients
  ▪ most return to a normotensive BP within 2 wk

ECLAMPSIA

Definition
• the occurrence of one or more generalized convulsions and/or coma in the setting of preeclampsia and in the absence of other neurologic conditions

Epidemiology
• an eclamptic seizure occurs in approximately 0.5% of mildly preeclamptic women and 2-3% of severely preeclamptic women

Risk Factors
• same as risk factors for Preeclampsia, see above

Clinical Manifestations
• eclampsia is a clinical diagnosis
• typically tonic-clonic and lasting 60-75 s
• one of the signs of an impending seizure is hyperreflexia
• symptoms that may occur before the seizure include persistent frontal or occipital headache, blurred vision, photophobia, right upper quadrant or epigastric pain, and altered mental status
• in up to one third of cases, there is no proteinuria or blood pressure is less than 140/90 mmHg prior to the seizure
• in general, women with typical eclamptic seizures who do not have focal neurologic deficits or prolonged coma do not require diagnostic evaluation including imaging

Management
• ABCs
• roll patient into LLDP
• supplemental O₂ via face mask to treat hypoxemia due to hypoventilation during convulsive episode
• aggressive antihypertensive therapy for sustained diastolic pressures ≥105 mmHg or systolic blood pressures ≥160 mmHg with hydralazine or labetalol
• prevention of recurrent convulsions: to prevent further seizures and the possible complications of repeated seizure activity (e.g. rhabdomyolysis, metabolic acidosis, aspiration pneumonitis, etc.) MgSO₄ is now the drug of choice, with previously used agents including diazepam and phenytoin
• the definitive treatment of eclampsia is DELIVERY, irrespective of gestational age, to reduce the risk of maternal morbidity and mortality from complications of the disease
• mode of delivery is dependent on clinical situation and fetal-maternal condition

Preeclampsia Investigations

<table>
<thead>
<tr>
<th>CBC</th>
<th>LDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver enzymes</td>
<td>Albumin</td>
</tr>
<tr>
<td>INR and aPTT</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>Cr</td>
<td>Urine (dip ± 24 h collection)</td>
</tr>
</tbody>
</table>

HELLP Syndrome

<table>
<thead>
<tr>
<th>Hemolysis</th>
<th>Elevated Liver enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Platelets</td>
<td></td>
</tr>
</tbody>
</table>

Differential Diagnosis of Cause for Seizure in a Pregnant Woman

• Stroke
• Hypertensive disease (hypertensive encephalopathy, pheochromocytoma)
• Space-occupying lesion of the CNS
• Metabolic disorders (hypoglycemia, SIADH)
• Infection (meningitis, encephalitis)
• Idiopathic epilepsy
• Use of illicit drugs
• Cerebral vasculitis

Note
Eclampsia prior to 20 wk of gestation is rare and should raise the possibility of an underlying molar pregnancy or antiphospholipid syndrome.

MgSO₄ toxicity

<table>
<thead>
<tr>
<th>Flushing</th>
<th>Hyporeflexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somanolence</td>
<td>Respiratory and cardiac depression</td>
</tr>
<tr>
<td>Weakness</td>
<td>Note: Increased risk of toxicity with concurrent calcium channel blocker use or renal disease</td>
</tr>
</tbody>
</table>

Treatment:

• Stop MgSO₄
• Calcium gluconate 10% in 10 mL via IV
Nausea and Vomiting

Epidemiology
- affects 50-90% of pregnant women
- often limited to T1 but may persist

Management
- r/o other causes of N/V
- weigh frequently, assess level of hydration, test urine for ketones
- non-pharmacological:
  - avoid mixing fluids and solids, frequent small meals
  - stop prenatal vitamins (folic acid must continue until >12 wk)
  - increase sleep/rest
  - ginger (maximum 1000 mg/d)
  - acupuncture, acupressure
- pharmacological:
  - first line: Diclectin® (10 mg doxylamine succinate with vitamin B₆) 4 tablets PO daily to maximum of 8 tablets
  - if no improvement, try dimenhydrinate (50-100 mg q4-6h PO), followed by hydroxyzine, pyridoxine, phenothiazine, or metoclopramide
  - vitamin B₆ lollipops
  - if patient dehydrated, assess fluid replacement needs and resuscitate accordingly
- severe/refractory:
  - consider homecare with IV fluids and parenteral anti-emetics, hospitalization

Hyperemesis Gravidarum

Definition
- intractable nausea and vomiting, usually presents in T1 then diminishes; occasionally persists throughout pregnancy
- affects ~1% of pregnancies

Etiology
- multifactorial with hormonal, immunologic and psychologic components
- rapidly rising β-hCG ± estrogen levels may be implicated

Investigations
- r/o systemic causes: GI inflammation, pyelonephritis, thyrotoxicosis
- r/o obstetrical causes: multiple gestation, GTN, HELLP syndrome
- CBC, electrolytes, BUN, creatinine, LFTs, urinalysis
- ultrasound

Management
- thiamine supplementation may be indicated
- non-pharmacological: (see Nausea and Vomiting, above)
- pharmacological options
  - Diclectin® (see dosage Nausea and Vomiting, above)
  - Dimenhydrinate can be safely used as an adjunct to Diclectin® (1 suppository bid or 25 mg PO qid)
  - other adjuncts: hydroxyzine, pyridoxine, phenothiazine, metoclopramide
  - also consider: ondansetron or methylprednisolone
  - if severe: admit to hospital, NPO initially then small frequent meals, correct hypovolemia, electrolyte disturbance and ketosis, TPN (if very severe) to reverse catabolic state

Complications
- maternal
  - dehydration, electrolyte and acid-base disturbances
  - Mallory-Weiss tear
  - Wernicke's encephalopathy, if protracted course
  - death
- fetal: usually none, IUGR is 15x more common in women losing >5% of pre-pregnancy weight
Jaundice in Pregnancy

Epidemiology
- affects 1 in 1500 pregnancies

Etiology
- viral hepatitis (most common)
- unique to pregnancy (see Table 12)
- cholestatic jaundice of pregnancy
- HELLP syndrome
- hepatic rupture, hematoma and infarct
- AFLP
- hyperemesis gravidarum (rarely causes hepatic dysfunction)
- pre-existing conditions (see Gastroenterology, Liver/Biliary Tract, G28, G40)

<table>
<thead>
<tr>
<th>HELLP Syndrome</th>
<th>Cholestatic Jaundice of Pregnancy</th>
<th>Hepatic Infarct, Hematoma, and Rupture</th>
<th>Acute Fatty Liver of Pregnancy (AFLP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Hemolysis, elevated liver enzymes, low platelets Pathogenesis unknown</td>
<td>Clinical syndrome characterized by intense pruritus that precedes jaundice by 7-14 d Pathogenesis unknown, may be due to increased sensitivity to high levels of estrogen or abnormal progesterational steroids</td>
<td>Rare consequence of preeclampsia, typically occurring in T3 Vasospasm-induced hepatic infarction can lead to hematoma formation; hematoma can lead to rupture</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Affects 20% of women with severe preeclampsia Presents &gt;27 wk GA (11% sooner); up to 30% of cases present AFTER delivery and with no previous signs of hypertension</td>
<td>17-29 wk GA High incidence in Chile and Scandinavia; rare in Asian and African populations</td>
<td>1 in 7,000 deliveries 3rd trimester (28-40 wk GA) Maternal mortality as high as 75%; resolution of hepatic dysfunction with delivery or termination of pregnancy</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Epigastric, RUQ or chest pain, N/V, symptoms of preeclampsia (headache, blurred vision, thirst) ± jaundice Atypical presentations: asymptomatic reduction in platelet count, &quot;flu-like&quot; symptoms</td>
<td>Intense pruritus (usually, worst on palms and soles of feet) ± icterus (1-2 wk later) Steatorrhea unusual</td>
<td>Hemoperitoneum (paracentesis, U/S, CT, MRI showing ruptured liver) Acute nausea/vomiting, severe upper abdominal pain preceding jaundice Confusion Preeclampsia Pruritus Range in presentation: • Mild to fulminant</td>
</tr>
<tr>
<td>Investigations</td>
<td>AST (70-663 U/L), total bilirubin slightly increased, low platelet count (7-99), elevated LDH ± elevated D-dimers, tissue polypeptide antigen (TPA) and fibronectin, fragmented RBCs on smear Liver biopsy (rarely done)</td>
<td>ALT &lt;500 IU, ALP and GGT markedly elevated (to levels consistent with moderate to severe cholestasis)</td>
<td>Elevated PTT and low serum fibrinogen AST &gt; ALT Hypoglycemia Preeclampsia and HELLP features Liver biopsy to establish diagnosis • If liver biopsy not possible, CT most useful</td>
</tr>
<tr>
<td>Management</td>
<td>Supportive care (in ICU) and prompt delivery</td>
<td>Ursodeoxycholic acid (20-25 mg/kg/d) Pruritus: cholestyramine Prophylactic vitamin K before delivery Consider induction of labour (see Induction of Labour, OB36)</td>
<td>Aggressive: rapid delivery and trauma surgery to repair liver</td>
</tr>
<tr>
<td>Notes</td>
<td>Complications: sepsis, multi-system organ failure, hepatic failure, DIC, death (rare)</td>
<td>Selenium may be protective against cholestasis Strong familial predisposition Correlates with oral contraceptive sensitivity</td>
<td>Complications include death (mother and fetus) if untreated</td>
</tr>
</tbody>
</table>
Urinary Tract Infection (UTI)

Etiology
- increased urinary stasis from mechanical and hormonal (progesterone) factors
- organisms include GBS as well as those that occur in non-pregnant women

Epidemiology
- most common medical complication of pregnancy
- asymptomatic bacteriuria in 2-7% of pregnant women, more frequently in multiparous women
- note: asymptomatic bacteriuria should be treated in pregnancy due to increased risk of pyelonephritis.

Clinical Features
- may be asymptomatic
- dysuria, urgency, and frequency in cystitis
- fever, flank pain, costovertebral angle tenderness in pyelonephritis

Investigations
- urinalysis, urine C&S
- cystoscopy, and renal function tests in recurrent infections

Management
- uncomplicated UTI
  - first line: amoxicillin (250-500 mg PO q8h x 7 d)
  - alternatives: nitrofurantoin (100 mg PO bid x 7 d)
  - follow with monthly urine cultures
- pyelonephritis
  - hospitalization and IV antibiotics

Prognosis
- complications if untreated: acute cystitis, pyelonephritis, and possible PPROM
- recurrence is common

Infections During Pregnancy

Table 13. Infections During Pregnancy

<table>
<thead>
<tr>
<th>Infection</th>
<th>Agent</th>
<th>Source of Transmission</th>
<th>Greatest Transmission Risk to Fetus</th>
<th>Effects on Fetus</th>
<th>Effects on Mother</th>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicken Pox</td>
<td>Varicella zoster virus</td>
<td>To mom: direct, respiratory To baby: transplacental</td>
<td>13-30 wk GA, and 5 d pre- to 2 d post-delivery</td>
<td>Congenital varicella syndrome (limb aplasia, chorioretinitis, cataracts, cutaneous scars, cortical atrophy, IUGR, hydrops), preterm labour (prematurity)</td>
<td>Fever, malaise, vesicular pruritic lesions</td>
<td>Clinical, ± vesicle fluid culture, ± serology</td>
<td>VZIG for mother if exposed, decreases congenital varicella syndrome Note: Do not administer vaccine during pregnancy (live attenuated)</td>
</tr>
<tr>
<td>*CMV</td>
<td>DNA virus</td>
<td>To mom: blood/organ transfusion, sexual contact To baby: transplacental, during delivery, breast milk</td>
<td>T1-T3</td>
<td>5-10% develop CNS involvement (mental retardation, cerebral calcification, hydrocephalus, microcephaly, deafness, chorioretinitis)</td>
<td>Asymptomatic or flu-like</td>
<td>Serologic screen; isolate virus from urine or secretion culture</td>
<td>No specific treatment; maintain good hygiene and avoid high risk situations</td>
</tr>
<tr>
<td>Erythema Infectiosum (Fifth Disease)</td>
<td>Parovirus B19</td>
<td>To mom: respiratory, infected blood products To baby: transplacental</td>
<td>10-20 wk GA</td>
<td>Spontaneous abortion (SA), stillbirth, hydrops in utero</td>
<td>Flu-like, rash, arthritis; often asymptomatic</td>
<td>Serology, viral PCR, maternal AFP, if IgM present, follow fetus with U/S for hydrops</td>
<td>If hydrops occurs, consider fetal transfusion</td>
</tr>
</tbody>
</table>
### Table 13. Infections During Pregnancy (continued)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Agent</th>
<th>Source of Transmission</th>
<th>Greatest Transmission Risk to Fetus</th>
<th>Effects on Fetus</th>
<th>Effects on Mother</th>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>DNA virus</td>
<td>To mom: blood, saliva, semen, vaginal secretions To baby: transplacental, breast milk</td>
<td>T3 10% vertical transmission if asymptomatic HBsAg +ve; 85-90% if HBsAg and HBeAg +ve</td>
<td>Prematurity, low birth weight, neonatal death</td>
<td></td>
<td>Serologic screening for all pregnancies</td>
<td>Rx neonate with HBIG and vaccine (at birth, 1, 6 mo); 90% effective</td>
</tr>
<tr>
<td>*Herpes Simplex Virus</td>
<td>DNA virus</td>
<td>To mom: intimate mucocutaneous contact To baby: transplacental, during delivery</td>
<td>Delivery (if genital lesions present); less commonly in uterus</td>
<td>Disseminated herpes (20%); CNS sequelae (35%); self-limited infection</td>
<td></td>
<td>Clinical diagnosis</td>
<td>Acyclovir for symptomatic women, suppressive therapy at 36 wk controversial C/S if active genital lesions, even if remote from vulva</td>
</tr>
<tr>
<td>HIV</td>
<td>RNA retrovirus</td>
<td>To mom: blood, semen, vaginal secretions To baby: in utero, during delivery, breast milk</td>
<td>1/3 in utero, 1/3 at delivery, 1/3 breastfeeding</td>
<td>IUGR, preterm labour, premature rupture of membranes</td>
<td></td>
<td>Serology, viral PCR</td>
<td>All pregnant women are offered screening</td>
</tr>
<tr>
<td>*Rubella</td>
<td>ssRNA togavirus</td>
<td>To mom: respiratory droplets (highly contagious) To baby: transplacental</td>
<td>T1</td>
<td>SA or congenital rubella syndrome (hearing loss, cataracts, CV lesions, MR, IUGR, hepatitis, CNS defects, osseous changes)</td>
<td></td>
<td>Serologic testing; all pregnant women screened (immune if titre &gt;1:16); infection if IgM present or &gt;4x increase in IgG</td>
<td>No specific treatment; offer vaccine following pregnancy</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Spirochete</td>
<td>To mom: sexual contact To baby: transplacental</td>
<td>T1-T3</td>
<td>Risk of PTL, multisystem involvement, fetal death</td>
<td></td>
<td>VDRL screening for all pregnancies; if positive, requires confirmatory testing</td>
<td>Pen G 2.4 M U IM 1 dose if early syphilis 3 doses if late syphilis, monitor VDRL, monthly if Pen G allergic; Clindamycin 500mg IV q8h</td>
</tr>
<tr>
<td>*Toxoplasmosis</td>
<td>Protozoa (Toxoplasma gondii)</td>
<td>To mom: raw meat, unpasteurized goat’s milk, cat feces/urine To baby: transplacental</td>
<td>T3 (but most severe if infected in T1); only concern if primary infection during pregnancy</td>
<td>Congenital toxoplasmosis (chorioretinitis, hydrocephaly, intracranial calcification, MR, microcephaly)</td>
<td>Majority subclinical; may have flu-like symptoms</td>
<td>IgM and IgG serology; PCR of amniotic fluid</td>
<td>Self-limiting in mother; spiramycin decreases fetal morbidity but not rate of transmission</td>
</tr>
</tbody>
</table>

* Indicates TORCH infection

### Venous Thromboembolism (VTE)

**Epidemiology**
- incidence 0.5-3/1,000 pregnancies occurring with approximately equal frequency in all three trimesters and postpartum

**Risk Factors**
- previous VTE, age >35, obesity, infection, bedrest/immobility, shock/dehydration, thrombophilias (see Hematology, H31)
Table 14. Risk Factors for VTE Specific to Pregnancy

<table>
<thead>
<tr>
<th>Hypercoagulability</th>
<th>Stasis</th>
<th>Endothelial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased factors:</td>
<td>Increased resistance to activated protein C</td>
<td>Vascular damage at delivery (C/S or SVD)</td>
</tr>
<tr>
<td>II, V, VII, VIII, IX, X, XII, fibrinogen</td>
<td>Antithrombin can be normal or reduced</td>
<td>Uterine instrumentation</td>
</tr>
<tr>
<td>Increased platelet aggregation</td>
<td>Increased venous tone</td>
<td>Peripartum pelvic surgery</td>
</tr>
<tr>
<td>Decreased protein S, tPA, factors XI, XIII</td>
<td>Decreased venous flow in lower extremity by T3</td>
<td></td>
</tr>
<tr>
<td>Antithrombin can be normal or reduced</td>
<td>Uterus is mechanical impediment to venous return</td>
<td></td>
</tr>
<tr>
<td>Increased resistance to activated protein C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased venous tone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased venous flow in lower extremity by T3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterus is mechanical impediment to venous return</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% decrease in venous flow in lower extremity by T3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features
- most DVTs occur in the iliofemoral or calf veins with a predilection for the left leg
- signs of a pulmonary embolism are non-specific (as in non-pregnant women)
- unexplained spontaneous fetal loss

Investigations
- duplex venous Doppler sonography for DVT
- CXR and V/Q scan or Spiral CT for PE

Management
- before initiating treatment, obtain a baseline CBC, including platelets, and aPTT
- warfarin is contraindicated during pregnancy due to its potential teratogenic effects
- unfractionated heparin
  - bolus of 5,000 IU followed by an infusion of ~30,000 IU/24h
  - measure aPTT 6 h after the bolus
  - maintain aPTT at a therapeutic level (1.5-2 x normal)
  - repeat q24h once therapeutic
  - heparin-induced thrombocytopenia (HIT) uncommon (3%) but serious complication
  - LMWH can also be used in pregnancy
- compression stockings
- poor evidence to support a recommendation for or against avoidance of prolonged sitting
- VTE prophylaxis:
  - women on long-term anticoagulation: full therapeutic anticoagulation throughout pregnancy and for 6-12 wk postpartum
  - women with a non-active PMHx of VTE: unfractionated heparin regimens suggested
- routine VTE prophylaxis:
  - insufficient evidence in pregnancy to recommend routine use of LMWH
  - current prophylaxis regimens for acquired thrombophilias (e.g. APS syndrome) include low dose Aspirin® in conjunction with prophylactic heparin

Bleeding in Pregnancy

First and Second Trimester Bleeding

Approach to the Patient with Bleeding in T1/T2
- history
  - risk factors for ectopic pregnancy (previous ectopic pregnancies, history of STI/PID, IUD use, previous pelvic surgery, smoking)
  - previous spontaneous abortion
  - recent trauma
  - characteristics of the bleeding (including any tissue passed)
  - characteristics of the pain (cramping pain suggests SA)
  - history of coagulopathy
  - gynecological/obstetric history
  - dizziness (significant blood loss, may be associated with ruptured ectopic)
  - fever (may be associated with septic abortion)
- physical
  - vitals (including orthostatic changes)
  - abdomen (SFH, tenderness, presence of contractions)
  - perineum (signs of trauma, genital lesions)
  - speculum exam (cervical os open or closed, presence of active bleeding/clots/tissue)
  - pelvic exam (uterine size, adnexal mass, uterine/adnexal tenderness)
Investigations
- β-hCG (lower than expected for GA in spontaneous abortion (SA), ectopic pregnancy)
- U/S (confirm intrauterine pregnancy and fetal viability)
- CBC
- group and screen

Treatment
- IV resuscitation for hemorrhagic shock
- treat the underlying cause

Spontaneous Abortions
- see Termination of Pregnancy, OB11 for therapeutic abortions

Table 15. Classifications of Spontaneous Abortions

<table>
<thead>
<tr>
<th>Type</th>
<th>History</th>
<th>Clinical</th>
<th>Management (± Rhogam®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threatened</td>
<td>Vaginal bleeding ± cramping</td>
<td>Cervix closed and soft U/S shows viable fetus</td>
<td>Watch and wait &lt;5% go on to abort</td>
</tr>
</tbody>
</table>
| Inevitable   | Increasing bleeding and cramps ± rupture of membranes | Cervix closed until products start to expel, then external os opens U/S variable but usually nonviable fetus | a) Watch and wait 
b) Misoprostol 400-800 µg PO/PV 
c) D&C ± oxytocin |
| Incomplete   | Extremely heavy bleeding and cramps ± passage of tissue noticed | Cervix open U/S products of conception | a) Watch and wait 
b) Misoprostol 400-800 µg PO/PV 
c) D&C ± oxytocin |
| Complete     | Bleeding and complete passage of sac and placenta | Cervix open U/S no products of conception | No D&C – expectant management |
| Missed       | No bleeding (fetal death in uterus)          | Cervix closed U/S may show SGA, no fetal heart activity; nonviable fetus | a) Watch and wait 
b) Misoprostol 400-800 µg PO/PV 
c) D&C ± oxytocin |
| Recurrent    | 3+ consecutive spontaneous abortions         |                                      | Evaluate mechanical, genetic, environmental and other risk factors |
| Septic       | Contents of uterus infected – infrequent     |                                      | D&C IV broad spectrum antibiotics |

Ectopic Pregnancy

Definition
- embryo implants outside of the endometrial cavity

Epidemiology
- 1/100 pregnancies
- fourth leading cause of maternal mortality, leading cause of death in first trimester
- increase in incidence over the last 3 decades
- three commonest locations for ectopic pregnancy: ampullary (70%), isthmic (12%), fimbrial (11%)

Etiology
- 50% due to damage of fallopian tube cilia following PID
- intrinsic abnormality of the fertilized ovum
- conception late in cycle
- transmigration of fertilized ovum to contralateral tube

Clinical Features of Ectopic Pregnancy

**VFs and 15**
- Temperature >38°C (20%)
- Tenderness: abdominal (90%) ± rebound (45%)
- Tenderness on bimanual examination, cervical motion tenderness
- Tissue: palpable adnexal mass (50%) (half have contralateral mass due to lutein cyst)
- Signs of pregnancy (e.g. Chadwick’s sign, Hegar’s sign)

More than half of patients with ectopic pregnancy have no risk factors.
**Figure 3. Sites of ectopic pregnancy implantation**

Ampullary (70%) > isthmal (12%) > fimbrial (11%) > ovarian (3%) > interstitial (2%) > abdominal (1)

**Risk Factors**
- previous ectopic pregnancy
- gynecologic:
  - IUD use – increased risk of ectopic if pregnancy occurs
  - history of PID (especially infection with C. trachomatis), salpingitis
  - infertility
  - clomiphene citrate (for induction of ovulation)
- previous procedures:
  - any surgery on fallopian tube (for previous ectopic, tubal ligation, etc.)
  - abdominal surgery for ruptured appendix, etc.
  - IVF pregnancies following ovulation induction (7% ectopic rate)
- smoking
- structural:
  - uterine leiomyomas
  - adhesions
  - abnormal uterine anatomy (e.g. T-shaped uterus)

**Investigations**
- serial β-hCG levels; normal doubling time with intrauterine pregnancy is 1.6-2.4 d in early pregnancy
  - rise of <20% of β-hCG is 100% predictive of a nonviable pregnancy
  - prolonged doubling time, plateau or decreasing levels before 8 wk implies nonviable gestation but does not provide information on location of implantation
  - 85% of ectopic pregnancies demonstrate abnormal β-HCG doubling
- ultrasound
  - U/S is only definitive if fetal cardiac activity is detected in the tube or uterus
  - intrauterine sac should be visible when serum β-hCG is
    - >1,500 mIU/mL (transvaginal)
    - >6,000 mIU/mL or 6 wk GA (transabdominal)
  - specific finding on transvaginal U/S is a tubal ring
- laparoscopy (for definitive diagnosis)

**Treatment**
- goals of treatment: conservative (preserve tube if possible), maintain hemodynamic stability
- surgical (laparoscopy)
  - linear salpingostomy if tube salvageable
  - salpingectomy if tube damaged or ectopic is ipsilateral recurrence
- 15% risk of persistent trophoblast; must monitor β-hCG titre weekly until they reach non-detectable levels
- consider Rhogam® if Rh negative
- may require laparotomy if patient is unstable, extensive abdominal surgical history, etc.
• medical = methotrexate (for indications see Figure 4)
  • use 50 mg/m² body surface area, given in a single IM dose
  • this is 1/5 to 1/6 chemotherapy dose, therefore minimal side effects (reversible hepatic
dysfunction, diarrhea, gastritis, dermatitis)
  • follow β-hCG levels weekly until β-hCG is non-detectable
  • plateau or rising levels suggest persisting trophoblastic tissue (requires further treatment)
  • 82-95% success rate up to 25% will require a second dose
  • tubal patency following methotrexate treatment approaches 80%

Prognosis
• 9% of maternal deaths during pregnancy
• 40-60% of patients will become pregnant again after surgery
• 10-20% will have subsequent ectopic pregnancy

Table 16. Comparison of Placenta Previa versus Abruptio Placentae

<table>
<thead>
<tr>
<th>Placenta Previa</th>
<th>Abruptio Placentae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Abnormal location of the placenta near, partially or completely over the internal cervical os</td>
</tr>
<tr>
<td>Premature separation of a normally implanted placenta after 20 wk GA</td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
<tr>
<td>Epidemiology</td>
<td>0.5-0.8% of all pregnancies</td>
</tr>
<tr>
<td>1-2% of all pregnancies</td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td>History of placenta previa (4-8% recurrence risk)</td>
</tr>
<tr>
<td>• Multiparity</td>
<td></td>
</tr>
<tr>
<td>• Increased maternal age</td>
<td></td>
</tr>
<tr>
<td>• Multiple gestation</td>
<td></td>
</tr>
<tr>
<td>• Uterine tumour (e.g. fibroids) or other uterine anomalies</td>
<td></td>
</tr>
<tr>
<td>• Uterine scar due to previous abortion, CS, D&amp;C, myomectomy</td>
<td></td>
</tr>
<tr>
<td>• Previous abruption (recurrence rate 5-16%)</td>
<td></td>
</tr>
<tr>
<td>• Maternal hypertension (chronic or gestational hypertension in 50% of abruptions) or vascular disease</td>
<td></td>
</tr>
<tr>
<td>• Cigarette smoking (&gt; 1 pack/d), excessive alcohol consumption, cocaine</td>
<td></td>
</tr>
<tr>
<td>• Multiparity and/or maternal age &gt; 35</td>
<td></td>
</tr>
<tr>
<td>• PPROM</td>
<td></td>
</tr>
<tr>
<td>• Rapid decompression of a distended uterus (polyhydramnios, multiple gestation)</td>
<td></td>
</tr>
<tr>
<td>• Uterine anomaly, fibroids</td>
<td></td>
</tr>
<tr>
<td>• Trauma (e.g. motor vehicle collision, maternal battery)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bleeding</th>
<th>PAINLESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placenta Accreta</td>
<td>AT myometrium (most common)</td>
</tr>
<tr>
<td>Placenta Previa</td>
<td>INTO myometrium</td>
</tr>
<tr>
<td>Placenta Percreta</td>
<td>PASSES through myometrium</td>
</tr>
</tbody>
</table>

Antepartum Hemorrhage

Definition
• vaginal bleeding from 20 wk to term

Differential Diagnosis
• bloody show (shedding of cervical mucous plug) – most common etiology in T3
• placenta previa
• abruptio placenta – most common pathological etiology in T3
• vasa previa
• cervical lesion (cervicitis, polyp, ectropion, cervical cancer)
• uterine rupture
• other: bleeding from bowel or bladder, placenta accreta, abnormal coagulation

Figure 4. Algorithm for suspected ectopic pregnancy
**Placenta Previa**

**Definition**
- placenta implanted in the lower segment of the uterus, presenting ahead of the leading pole of the fetus
- the distance of the placental edge from the internal os is described in "millimeters away" from the internal os or "millimeters of overlap" over the internal os.
- greater than 20 millimeters of overlap over the internal os in the third trimester of pregnancy is highly predictive of the need for a C section.
- any degree of overlap after 35 wk is an indication for a C section

**Clinical Features**
- PAINLESS bright red vaginal bleeding (recurrent), may be minimized and cease spontaneously, but can become catastrophic
- mean onset of bleeding is 30 wk GA, but onset depends on degree of previa
- **physical exam**
  - uterus soft and non-tender
  - presenting fetal part high or displaced
  - FHR usually normal
  - shock/anemia correspond to degree of apparent blood loss
- **complications**
  - fetal
    - perinatal mortality low but still higher than with a normal pregnancy
    - prematurity (bleeding often dictates early C/S)
    - intrauterine hypoxia (acute or IUGR)
    - fetal malpresentation
    - PPROM
    - risk of fetal blood loss from placenta, especially if incised during C/S
  - maternal
    - <1% maternal mortality
    - hemorrhage and hypovolemic shock, anemia, acute renal failure, pituitary necrosis (Sheehan syndrome)
    - placenta accreta – especially if previous uterine surgery, anterior placenta previa
    - hysterectomy

**Investigations**
- transvaginal U/S is more accurate than transabdominal U/S at diagnosing placenta previa at any gestational age
- if the placenta lies between 20 mm of overlap and 20 mm away from the internal os after 26 wk regular transvaginal ultrasounds should be repeated at regular intervals – continued change in the placental location is likely.

**Management**
- goal: keep pregnancy intrauterine until the risk of delivery < risk of continuing pregnancy
- stabilize and monitor
  - maternal stabilization: large bore IV with hydration, O2 for hypotensive patients
  - maternal monitoring: vitals, urine output, blood loss, bloodwork (hematocrit, CBC, INR/PTT, platelets, fibrinogen, FDP, type and cross match)
  - electronic fetal monitoring
  - U/S assessment: when fetal and maternal condition permit, determine fetal viability, gestational age and placental status/position
- Rhogam® if mother is Rh negative
  - Kleihauer-Betke test to determine extent of fetomaternal transfusion so that appropriate dose of Rhogam® can be given
- **GA <37 wk and minimal bleeding:** expectant management
  - admit to hospital
  - limited physical activity, no douches, enemas, or sexual intercourse
  - consider corticosteroids for fetal lung maturity
  - delivery when fetus is mature or hemorrhage dictates
- **GA ≥37 wk, profuse bleeding or L/S ratio is >2:1:** deliver by C/S
Abruptio Placentae

Clinical Features

- classification
  - total (fetal death inevitable) vs. partial
  - external/revealed/apparent: blood dissects downward toward cervix
  - internal/concealed (20%): blood dissects upward toward fetus
  - most are mixed

- presentation
  - PAINFUL (80%) vaginal bleeding (bleeding not always present if abruption is concealed), uterine tenderness, uterine contractious
  - pain: sudden onset, constant, localized to lower back and uterus
  - shock/anemia out of proportion to apparent blood loss
  - ± fetal distress, fetal demise (15% present with demise), bloody amniotic fluid (fetal presentation typically normal)
  - ± coagulopathy

Complications

- fetal complications: perinatal mortality 25-60%, prematurity, intrauterine hypoxia
- maternal complications: <1% maternal mortality, DIC (in 20% of abruptions), acute renal failure, anemia, hemorrhagic shock, pituitary necrosis (Sheehan syndrome), amniotic fluid embolus

Investigations

- clinical diagnosis, U/S not sensitive for diagnosing abruption (sensitivity = 15%)

Management

- maternal stabilization: large bore IV with hydration; O2 for hypotensive patients
- maternal monitoring: vitals, urine output, blood loss, bloodwork (hematocrit, CBC, PTT/PTT, platelets, fibrinogen, FDP, type and cross match)
- EFM
- blood products on hand (red cells, platelets, cryoprecipitate) because of DIC risk
- Rhogam® if Rh negative
  - Kleihauer-Betke test may confirm abruption
- mild abruption:
  - GA <37 wk: use serial Hct to assess concealed bleeding, deliver when fetus is mature or when hemorrhage dictates
  - GA ≥37 wk: stabilize and deliver
- moderate to severe abruption:
  - hydrate and restore blood loss and correct coagulation defect if present
  - vaginal delivery if no contraindication and no evidence of fetal or maternal distress OR fetal demise
  - C/S if live fetus and fetal or maternal distress develops with fluid/blood replacement, labour fails to progress or if vaginal delivery otherwise contraindicated

Vasa Previa

Definition

- unprotected fetal vessels pass over the cervical os; associated with velamentous insertion of cord into membranes of placenta or succenturiate (accessory) lobe

Epidemiology

- 1 in 5,000 deliveries – higher in twin pregnancies

Clinical Features

- PAINLESS vaginal bleeding and fetal distress (tachy- to bradyarrhythmia)
- 50% perinatal mortality, increasing to 75% if membranes rupture (most infants die of exsanguination)

Investigations

- Apt test (NaOH mixed with the blood) can be done immediately to determine if the source of bleeding is fetal (supernatant turns pink) or maternal (supernatant turns yellow)
- Wright stain on blood smear and look for nucleated red blood cells (in cord, not maternal blood)

Management

- emergency C/S (since bleeding is from fetus, a small amount of blood loss can have catastrophic consequences)
Multiple Gestation

Epidemiology
- incidence of twins is 1/80 and triplets 1/6,400 in North America
- 2/3 of twins are dizygotic (fraternal)
  - risk factors for dizygotic twins: IVF, increased maternal age, newly discontinued OCP, ethnicity (e.g. certain African regions)
- monzygous twinning occurs at a constant rate worldwide (1/250)
- determine zygosity by number of placentas, thickness of membranes, sex, blood type

Clinical Features

Table 17. Complications Associated with Multiple Gestation

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Utero-placental</th>
<th>Fetal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemesis gravidanum</td>
<td>Increased PROM/PTL</td>
<td>Prematurity*</td>
</tr>
<tr>
<td>GDM</td>
<td>Polyhydrannios</td>
<td></td>
</tr>
<tr>
<td>Gestational HTN</td>
<td>Placenta previa</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>Placental abruption</td>
<td></td>
</tr>
<tr>
<td>Increased physiological stress on all systems</td>
<td>PPH (uterine atony)</td>
<td>Malpresentation</td>
</tr>
<tr>
<td>Increased compressive symptoms</td>
<td>Unbilical cord prolapse</td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>C/S</td>
<td>Cord anomalies</td>
<td>Increased perinatal morbidity and mortality</td>
</tr>
<tr>
<td></td>
<td>(velamentous insertion, 2 vessel cord)</td>
<td>Twin-twin transfusion</td>
</tr>
</tbody>
</table>

*Most common cause of perinatal mortality in multiple gestation

Management
- U/S determination of chorionicity must be done within first trimester (ideally 8-12 wk GA)
- increased antenatal surveillance
  - serial U/S q2-3wk from 28 wk GA to assess growth (uncomplicated diamniotic dichorionitic)
  - increased frequency of ultrasounds in monochorionic diamniotic and monochorionic monoamniotic twins
  - Doppler flow studies weekly if discordant fetal growth (>30%)
  - BPP as needed
- may attempt vaginal delivery if twin A presents as vertex, otherwise C/S (40-50% of all twin deliveries, 15% of cases have twin A delivered vaginally and twin B delivered by C/S)
- mode of delivery depends on fetal weight, GA, presentation

The Ps of Multiple Gestation
Complications
- Increased rates of: Puking, Pallor (anemia), Preclampsia/PIH
- Pressure (compressive symptoms)
- PTL, PROM/PROM
- Polyhydrannios
- Placenta previa/abruptio
- PPH/APH
- Prolonged labour
- Cord Prolapse
- Prematurity
- Mal Presentation
- Perinatal morbidity and mortality
- Parental distress
- Postpartum depression

Figure 6. Classification of twin pregnancies
*Indicates time of cleavage
**Twin-Twin Transfusion Syndrome**

**Epidemiology**
- 10% of monochorionic twins
- concern if >30% discordance in estimated fetal weight

**Etiology**
- arterial blood from donor twin passes through placenta into vein of recipient twin

**Clinical Features**
- donor twin: IUGR, hypovolemia, hypotension, anemia, oligohydramnios
- recipient twin: hypervolemia, hypertension, CHF, polycythemia, edema, polyhydramnios, kernicterus in neonatal period

**Investigations**
- detected by U/S screening, Doppler flow analysis

**Management**
- therapeutic serial amniocentesis to decompress polyhydramnios of recipient twin and decrease pressure in cavity and on placenta
- intrauterine blood transfusion to donor twin if necessary
- laparoscopic occlusion of placental vessels

---

**Growth Discrepancies**

**Intrauterine Growth Restriction**

**Definition**
- infant weight <10th percentile for GA or <2,500 g

**Etiology/Risk Factors**
- maternal causes
  - malnutrition, smoking, drug abuse, alcoholism, cyanotic heart disease, Type 1 DM, SLE, pulmonary insufficiency, previous IUGR
  - maternal-fetal
    - any disease causing placental insufficiency
    - includes gestational HTN, chronic HTN, chronic renal insufficiency, gross placental morphological abnormalities (infarction, hemangiomas)
- fetal causes:
  - TORCH infections, multiple gestation, congenital anomalies

**Clinical Features**
- symmetric/Type I (20%): occurs early in pregnancy
  - head:abdomen ratio may be normal (>1 up to 32 wk; =1 at 32-34 wk; <1 after 34 wk GA)
  - usually associated with congenital anomalies or TORCH infections
- asymmetric/Type II (80%): occurs late in pregnancy
  - brain is spared, therefore head:abdomen ratio increased
  - usually associated with placental insufficiency
  - more favorable prognosis than Type I
  - complications
    - prone to meconium aspiration, asphyxia, polycythemia, hypoglycemia, and mental retardation
    - greater risk of perinatal morbidity and mortality

**Investigations**
- SFH measurements at every antepartum visit
- if mother at high risk or SFH lags >2 cm behind GA:
  - anatomy U/S for BPD, head and abdominal circumference, femur length and fetal weight, AFV (decrease associated with IUGR)
  - ± BPP
  - Doppler analysis of umbilical cord blood flow

**Management**
- prevention via risk modification prior to pregnancy is ideal
- modify controllable factors: smoking, alcohol, nutrition and treat maternal illness
- bed rest in LLDP
- serial BPP (monitor fetal growth) and determine cause of IUGR, if possible
- delivery when extrauterine existence is less dangerous than continued intrauterine existence (abnormal function tests, absent growth, severe oligohydramnios) especially if GA >34 wk
- liberal use of C/S since IUGR fetus withstands labour poorly

---

**TORCH**
- Toxoplasmosis
- Others: e.g. syphilis
- Rubella
- CMV
- HSV
- See Table 13, OB20

---

**Differential Diagnosis of Incorrect Uterine Size for Dates**
- Inaccurate dates
- Maternal: diabetes mellitus
- Maternal-fetal: polyhydramnios, oligohydramnios
- Fetal: abnormal karyotype, IUGR, macrosomia, fetal anomaly, abnormal lie, multiple gestation

---

**Monitoring Fetal Growth with U/S**
Done biweekly to show growth beyond the margin of error.
### Macrosomia

**Definition**
- infant weight >90th percentile for a particular GA or >4,000 g

**Etiology/Risk Factors**
- maternal obesity, GDM, past history of macrosomic infant, prolonged gestation, multiparity

**Clinical Features**
- increased risk of perinatal mortality
- CPD and birth injuries (shoulder dystocia, fetal bone fracture) more common
- complications of DM in labour (see Medical Conditions in Pregnancy, OB13)

**Investigations**
- serial SFH
- further investigations if mother at high risk or SFH >2 cm ahead of GA
- U/S predictors
  - polyhydramnios
  - third trimester AC >1.5 cm/wk
  - HC/AC ratio <10th percentile
  - FL/AC ratio <20th percentile

**Management**
- prophylactic C/S is a reasonable option where EFW >5,000 g in non-diabetic woman and EFW >4,500 g in diabetic woman
- no evidence that prophylactic C/S improves outcomes
- early induction of labour is not recommended for non-diabetic mothers
- risks and benefits of early induction (risk of C/S vs. risk of dystocia) must be weighed in diabetic mothers, as current research is unclear

### Polyhydramnios/Oligohydramnios

**Table 18. Polyhydramnios and Oligohydramnios**

<table>
<thead>
<tr>
<th>Polyhydramnios</th>
<th>Oligohydramnios</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>AFI &gt; 25 cm</td>
</tr>
<tr>
<td>U/S: single deepest pocket &gt;8 cm</td>
<td>AFI &lt; 5 cm</td>
</tr>
<tr>
<td>U/S: single deepest pocket ≤2 cm</td>
<td></td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Idiopathic most common</td>
</tr>
<tr>
<td>Maternal:</td>
<td>Type 1 DM: abnormalities of transchorionic flow</td>
</tr>
<tr>
<td>Maternal-fetal:</td>
<td>Chorioangiomas</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td></td>
</tr>
<tr>
<td>Fetal hydrops (increased erythroblastosis)</td>
<td></td>
</tr>
<tr>
<td>Fetal:</td>
<td>Chromosomal anomaly (up to 2/3 of fetuses have severe polyhydramnios)</td>
</tr>
<tr>
<td>Respiratory: cystic adenomatoid malformed lung</td>
<td></td>
</tr>
<tr>
<td>CNS: anencephaly, hydrocephalus, meningocele</td>
<td></td>
</tr>
<tr>
<td>GI: tracheoesophageal fistula, duodenal atresia, facial clefts (interfer with swallowing)</td>
<td></td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Occur in 0.2 to 1.6% of all pregnancies</td>
</tr>
<tr>
<td><strong>Clinical Features and Complications</strong></td>
<td>Uterus large for dates, difficulty palpating fetal parts and hearing FHR</td>
</tr>
<tr>
<td>Maternal complications:</td>
<td>Pressure symptoms from overstretched uterus</td>
</tr>
<tr>
<td>(dyspnea, edema, hydrenephrosis)</td>
<td></td>
</tr>
<tr>
<td>Obstetrical complications:</td>
<td>Cord prolapse, placental abruption, malpresentation, preterm labour, uterine dysfunction and PPH</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Occur in ~4.5% of all pregnancies</td>
</tr>
<tr>
<td>Severe form in &lt;0.7%</td>
<td></td>
</tr>
<tr>
<td>Common in pregnancies &gt;41 wk (~12%)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Features and Complications</strong></td>
<td>Uterus small for dates</td>
</tr>
<tr>
<td>Fetal complications:</td>
<td>15-25% have fetal anomalies</td>
</tr>
<tr>
<td>Amniotic fluid bands (T1) can lead to Potter’s facies, limb deformities, abdominal wall defects</td>
<td></td>
</tr>
<tr>
<td>Obstetrical complications:</td>
<td>Cord compression</td>
</tr>
<tr>
<td>Increased risk of adverse fetal outcomes</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypoplasia (late-onset)</td>
<td></td>
</tr>
<tr>
<td>Marker for infants who may not tolerate labour well</td>
<td></td>
</tr>
</tbody>
</table>
**Normal Labour and Delivery**

### Definition of Labour

- **true labour**: regular, painful contractions of increasing intensity associated with progressive **dilatation** and **effacement** of cervix and descent of presenting part, or progression of station
  - preterm (>20 but <36+6 wk GA)
  - term (37-41+6 wk GA)
  - post-term (>42 wk GA)
- **false labour**: Braxton-Hicks contractions
  - irregular contractions, with unchanged intensity and long intervals, occur throughout pregnancy and not associated with any dilatation, effacement or descent
  - often relieved by rest or sedation

### The Cervix

- **dilatation**: latent phase: 0-3 cm; active phase: 4-10 cm
- **effacement**: thinning of the cervix by percentage or length of cervix (cm)
- **consistency**: firm vs. soft
- **position**: posterior vs. anterior
- **application**: contact between the cervix and presenting part (i.e. well or poorly applied)
- see Bishop score (Table 23, OB36)

### The Fetus

- **fetal lie**: orientation of the long axis of the fetus with respect to the long axis of the uterus (longitudinal, transverse, oblique)
- **fetal presentation**
  - fetal part presenting at pelvic outlet
    - breech (complete, frank, footling) (see Figure 9, OB40)
    - cephalic (vertex, face, asynclitic)
    - transverse (shoulder)
    - compound (fetal extremity prolapses along with presenting part)
  - all except vertex are considered malpresentations (see **High Risk Labour and Delivery**, OB38)
- **fetal position**
  - position of presenting part of the fetus relative to the maternal pelvis
    - OA: most common presentation (“normal”) – left OA most common
    - OP: most rotate spontaneously to OA; may cause prolonged second stage of labour
    - OT: leads to arrest of dilatation
    - normally, fetal head enters maternal pelvis and engages in OT position
    - subsequently rotates to OA position (or OP in a small percentage of cases)

---

Table 18. Polyhydramnios and Oligohydramnios (continued)

<table>
<thead>
<tr>
<th>Management</th>
<th>Polyhydramnios</th>
<th>Oligohydramnios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine underlying cause:</td>
<td>Determine underlying cause:</td>
<td>Determine underlying cause:</td>
</tr>
<tr>
<td>• Screen for maternal disease/infection</td>
<td>• Complete fetal U/S evaluation</td>
<td>• Complete fetal U/S evaluation</td>
</tr>
<tr>
<td>• Complete fetal U/S evaluation</td>
<td>• Mild to moderate cases require no treatment</td>
<td>• Mild to moderate cases require no treatment</td>
</tr>
<tr>
<td>Depends on severity:</td>
<td><em>If severe, hospitalize and consider therapeutic amniocentesis</em></td>
<td><em>If severe, hospitalize and consider therapeutic amniocentesis</em></td>
</tr>
<tr>
<td>• If severe, hospitalize and consider therapeutic amniocentesis</td>
<td>Always warrants admission and investigation:</td>
<td>Always warrants admission and investigation:</td>
</tr>
<tr>
<td></td>
<td>• R/O ROM</td>
<td>• R/O ROM</td>
</tr>
<tr>
<td></td>
<td>• Fetal monitoring (NST, BPP)</td>
<td>• Fetal monitoring (NST, BPP)</td>
</tr>
<tr>
<td></td>
<td>• U/S Doppler studies (umbilical cord and uterine artery)</td>
<td>• U/S Doppler studies (umbilical cord and uterine artery)</td>
</tr>
</tbody>
</table>

**Prognosis**

- 2-5 fold increase in risk of perinatal mortality
- Poorer with early onset
- High mortality related to congenital malformations and pulmonary hypoplasia when diagnosed during T2

**Maternal Triage Assessment**

**ID**: Age, GPA, EDD, GA, GBS, Rh, Ser

**CC**

**HPI**: 4 key questions:

- **Contractions**: Since when, how close (q x min), how long (x s), how painful
- **Bleeding**: Since when, how much (pads), colour (pink mucous = show vs. brownish vs. bright red = clots), pain?, last U/S, trauma/intercourse?
- **Fluid (ROM)**: Since when, large gush vs. trickle, soaked pants?, clear vs. green vs. red?, continuous?
- **FM**: As much as usual?, When last movement?, Kick counts (lie still for 1-2 h, cold juice, feel FM – should have 6 movements in 2 h)

**HxPreg**: Any complications (HTN, GDM, infections), IPS/FTS screening, last ultrasound (BPP score, growth/estimated fetal weight, position), last vaginal exam

**POBHX**: Every previous pregnancy and outcome: Year, SVD/CS/miscarriage/abortion, baby size, length of labour, use of vacuum or forceps, complications

**PMHx, Meds, Allergies, SHx**

**O/E**: Maternal vitals, fetal heart tracing (baseline, variability, presence of accelerations/decelerations), Leopold’s, vaginal exam, U/S

**Reference point for describing fetal position:**

- Occiput for cephalic presentation
- Sacrum for breech presentation
- Mentum for face presentation
• attitude
  ▪ flexion/extension of fetal head relative to shoulders
    • brow presentation: head partially extended (requires C/S)
    • face presentation: head fully extended
      – mentum posterior always requires C/S, mentum anterior will deliver vaginally

• station
  ▪ position of presenting part relative to ischial spines – determined by vaginal exam
    • at ischial spines = station 0 = engaged
    • -5 to -1 cm above ischial spines or
    • +1 to +5 cm below ischial spines
    • alternatively stations can be placed on a scale from -3 to +3

---

Four Stages of Labour

First Stage of Labour
• latent phase
  ▪ uterine contractions typically infrequent and irregular
  ▪ slow cervical dilatation (usually to 3-4 cm) and effacement
• active phase
  ▪ rapid cervical dilatation to full dilatation (nulliparous ~1.2 cm/h, multiparous ~1.5 cm/h)
  ▪ phase of maximum slope on cervical dilatation curve (see Figure 10, OB43)
  ▪ painful, regular contractions q2-3 min, lasting 45-60 s
  ▪ contractions strongest at fundus, weakest at lower segment

Second Stage of Labour
• from full dilatation to delivery of the baby
• mother feels a desire to bear down and push with each contraction
• women may choose a comfortable position that enhances pushing efforts and delivery
  ▪ upright (semi-sitting, squatting) and LLDP are supported in the literature
• progress measured by descent

Third Stage of Labour
• separation and expulsion of the placenta
• can last up to 30 min before intervention indicated
• start oxytocin IV drip or give 10 U IM after delivery of anterior shoulder in anticipation of placental delivery, otherwise give after delivery of placenta
• routine oxytocin administration in third stage of labour can reduce the risk of PPH by >40%
Fourth Stage of Labour
• first postpartum hour
• monitor vital signs and bleeding
• repair lacerations
• ensure uterus is contracted (palpate uterus and monitor uterine bleeding)
• inspect placenta for completeness and umbilical cord for presence of 2 arteries and 1 vein
• 3rd and 4th stages of labour most dangerous to the mother (i.e. hemorrhage)

The Cardinal Movements of the Fetus During Delivery

<table>
<thead>
<tr>
<th>Movement Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Head floating, before engagement</td>
</tr>
<tr>
<td>2. Engagement, descent, flexion</td>
</tr>
<tr>
<td>3. Further descent, internal rotation, beginning extension</td>
</tr>
<tr>
<td>4. Complete rotation, beginning extension</td>
</tr>
<tr>
<td>5. Complete extension</td>
</tr>
<tr>
<td>6. Restitution (external rotation)</td>
</tr>
<tr>
<td>7. Delivery of anterior shoulder</td>
</tr>
<tr>
<td>8. Delivery of posterior shoulder</td>
</tr>
</tbody>
</table>

Figure 8. Cardinal movements of fetus during delivery
Adapted from illustration in Williams Obstetrics, 19th ed

Analgesic and Anesthetic Techniques in Labour and Birth

• pain or anxiety leads to high endogenous catecholamines, which produce a direct inhibitory effect on uterine contractility

Non-pharmacologic Pain Relief Techniques
• reduction of painful stimuli
  • maternal movement, position change, counter-pressure, abdominal compression
  • activation of peripheral sensory receptors
  • superficial heat and cold
  • immersion in water during labour
  • touch and massage, acupuncture and acupressure
  • TENS
  • intradermal injection of sterile water
  • aromatherapy
• enhancement of descending inhibitory pathways
  • attention focusing and distraction
  • hypnosis
  • music and audio analgesia
  • biofeedback

Pharmacologic Methods (see Anesthesia, A22)
• nitrous oxide (e.g. self-administered Entonox®)
• narcotics (usually combined with anti-emetic)
• pudendal nerve block
• perineal infiltration with local anesthetic
• regional anesthesia (epidural block, CSE, spinal)
Fetal Monitoring in Labour

- see online Fetal Heart Rate Tutorial

Vaginal Exam
- membrane status
- cervical effacement (thinning), dilatation, consistency, position, application
- fetal presenting part, position, station
- bony pelvis size and shape
- monitor progress of labour at regular intervals and document in a partogram

Intrapartum Fetal Monitoring
- intermittent fetal auscultation with Doppler device q15-30min for 1 min in first stage active phase following a contraction, q5min during second stage when pushing has begun
- continuous electronic FHR monitoring reserved for abnormal auscultation, prolonged labour, and labour which is induced or augmented
  - routine use of continuous electronic monitoring shown to lead to higher intervention rates and no improvement in outcome for the neonate
  - techniques for continuous monitoring include external (Doppler) vs. internal (fetal scalp electrode) monitoring
- fetal scalp sampling should be used in conjunction with electronic FHR monitoring and contraction monitoring (CTG) to resolve the interpretation of abnormal or atypical patterns

Electronic FHR Monitoring
- FHR measured by Doppler; contractions measured by tocometer
- described in terms of baseline FHR, variability (short term, long term) and periodicity (accelerations, decelerations)

Baseline FHR
- normal range is 110-160 bpm
- parameter of fetal well-being vs. distress

Variability
- physiologic variability is a normal characteristic of FHR
- variability is measured over a 15 min period and is described as: absent, minimal (less than 6 bpm), moderate (6-25 bpm), marked (greater than 25 bpm)
- normal variability indicates fetal acid-base status is acceptable
- can only be assessed by electronic fetal monitoring (CTG)
- variability decreases intermittently even in healthy fetus
- (see Table 21)

Periodicity
- accelerations: increase of ≥15 bpm lasting ≥15 s, in response to fetal movement or uterine contraction (or ≥10 bpm lasting ≥10 s if <32 wk GA)
- decelerations: 3 types, described in terms of shape, onset, depth, duration recovery, occurrence, and impact on baseline FHR and variability (see Table 20)

Table 19. Factors Affecting Fetal Heart Rate

<table>
<thead>
<tr>
<th>Maternal Factors</th>
<th>Fetal Tachycardia (FHR &gt;160)</th>
<th>Fetal Bradycardia (FHR &lt;110)</th>
<th>Decreased Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Hypothermia</td>
<td>Hypothermia</td>
<td>Infection</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Hypotension</td>
<td>Hypoglycemia</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Anemia</td>
<td>Rapid descent</td>
<td>Dysrhythmia</td>
<td>CNS anomalies</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>Heart block</td>
<td>Inactivity/sleep cycle, preterm fetus</td>
</tr>
</tbody>
</table>

Drugs
- Sympathomimetics
- ß-blockers
- Anesthetics
- Narcotics, sedatives
- Magnesium sulphate, ß-blockers

Uteroplacental
- Early hypoxia (abruption, HTN)
- Chorioamnionitis
- Late hypoxia (abruption, HTN)
- Acute cord prolapse
- Hypercontractility
- Hypoxia

Continuous CTG as a Form of EFM for Fetal Assessment during Labour
Cochrane DB Syst Rev 2006;3:CD006066

Purpose: To examine the effectiveness of continuous fetal heart monitoring (cardiotocography) during labour on improving health outcomes.

Methods: Systematic review comparing continuous fetal monitoring with no monitoring, intermittent auscultation, and intermittent monitoring.

Results: 12 trials (37,000 women) meeting search criteria were identified, of which 2 trials were high quality. Continuous electronic fetal heart monitoring did not have an effect on overall perinatal death rate compared to intermittent auscultation, with a relative risk (RR) of 0.85, 95% CI 0.59-1.23. Continuous monitoring also led to increased incidence of CS (RR 1.86, 95% CI 1.30 to 2.63, n=18,761, 10 trials) and instrument assisted vaginal delivery (RR 1.2, 95% CI 1.01 to 1.32, n = 18,181, nine trials). These results appeared consistent regardless if pregnancy was high risk, low risk, or preterm.

Conclusion: Continuous fetal cardiotocography does not significantly improve infant mortality or other standards of infant well-being. It increases the incidence of CS and instrument assisted vaginal delivery.

Fetal Scalp Blood Sampling
- indicated when atypical or abnormal fetal heart rate is suggested by clinical parameters including heavy meconium or moderately to severely abnormal FHR patterns, including unexplained low variability, repetitive late decelerations, complex variable decelerations, fetal cardiac arrhythmias
  - pH ≥7.25: normal, repeat if abnormal FHR persists
  - pH 7.21-7.24: repeat assessment in 30 min or consider delivery if rapid fall since last sample
  - pH ≤7.20: indicates fetal acidosis, delivery is indicated
contraindications
- known or suspected fetal blood dyscrasia (hemophilia, von Willebrand disease)
- active maternal infection (HIV, genital herpes)

### Table 20. Comparison of Decelerations

<table>
<thead>
<tr>
<th>Decelerations</th>
<th>Early Decelerations</th>
<th>Variable Decelerations</th>
<th>Complicated Variable Decelerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shape</td>
<td>Uniform shape with onset early in contraction, returns to baseline by end of contraction, mirrors contraction</td>
<td>Variable in shape, onset, and duration</td>
<td>To &lt;70 bpm for &gt;60 s</td>
</tr>
<tr>
<td>Gradual</td>
<td>Gradual deceleration</td>
<td>Most common type of periodicity seen during labour</td>
<td>Loss of variability or decrease in baseline after deceleration</td>
</tr>
<tr>
<td>Frequent</td>
<td>Often repetitive; no effect on baseline FHR or variability</td>
<td>Often with abrupt drop in FHR; usually no effect on baseline FHR or variability</td>
<td>Biphasic deceleration</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign, due to vagal response to head compression</td>
<td>Due to cord compression or, in second stage, forceful pushing with contractions</td>
<td>Slow return to baseline</td>
</tr>
<tr>
<td>FHR</td>
<td>FHR (baseline)</td>
<td>FHR (baseline)</td>
<td>FHR &lt;70 bpm for &gt;60 s</td>
</tr>
</tbody>
</table>

### Table 21. Classification of Intrapartum EFM Tracings

<table>
<thead>
<tr>
<th>Category</th>
<th>Normal Tracing</th>
<th>Atypical Tracing*</th>
<th>Abnormal Tracing*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>110-160 bpm</td>
<td>Bradycardia 100-110 bpm Tachycardia &gt;160 for 30-80 min Rising baseline</td>
<td>Bradycardia &lt;100 bpm Tachycardia &gt;160 bpm for &gt;80 min Erratic baseline</td>
</tr>
<tr>
<td>Variability</td>
<td>6-25 bpm ≤5 bpm for &lt;40 min</td>
<td>≤5 bpm for 40-80 min</td>
<td>&lt;5 bpm for &gt;80 min ≤25 bpm for &gt;10 min</td>
</tr>
<tr>
<td>Decelerations</td>
<td>None Early decelerations Occasional uncomplicated variable decelerations</td>
<td>Repetitive (≥3) uncomplicated variable decelerations Occasal late decelerations Any prolonged deceleration 2-3 min</td>
<td>Repetitive (≥3) complicated variable decelarations Repetitive late decelerations Any prolonged deceleration &gt;3 min</td>
</tr>
<tr>
<td>Accelerations</td>
<td>Accelerations spontaneous or during scalp stimulation</td>
<td>Absent with scalp stimulation</td>
<td>Nearly absent</td>
</tr>
<tr>
<td>Action</td>
<td>EFM may be interrupted for ≤30 min if mother/fetus stable</td>
<td>Further assessment required</td>
<td>Action required: review clinical situation, obtain scalp pH, prepare for possible delivery</td>
</tr>
</tbody>
</table>

Adapted from SOGC guidelines, September 2008
*Previous classification was “reassuring” vs. “non-reassuring”, but distinction is now made between tracings that have some concerning changes but do not require immediate action (atypical) versus those with major concerns requiring immediate intervention (abnormal)

### Approach to the Management of Abnormal FHR

POISON – ER
- Position (LLPD)
- O₂ (100% by mask)
- IV fluids (corrects maternal hypotension)
- Fetal scalp stimulation
- Fetal scalp electrode
- Fetal scalp pH
- Stop Oxygen
- Notify MD

Vaginal Exam to r/o cord prolapse

Rule out fever, dehydration, drug effects, prematurity
- If above fails, consider C/S

### Fetal Oxygenation

- uterine contractions during labour decrease uteroplacental blood flow, which results in reduced oxygen delivery to the fetus
- most fetuses tolerate this reduction in flow and have no adverse effects
- distribution of oxygen to the fetus depends on maternal, uteroplacental and fetal factors
• fetal response to hypoxia/asphyxia
  ▪ decreased movement, tone, and breathing activities
  ▪ redistribution of fetal blood flow
  ▪ increased flow to brain, heart, and adrenals
  ▪ decreased flow to kidneys, lungs, gut, liver and peripheral tissues
  ▪ increase in blood pressure
  ▪ transient fetal bradycardia followed by fetal tachycardia
  ▪ anaerobic metabolism (decreased pH)

Table 22. Factors Affecting Fetal Oxygenation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mechanism</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td>Decreased maternal oxygen carrying capacity</td>
<td>Significant anemia (iron deficiency, hemoglobinopathies), carboxyhemoglobin (smokers)</td>
</tr>
<tr>
<td></td>
<td>Decreased uterine blood flow</td>
<td>Hypotension (blood loss, sepsis), regional anestheisa, maternal positioning</td>
</tr>
<tr>
<td></td>
<td>Chronic maternal conditions</td>
<td>Vasculopathies (SLE, Type 1 DM, chronic HTN), antiphospholipid syndrome, cyanotic heart disease, COPD</td>
</tr>
<tr>
<td>Uteroplacental</td>
<td>Uterine hypertonus</td>
<td>Placental abruption, hyperstimulation secondary to oxytocin, prostaglandins or normal labour</td>
</tr>
<tr>
<td></td>
<td>Uteroplacental dysfunction</td>
<td>Placental abruption, placental infarction (dysfunction marked by IUGR, oligohydramnios, abnormal Doppler studies), chorioamnionitis, placentoid edema (diabetes, hydrops), placental senescence (post-dates)</td>
</tr>
<tr>
<td>Fetal</td>
<td>Cord compression</td>
<td>Oligohydramnios, cord prolapse or entanglement</td>
</tr>
<tr>
<td></td>
<td>Decreased fetal oxygen carrying capacity</td>
<td>Significant anemia (isoimmunization, feto-maternal bleed), carboxyhemoglobin (exposure to smokers)</td>
</tr>
</tbody>
</table>

Induction of Labour

Definition
• artificial initiation of labour before its spontaneous onset for the purpose of delivery of the fetus and placenta

Prerequisites for Labour Induction
• capability for C/S if necessary
• maternal
  ▪ short, thin, soft, anterior cervix with open os (“inducible” or “ripe”)
  ▪ if cervix is not ripe, use prostaglandin vaginal insert (Cervidil®), prostaglandin gel (Prepidil®), or Foley catheter
• fetal
  ▪ normal fetal heart tracing
  ▪ cephalic presentation
  ▪ adequate fetal monitoring available
  ▪ likelihood of success determined by Bishop score
    ▪ cervix considered unfavourable if <6
    ▪ cervix favourable if ≥6
    ▪ score of 9-13 associated with high likelihood of vaginal delivery

Table 23. Bishop Score

<table>
<thead>
<tr>
<th>Cervical characteristic</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position</td>
<td>Posterior</td>
<td>Mid</td>
<td>Anterior</td>
<td>–</td>
</tr>
<tr>
<td>Consistency</td>
<td>Firm</td>
<td>Medium</td>
<td>Soft</td>
<td>–</td>
</tr>
<tr>
<td>Effacement (%)</td>
<td>0-30</td>
<td>40-50</td>
<td>60-70</td>
<td>≥80</td>
</tr>
<tr>
<td>Dilatation (cm)</td>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
<td>≥5</td>
</tr>
<tr>
<td>Station of fetal head</td>
<td>-3</td>
<td>-2</td>
<td>-1, 0</td>
<td>+1, +2, +3</td>
</tr>
</tbody>
</table>

Indications
• post-dates pregnancy (generally >41 wk) = most common reason for induction
• maternal factors
  ▪ diabetes mellitus = second most common reason for induction
  ▪ gestational HTN
  ▪ other maternal medical problems, e.g. renal or lung disease
• maternal-fetal factors
  ▪ isoimmunization, PROM, chorioamnionitis, post-term pregnancy

Induction vs. Augmentation
Induction is the artificial initiation of labour.
Augmentation promotes contractions when spontaneous contractions are inadequate.

Induction is indicated when the risk of continuing pregnancy exceeds the risks associated with induced labour and delivery.

Consider the Following before Induction
• Indication for induction
• Contraindications
• GA
• Cervical favourability
• Fetal presentation
• Potential for CPD
• Fetal well-being/FHR
• Membrane status
• fetal factors
  ▪ suspected fetal jeopardy as evidenced by biochemical or biophysical indications
  ▪ fetal demise, IUGR

Risks
• failure to achieve labour and/or vaginal birth
• uterine hyperstimulation and fetal compromise
• maternal side effects to medications
• uterine atony and PPH
• uterine rupture

Contraindications
• maternal
  ▪ prior classical or inverted T-incision or uterine surgery (e.g. myomectomy)
  ▪ unstable maternal condition
  ▪ active maternal genital herpes
  ▪ invasive cervical carcinoma
  ▪ pelvic structure deformities
• maternal-fetal
  ▪ placenta previa or vasa previa
  ▪ cord presentation
• fetal
  ▪ fetal distress, malpresentation, preterm fetus without lung maturity

Induction Methods

CERVICAL RIPENING

Definition
• use of medications or other means to soften, efface and dilate the cervix to increase likelihood of induction success
• ripening of an unfavourable cervix (Bishop score <6) is warranted prior to induction of labour

Methods
• intravaginal prostaglandin PGE2 gel (Prostin® gel): long and closed cervix
  ▪ recommended dosing interval of prostaglandin gel is every 6 to 12 h up to 3 doses
  ▪ continuous release, can be removed if needed
  ▪ controlled release PGE2
• Foley catheter placement to mechanically dilate the cervix

INDUCTION OF LABOUR

Amniotomy
• artificial rupture of membranes (amniotomy) to stimulate PG synthesis and secretion; may try this as initial measure if cervix is dilated
• few studies address the value of amniotomy alone for induction of labour
• amniotomy plus intravenous oxytocin: more women delivered vaginally at 24 h than amniotomy alone (relative risk = 0.03) and had fewer instrumental vaginal deliveries (relative risk = 5.5)

Oxytocin
• oxytocin (Pitocin®): 10 U in 1L NS, run at 0.5-2 mU/min IV increasing by 1-2 mU/min q20-60 min to a max of 36-48 mU/min
  ▪ reduces rate of unsuccessful vaginal deliveries within 24 h when used alone (8.3% vs. 54%, RR 0.16)
  ▪ ideal dosing regime of oxytocin is not known
  ▪ current recommendations: use the minimum dose to achieve active labour and increase q30min as needed
  ▪ reassessment should occur once a dose of 20 mU/min is reached
• potential complications
  ▪ hyperstimulation/tetanic contraction (may cause fetal distress or rupture of uterus)
  ▪ uterine muscle fatigue, uterine atony (may result in PPH)
  ▪ vasopressin-like action causing anti-diuresis

Augmentation of Labour
• augmentation of labour is used to promote adequate contractions when spontaneous contractions are inadequate and cervical dilatation or descent of fetus fails to occur
• oxytocin (0.5-2 mU/min IV increasing by 1-2 mU/min q20-60 min to a max of 36-48 mU/min)
Preterm Labour

Definition
• labour occurring between 20 and 37 wk gestation

Etiology
• idiopathic (most common)
• maternal: infection (recurrent pyelonephritis, untreated bacteriuria, chorioamnionitis), genital infection (bacterial vaginosis is associated with a 2-fold increase in relative risk of preterm birth), HTN, DM, chronic illness, mechanical factors, previous obstetric, gynecological and abdominal surgeries, socio-environmental (poor nutrition, smoking, drugs, alcohol, stress)
• maternal-fetal: PPROM (common), polyhydramnios, placenta previa or abruption, placental insufficiency
• fetal: multiple gestation, congenital abnormalities of fetus, fetal hydrops
• uterine: incompetent cervix, excessive enlargement (hydramnios), malformations (leiomyomas, septate uterus)

Epidemiology
• preterm labour complicates about 10% of pregnancies

Risk Factors and Prediction of PTL
• maternal risk scoring using above etiologies fails to identify up to 70% of preterm deliveries and is therefore of limited use
• prior history of spontaneous PTL: most important risk factor
• prior history cervical excisions or mechanical dilatation
• cervical length: measured by transvaginal U/S (cervical length >30 mm has high negative predictive value for PTL before 34 wk)
• identification of bacterial vaginosis (Rx metronidazole) and ureaplasma urealyticum (Rx erythromycin) infections: routine screening not supported by current data but it is reasonable to screen high risk women
• fetal fibronectin: a glycoprotein in amniotic fluid and placental tissue functioning to maintain integrity of chorionic-decidual interface in asymptomatic women
  • positive if >50 ng/mL
  • in symptomatic women (i.e. preterm contractions), fetal fibronectin is most effectively combined with U/S detecting cervical length
  • if cervical length is not short and fetal fibronectin is negative, preterm labour is highly unlikely

Clinical Features
• regular contractions (2 in 10 min)
• cervix >2 cm dilated or 80% effaced or documented change in cervix

Management
A. Initial
• transfer to appropriate facility if stable
• hydration (NS at 150 mL/h)
• bed rest in LLDP
• sedation (morphine)
• avoid repeated pelvic exams (increased infection risk)
• U/S examination of fetus (GA, BPP, position, placenta location, estimated fetal weight)
• prophylactic antibiotics; controversial but may help delay delivery, important to consider if PPROM

B. Suppression of Labour – Tocolysis
• does not inhibit preterm labour completely, but may buy time to allow for betamethasone valerate (Celestone®) and/or transfer to appropriate centre
• requirements (all must be satisfied)
  • preterm labour
  • live, immature fetus, intact membranes, cervical dilatation of <4 cm
  • absence of maternal or fetal contraindications
• contraindications
  • maternal: bleeding (placenta previa or abruption), maternal disease (hypertension, diabetes, heart disease), preeclampsia or eclampsia, chorioamnionitis
  • fetal: erythroblastosis fetalis, severe congenital anomalies, fetal distress/demise, IUGR, multiple gestation (relative)
• tocolytic procedure
  • should be used only for <48 h and/or until transfer to an appropriate facility for care of the premature infant

Positive fetal fibronectin in cervicovaginal fluid (>50 ng/mL) at 24 wk gestation predicted spontaneous PTL at <34 wk with sensitivity of 23%, specificity of 97%, PPV of 25%, NPV of 96%.
• agents
  • calcium channel blockers: Nifedipine
    • 20 mg PO loading dose followed by 20 mg PO 90 min later. 20 mg can be continued q3-8h for 72 h or to a max of 180 mg
    • 10 mg PO q20min x 4 doses
  • prostaglandin synthesis inhibitors: Indomethacin
    • 1st line for early preterm labour (<30 wk GA) or polyhydramnios
    • 50-100 mg PO loading dose followed by 25 mg q4-6h
    • Magnesium sulphate was previously used for tocolysis. Currently, its primary use in obstetrics is limited to neuroprotection.

C. Enhancement of Fetal Pulmonary Maturity
• betamethasone valerate (Celestone®) 12 mg IM q24h x 2 or dexamethasone 6 mg IM q12h x 4
• 28-34 wk GA: reduces incidence of RDS
• 24-28 wk GA: reduces severity of RDS, overall mortality and rate of IVH
• specific maternal contraindications: active TB

D. Cervical Cerclage
• definition: placement of cervical sutures at the level of the internal os, usually at the end of the first trimester and removed in the third trimester
• indications: cervical incompetence (i.e. cervical dilation and effacement in the absence of increased uterine contractility)
  • emerging evidence indicates that progesterone suppositories are superior to cerclage in preventing preterm labour late in pregnancy
  • diagnosis of cervical incompetence
    • obstetrical Hx: silent cervical dilation
    • ability of cervix to hold an inflated Foley catheter during a hysterosonogram
  • proven benefit in the prevention of PTL in women with primary structural abnormality of the cervix (e.g. conization of the cervix, connective tissue disorders)
  • benefit is variable in those with secondary cervical incompetence causing premature ripening of the cervix (e.g. infection, abnormal placentation)

Prognosis
• prematurity is the leading cause of perinatal morbidity and mortality
• 30 wk or 1,500 g (3.3 lb) = 90% survival
• 33 wk or 2,000 g (4.4 lb) = 99% survival
• morbidity due to asphyxia, hypoxia, sepsis, RDS, intraventricular cerebral hemorrhage, thermal instability, retinopathy of prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis

Prevention of Preterm Labour
• currently there are no agents approved by Health Canada to arrest preterm labour
• preventative measures: good prenatal care, identify pregnancies at risk, treat silent vaginal infection or UTI, patient education
• transvaginal ultrasound of cervical length is recommended only for high-risk pregnancies

Premature Rupture of Membranes

Definitions
• PROM or amniorrhexis: rupture of membranes prior to labour at any GA
• prolonged ROM: >24 h elapsed between rupture of membranes and onset of labour
• preterm ROM: ROM occurring before 37 wk gestation (associated with PTL)
• PPROM: rupture of membranes before 37 wk AND prior to onset of labour

Risk Factors
• maternal: multiparity, cervical incompetence, infection (cervicitis, vaginitis, STI, UTI), family history of PROM, low socioeconomic class/poor nutrition
• fetal: congenital anomaly, multiple gestation
• other risk factors associated with PTL

Clinical Features
• history of fluid gush or continued leakage

Investigations
• sterile speculum exam (avoid introduction of infection)
  • pooling of fluid in the posterior fornix
  • may observe fluid leaking out of cervix on cough/Valsalva ("cascade")
  • nitrazine (amniotic fluid turns nitrazine paper blue)
  • low specificity as can be positive with blood, urine or semen
• ferning (high salt in amniotic fluid evaporates, looks like ferns under microscope)
• U/S to r/o fetal anomalies, assess GA and BPP

Cerclage for Short Cervix on Ultrasonography in Women With Singleton Gestations and Previous Preterm Birth
Obstet Gynecol 2011;117:663-671

Purpose: To determine if cerclage prevents preterm birth (<35 wk gestation) and perinatal morbidity and mortality among women with previous spontaneous preterm birth, asymptomatic singleton gestation, and short cervical length (<25 mm before 24 wk gestation) on transvaginal ultrasound.

Methods: Meta-analysis of randomized trials identified using searches on MEDLINE, PUBMED, EMBASE and the Cochrane Library.

Results: 5 trials included. Preterm birth was significantly lower among women receiving cerclage versus those not (RR = 0.70, 95% CI: 0.55, 0.88). Cerclage also significantly reduced preterm birth before 24, 28, 32, and 37 wk of gestation. Perinatal mortality and morbidity were significantly lower in the cerclage group (RR = 0.84, 95% CI: 0.45, 0.91).

Conclusions: Cerclage significantly prevents preterm birth and perinatal mortality and morbidity in this specific group of women.
Management
- admit for expectant management and monitor vitals q4h, daily BPP and WBC count
- avoid introducing infection with examinations (do NOT do a bimanual exam)
- cultures (cervix for GC, lower vagina for GBS)
- assess fetal lung maturity by L/S ratio of amniotic fluid
  - consider administration of betamethasone valerate (Celestone®) to accelerate maturity if <32 wk and no evidence of infection
  - consider tocolysis for 48 h to permit administration of steroids if PPROM induces labour
- if not in labour or labour not indicated, consider antibiotics (controversial)
  - studies show broad spectrum coverage increases the time to onset of labour from PROM by 5-7 d with no increase in maternal or neonatal morbidity or mortality
- deliver urgently if evidence of fetal distress and/or chorioamnionitis

Table 24. PROM Management

<table>
<thead>
<tr>
<th>Degree of Prematurity</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24 wk</td>
<td>Consider termination (poor outcome due to pulmonary hypoplasia)</td>
</tr>
<tr>
<td>24-25 wk</td>
<td>Individual consideration with counselling of parents re: risks to preterm infants</td>
</tr>
<tr>
<td>26-34 wk</td>
<td>Expectant management as prematurity complications are significant</td>
</tr>
<tr>
<td>34-36 wk</td>
<td>“Grey zone” where risk of death from RDS and neonatal sepsis is the same</td>
</tr>
<tr>
<td>≥37 wk</td>
<td>Induction of labour since the risk of death from sepsis is greater than RDS</td>
</tr>
</tbody>
</table>

Prognosis
- varies with gestational age
- 90% of women with PROM at 28-34 wk GA go into spontaneous labour within 1 wk
- 50% of women with PROM at <26 wk GA go into spontaneous labour within 1 wk
- complications: cord prolapse, intrauterine infection (chorioamnionitis), premature delivery, limb contracture

Breech Presentation

Definition
- fetal buttocks or lower extremity is the presenting part as determined on U/S (see Figure 9)
- complete (10%): flexion at hips and knees
- frank (60%): flexion at hips, extension at knees
- most common type of breech presentation
- most common breech presentation to be delivered vaginally
- footling (30%): may be single or double with extension at hip(s) and knee(s) so that foot is the presenting part

Epidemiology
- occurs in 3-4% of pregnancies at term (25% before 28 wk)

Risk Factors
- maternal: pelvis (contracted), uterus (shape abnormalities, intrauterine tumours, fibroids), extraterine tumours causing compression, grand multiparity
- maternal-fetal: placenta (previa), amniotic fluid (poly/oligohydramnios)
- fetal: prematurity, multiple gestation, congenital malformations (found in 6% of breeches; 2-3% if in vertex presentations), abnormalities in fetal tone and movement, aneuploidy

Management
- ECV: repositioning of fetus within uterus under U/S guidance
  - overall success rate of 65%
  - criteria: <37 wk, singleton, unengaged presenting part, reactive NST
  - contraindications: previous T3 bleed, prior classical C/S, previous myomectomy, oligohydramnios, PROM, placenta previa, abnormal U/S, suspected IUGR, hypertension, uteroplacental insufficiency, nuchal cord
  - risks: abruption, cord compression
  - method: tocometry, followed by ultrasound guided transabdominal manipulation of fetus with consistent fetal heart monitoring
  - if patient Rh negative, give Rhogam® prior to procedure
  - good prognostic factors (for a successful version)
    - multiparous, good fluid volume, small baby, skilled obstetrician
  - pre- or early labour ultrasound to assess type of breech presentation, fetal growth, estimated weight, attitude of fetal head; if ultrasound unavailable, recommend C/S
  - trial of labour and elective C/S should be presented as options with the risks and benefits outlined; obtain informed consent

Criteria for Vaginal Breech Delivery
- Frank or complete breech, GA ≥36 wk
- EFW 2,500-3,800 g based on clinical and U/S assessment (5.5–8.5 lb)
- Fetal head flexed
- Continuous fetal monitoring
- 2 experienced obstetricians, assistant, and anaesthetist present
- Ability to perform emergency C/S within 30 min if required
• method for vaginal breech delivery:
  ▪ encourage effective maternal pushing efforts
  ▪ at delivery of after-coming head, assistant must apply suprapubic pressure to flex and engage fetal head
  ▪ delivery can be spontaneous or assisted; avoid fetal traction
  ▪ apply fetal manipulation only after spontaneous delivery to level of umbilicus
• C/S recommended if: the breech has not descended to the perineum in the second stage of labour after 2 h, in the absence of active pushing, or if vaginal delivery is not imminent after 1 h of active pushing
• contraindications to vaginal breech delivery:
  ▪ cord presentation
  ▪ clinically inadequate maternal pelvis
  ▪ fetal factors incompatible with vaginal delivery (see OB37)

Prognosis
• regardless of route of delivery, breech infants have lower birth weights and higher rates of perinatal mortality, congenital anomalies, abruption and cord prolapse

Vaginal Birth After Cesarean (VBAC) aka Trial of Labour After Cesarean (TOLAC)
• recommended after previous low transverse incision
• success rate varies with indication for previous C/S (generally 60-80%)
• risk of uterine rupture (<1% with low transverse incision)

Contraindications
• previous classical, inverted T, or unknown uterine incision, or complete transection of uterus (6% risk of rupture)
• history of hysterotomy or previous uterine rupture
• multiple gestation
• non-vertex presentation or placenta previa
• inadequate facilities or personnel for emergency C/S

Prolonged Pregnancy

Definition
• pregnancy beyond 42 wk GA

Epidemiology
• 41 wk GA: up to 27%
• 42 wk GA: 4-14%

Etiology
• most cases idiopathic
• anencephalic fetus with no pituitary gland
• placental sulfatase deficiency (X-linked recessive condition in 1/2,000-1/6,000 infants) – rare

Clinical Features
• postmaturity syndrome: 10-20% of post-term pregnancies (fetal weight loss, reduction in subcutaneous fat, scaling, dry skin from placental insufficiency, long thin body, open-eyed, alert and worried look, long nails, palms and soles wrinkled)
• with increasing GA, higher rates of: intrauterine infection, asphyxia, meconium aspiration syndrome, placental insufficiency, placental aging and infarction, macrosomia, dystocia, fetal distress, operative deliveries

Management
• GA 40-41 wk: expectant management
  ▪ no evidence to support IOL or C/S unless other risk factors for morbidity are present (see prognosis)
• GA >41 wk: offer IOL if vaginal delivery is not contraindicated
• IOL shown to decrease C/S, fetal heart rate changes, meconium staining, macrosomia and death when compared with expectant management
• GA >41 wk and expectant management elected: serial fetal surveillance
  ▪ fetal movement count by the mother
  ▪ BPP q3-4d
  ▪ If AFI is decreased, labour will be induced
**Prognosis**
- If >41 wk, perinatal mortality 2-3x higher (due to progressive uteroplacental insufficiency)
- Morbidity increased with hypertension in pregnancy, DM, abruption, IUGR and multiple gestation

**Intrauterine Fetal Death**

**Definition**
- Fetal death in utero after 20 wk GA

**Epidemiology**
- 1% of pregnancies

**Etiology**
- 50% idiopathic
- 50% secondary to HTN, DM, erythroblastosis fetalis, congenital anomalies, umbilical cord or placental complications, intrauterine infection, APS

**Clinical Features**
- Decreased perception of fetal movement by mother
- SFH and maternal weight not increasing
- Absent fetal heart tones (not diagnostic)
- High MSAFP

**Management**
- Diagnosis: Absent cardiac activity and fetal movement on U/S required for diagnosis
- Determine secondary cause
  - Maternal: HbA1c, Kleihauer-Betke, VDRL, ANA, antibody screens, INR/PTT, serum/urine toxicology screens, cervical and vaginal cultures, TORCH screen
  - Fetal: Chromosomes, cord blood, skin biopsy, genetics evaluation, autopsy
  - Placenta: Pathology, bacterial cultures

**Treatment**
- Induction of labour
- Monitor for maternal coagulopathy (10% risk of DIC)
- Parental psychological care as per hospital protocol
- Comprehensive discussion within 3 mo about final investigation and post-mortem results, help make plans for future pregnancies

**Complications of Labour and Delivery**

**Meconium in Amniotic Fluid**

**Epidemiology**
- Present early in labour in 10% of pregnancies
- In general, meconium may be present in up to 25% of all labours; usually NOT associated with poor outcome, but extra care is required at time of delivery to avoid aspiration

**Etiology**
- Likely cord compression ± uterine hypertonus
- May indicate undiagnosed breech
- Increasing meconium during labour may be a sign of fetal distress

**Features**
- Consistency and colour:
  - Light yellow/green or dark green-black in colour.
  - May be watery or thicker

**Treatment**
- Call respiratory therapy, neonatology or pediatrics to delivery room
- Oropharynx suctioning upon head expulsion or immediately after delivery if baby not breathing spontaneously (do NOT stimulate infant before)
- Consider amnioinfusion of ~800 mL of IV NS over 50-80 min during active stage of labour and a maintenance dose of ~3 mL/min until delivery
- Closely monitor FHR for signs of fetal distress

DIC: Generalized Coagulation and Fibrinolysis Leading to Depletion of Coagulation Factors

**Obstetrical Causes**
- Abruption
- Gestational HTN
- Fetal demise
- PPH

**DIC-specific Bloodwork**
- Platelets
- aPTT and PT
- FDP
- Fibrinogen

**Treatment**
- Treat underlying cause
- Supportive
  - Fluids
  - Blood products
  - FFP, platelets, cryoprecipitate
  - Consider anti-coagulation as VTE prophylaxis

Dark green or black meconium is associated with lower APGARS and increased risk of meconium aspiration.
Abnormal Progression of Labour (Dystocia)

**Definition**
- expected patterns of descent of the presenting part and cervical dilatation fail to occur in the appropriate time frame; can occur in all stages of labour (see Figure 10)
- during active phase: >4 h of <0.5 cm/h
- during 2nd phase: >1 h with no descent during active pushing

**Etiology**
- **Power** (leading cause): contractions (hypotonic, incoordinate), inadequate maternal expulsive efforts
- **Passenger**: fetal position, attitude, size, anomalies (hydrocephalus)
- **Passage**: pelvic structure (CPD), maternal soft tissue factors (tumours, full bladder or rectum, vaginal septum)
- **Psyche**: hormones released in response to stress may contribute to dystocia. Psychological and physiological stress should be evaluated as part of the management once dystocia has been diagnosed

**Figure 10. Normal and abnormal courses of the first stage of labour**

**Arrest Disorder (Curve C)**
- arrest of dilatation
  - dilatation progress does not occur for ≥2 h in a patient who has entered the active phase
  - arrest usually occurs at a cervical dilatation of 5-8 cm
- arrest of descent
  - no progress in station for >1 h during second stage
  - should search for factors causing CPD (nearly 50% require C/S)
  - CPD diagnosed if adequate contractions measured by intrauterine pressure catheter (IUPC) with no descent/dilatation for >2 h
  - if CPD ruled out, IV oxytocin and amniotomy can be attempted

**Protraction Disorders (Curve D)**
- protraction of dilatation: slope of cervical dilatation <1.2 cm/h in primigravida or <1.5 cm/h in multigravida
- protraction of descent: a rate of descent of <1.0 cm/h in primigravida or 2.0 cm/h in multigravida
- treatment: oxytocin augmentation if contractions are inadequate ± amniotomy

**Prolonged Latent Phase (Curve E)**
- ≥20 h in primigravida or ≥14 h in multigravida during which labour has not progressed to the active phase
- most often due to false labour (avoid amniotomy for fear of false labour and increased risk of intrauterine infection)
- premature or excessive use of sedation or analgesia may play a role
- careful search for factors of CPD should be made
- management: oxytocin augmentation if diagnosis of labour is certain, otherwise rest ± sedation

**Risks of Dystocia**
- inadequate progression of labour is associated with an increased incidence of:
  - maternal stress
  - maternal infection
  - postpartum hemorrhage
  - need for neonatal resuscitation
Shoulder Dystocia

Definition
- Impaction of anterior shoulder of fetus against symphysis pubis after fetal head has been delivered
- Life threatening emergency

Etiology/Epidemiology
- Incidence 0.15-1.4% of deliveries
- Occurs when breadth of shoulders is greater than biparietal diameter of the head

Risk Factors
- Maternal: obesity, diabetes, multiparity
- Fetal: prolonged gestation, macrosomia
- Labor
  - Prolonged 2nd stage
  - Prolonged deceleration phase (8-10 cm)
  - Instrumental midpelvic delivery

Clinical Features
- “turtle sign”: head delivered but retracts against inferior portion of pubic symphysis
- Complications
  - Chest compression by vagina or cord compression by pelvis can lead to hypoxia
  - Brachial plexus injury (Erb’s palsy: C5-C7; Klumpke’s palsy: C8-T1)
  - 90% resolve within 6 mo
  - Fetal fracture (clavicle, humerus, cervical spine)
  - Maternal perineal injury, may result in PPH

Treatment
- Goal: to displace anterior shoulder from behind symphysis pubis; follow a stepwise approach of maneuvers until goal achieved (see sidebar)
- Other options:
  - Cleidotomy (deliberate fracture of neonatal clavicle)
  - Zavanelli maneuver: replacement of fetus into uterine cavity and emergent C/S
  - Symphysiotomy

Prognosis
- 1% risk of long term disability for infant

Approach to the Management of Shoulder Dystocia
ALARMER
- Apply suprapubic pressure and ask for help
- Legs in full flexion (McRobert’s maneuver)
- Anterior shoulder disimpaction (suprapubic pressure)
- Release posterior shoulder by rotating it anteriorly with hand in the vagina under adequate anesthesia
- Manual corkscrew i.e. rotate the fetus by the posterior shoulder until the anterior shoulder emerges from behind the maternal symphysis
- Episiotomy
- Rollover (on hands and knees)
- *Note that suprapubic pressure and McRoberts maneuver together will resolve 90% of cases

Umbilical Cord Prolapse

Definition
- Descent of the cord to a level adjacent to or below the presenting part, causing cord compression between presenting part and pelvis

Etiology/Epidemiology
- Increased incidence with prematurity/PROM, fetal malpresentation (~50% of cases), low-lying placenta, polyhydramnios, multiple gestation, CPD
- Incidence: 0.17-0.63%

Clinical Features
- Visible or palpable cord
- FHR changes (variable decelerations, bradycardia or both)

Treatment
- Emergency C/S
- O2 to mother, monitor fetal heart
- Alleviate pressure of the presenting part on the cord by placing digit in vagina (maintain this position until C/S)
- Keep cord warm and moist by replacing it into the vagina ± applying warm saline soaks
- Position mother in Trendelenburg or knee-to-chest position
- If fetal demise or too premature (<22 wk), allow labour and delivery

Umbilical Cord Accident Causes
- Nuchal cord
  - Type A (looped)
  - Type B (hitched)
- Body loop
- Single artery
- True knot
- Torsion
- Velamentous
- Short cord < 35 cm
- Long cord > 80 cm
Uterine Rupture

Etiology/Epidemiology
- associated with previous uterine scar (in 40% of cases), hyperstimulation with oxytocin, grand multiparity and previous intrauterine manipulation
- generally occurs during labour, but can occur earlier with a classical incision
- 0.5-0.8% incidence, up to 12% with classical incision

Clinical Features
- prolonged fetal bradycardia – most common presentation
- acute onset abdominal pain
- hyper or hypotonic uterine contractions
- vaginal bleed

Risk Factors:
- uterine scarring (i.e. previous uterine surgeries including Cesarean, perforation with D&C)
- excessive uterine stimulation (i.e. protracted labour, oxytocin)
- uterine trauma (i.e. operative equipment, ECV)
- multiparity
- uterine abnormalities

Treatment
- rule out placental abruption
- immediate delivery for fetal survival
- maternal stabilization (may require hysterectomy)

Complications
- maternal mortality 1-10%
- maternal hemorrhage, shock, DIC
- amniotic fluid embolus
- hysterectomy if uncontrollable hemorrhage
- fetal distress, associated with 50% fetal mortality

Amniotic Fluid Embolus

Definition
- amniotic fluid debris in maternal circulation triggering an anaphylactoid immunologic response

Etiology/Epidemiology
- rare intrapartum or immediate postpartum complication
- 60-80% maternal mortality rate, accounts for 10% of all maternal deaths
- leading cause of maternal death in induced abortions and miscarriages
- 1/8,000-1/80,000 births

Risk Factors
- placental abruption
- rapid labour
- multiparity
- uterine rupture
- uterine manipulation

Differential Diagnosis
- pulmonary embolus, drug-induced anaphylaxis, septic shock, eclampsia, HELLP syndrome, abruptio, chronic coagulopathy

Clinical Features
- sudden onset of respiratory distress, cardiovascular collapse (hypotension, hypoxia) and coagulopathy
- seizure in 10%
- ARDS and left ventricular dysfunction seen in survivors

Management
- supportive measures (high flow O₂, ventilation support, fluid resuscitation, inotropic support, ± intubation), coagulopathy correction
- ICU admission

Maternal Mortality Causes
- Thromboembolism
- Cardiac event
- Suicide
- Sepsis
- Eclectic pregnancy
- Hypertension
- Amniotic-fluid embolism
- Hemorrhage

* In Canada (2005), lifetime risk of maternal death is 1 in 11,000
**Chorioamnionitis**

**Definition**
- infection of the chorion, amnion and amniotic fluid typically due to ascending infection by organisms of normal vaginal flora

**Etiology/Epidemiology**
- incidence 1-5% of term pregnancies and up to 25% in preterm deliveries
- ascending from vagina
- predominant microorganisms include GBS, Bacteroides and Prevotella species, E. coli and anaerobic Streptococcus

**Risk Factors**
- prolonged ROM, long labour, multiple vaginal exams during labour, internal monitoring
- bacterial vaginosis and other vaginal infections

**Clinical Features**
- maternal fever, maternal or fetal tachycardia, uterine tenderness, foul and purulent cervical discharge

**Investigations**
- CBC: leukocytosis
- amniotic fluid: leukocytes or bacteria

**Treatment**
- IV antibiotics
  - ampicillin (2 g IV q6h) and gentamicin (1.5 mg/kg q8h)
  - anaerobic coverage i.e. clindamycin if C/S
- expedient delivery regardless of gestational age

**Complications**
- bacteremia of mother or fetus, wound infection if C/S, pelvic abscess, infant meningitis

**Operative Obstetrics**

**Operative Vaginal Delivery**

**Definition**
- forceps or vacuum extraction

**Indications**
- fetal
  - atypical or abnormal fetal heart rate tracing
  - consider if second stage is prolonged as this may be due to poor contractions or failure of fetal head to rotate
- maternal
  - need to avoid voluntary expulsive effort (e.g. cardiac/cerebrovascular disease)
  - exhaustion, lack of cooperation and excessive analgesia may impair pushing effort

**Forceps**

**Outlet Forceps Position**
- head visible between labia in between contractions
- sagittal suture in or close to AP diameter
- rotation cannot exceed 45°

**Low Forceps Position**
- presenting part at station +2 or greater
- subdivided based on whether rotation less than or greater than 45 degrees

**Mid Forceps Position**
- presenting part below spines but above station +2
- rarely done

**Types of Forceps**
- Simpson forceps for OA presentations
- Kielland (rotational) forceps when rotation of head to OA is recessing
- Piper forceps for breech
Vacuum Extraction

- traction instrument used as alternative to forceps delivery; aids maternal pushing

Table 25. Advantages and Disadvantages of Forceps versus Vacuum Extraction

<table>
<thead>
<tr>
<th></th>
<th>Forceps</th>
<th>Vacuum Extraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Higher overall success rate for vaginal delivery</td>
<td>Easier to apply</td>
</tr>
<tr>
<td></td>
<td>Decreased incidence of fetal morbidity</td>
<td>Less anesthesia required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less maternal self-tissue injury compared to forceps</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Greater incidence of maternal injury</td>
<td>Contraindicated if fetus at risk for coagulation defect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suitable only for vertex presentations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maternal pushing required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contraindicated in preterm delivery</td>
</tr>
<tr>
<td>Complications</td>
<td>Maternal: anesthesia risk, lacerations, injury to bladder, uterus or bone, pelvic nerve damage, PPH, infections</td>
<td>Increased incidence of cephalohematoma and retinal hemorhages compared to forceps</td>
</tr>
<tr>
<td></td>
<td>Fetal: fractures, facial nerve palsy, trauma to face/scalp, intracerebral hemorhoma, cephalohematoma, cord compression</td>
<td>Subglial hemorhage, subaponeurotic hemorhage, soft tissue trauma</td>
</tr>
</tbody>
</table>

Lacerations

- first degree: involves skin and vaginal mucosa but not underlying fascia and muscle
- second degree: involves fascia and muscles of the perineal body but not the anal sphincter
- third degree: involves the anal sphincter but does not extend through it
- fourth degree: extends through the anal sphincter into the rectal mucosa

Episiotomy

Definition
- incision in the perineal body at the time of delivery
- essentially a controlled second degree laceration
- midline: incision through central tendinous portion of perineal body and insertions of superficial transverse perineal and bulbocavernous muscle
  - better healing but increased risk of deep tear
  - mediolateral: incision through bulbocavernous, superficial transverse perineal muscle, and levator ani
  - reduced risk of extensive tear but poorer healing and more pain
  - easier to repair

Indications
- to relieve obstruction of the unyielding perineum
- instrumental delivery
- controversial between practitioners as to whether it is preferable to make a cut or let the perineum tear as needed
- current evidence suggests letting perineum tear and then repair as needed (restricted use)

Complications
- infection, hematoma, extension into anal musculature or rectal mucosa, fistula formation, incontinence

Cesarean Delivery

Epidemiology
- incidence 20-25%

Indications
- maternal: obstruction, active herpetic lesion on vulva, invasive cervical cancer, previous uterine surgery, underlying maternal illness (eclampsia, HELLP syndrome, heart disease)
- maternal-fetal: failure to progress, placental abruption or previa, vasa previa
- fetal: abnormal fetal heart tracing, malpresentation, cord prolapse, certain congenital anomalies

- after 3 pulls over 3 contractions with no progress, after 3 pop-offs with no obvious cause
- 20 min and delivery is not imminent
Types of Cesarean Incisions

- skin
  - transverse (aka Pfannensteil)
    - decreased exposure and slower entry
    - improved strength and cosmesis
  - vertical midline
    - rapid peritoneal entry and increased exposure
    - increased dehiscence
- uterine
  - low transverse (most common): in noncontractile segment
    - decreased chance for rupture in subsequent pregnancies
  - low vertical
    - used for very preterm infants, poorly developed maternal lower uterine segment
  - classical (rare): in thick, contractile segment
    - used for transverse lie, fetal anomaly, >2 fetuses, lower segment adhesions, obstructing fibroid

Risks/Complications

- anesthesia
- hemorrhage (average blood loss ~1,000 cc)
- infection (UTI, wound, endometritis)
  - single dose prophylactic antibiotic should be used (e.g. cefazolin 1-2 g)
- thromboembolism
- increased recovery time/hospital stay
- maternal mortality (<0.1%)

Puerperal Complications

- puerperium: 6 wk period of adjustment after pregnancy when pregnancy-induced anatomic and physiologic changes are reversed

Postpartum Hemorrhage

Definition

- loss of >500 mL of blood at the time of vaginal delivery, or >1,000 mL with C/S
- early – within first 24 h postpartum
- late – after 24 h but within first 6 wk

Epidemiology

- incidence 5-15%

Etiology (4 Ts)

1. Tone
   - uterine atony
     - most common cause of PPH
     - avoid by giving oxytocin with delivery of the anterior shoulder or placenta
     - occurs within first 24 h
     - due to:
       - labour (prolonged, precipitous, induced, augmented)
       - uterus (infection, over-distention)
       - placenta (abruption, previa)
       - maternal factors (grand multiparity, gestational HTN)
       - halothane anesthesia

2. Tissue
   - retained placental products
   - retained blood clots in an atonic uterus
   - gestational trophoblastic neoplasia

3. Trauma
   - laceration (vagina, cervix, uterus), episiotomy, hematoma (vaginal, vulvar, retroperitoneal), uterine rupture, uterine inversion

4. Thrombin
   - coagulopathy
     - most identified prior to delivery (low platelets increases risk)
     - includes hemophilia, DIC, Aspirin® use, ITP, TTP, vWD (most common)
     - therapeutic anti-coagulation

Common OR Questions

7 layers to dissect
Skin, fatty layer, fascia, muscle separation (rectus abdominis), peritoneum, bladder flap, uterus

Layers of the rectus sheath
Above the arcuate line: external oblique, internal oblique, rectus abdominis
Below the arcuate line: external oblique, transversus abdominis, rectus abdominis

Name of the obliterated umbilical ligament
Urachus

Uterine atony is the most common cause of PPH.

DDx of Early PPH – 4 Ts
Tone (atony)
Tissue (retained placenta, clots)
Trauma (laceration, inversion)
Thrombin (coagulopathy)

DDx of Late PPH
Retained products
± endometritis
Sub-involution of uterus
Investigations
- assess degree of blood loss and shock by clinical exam
- explore uterus and lower genital tract for evidence of tone, tissue or trauma
- may be helpful to observe red-topped tube of blood – no clot in 7–10 min indicates coagulation problem

Management
- ABCs
- 2 large bore IVs and crystalloids
- CBC, coagulation profile, cross and type 4 units pRBCs
- treat underlying cause

Medical Therapy
- oxytocin 20 U/L NS or RL IV continuous infusion
  - in addition can give 10 U IMM after delivery of the placenta
- methylergonovine maleate (ergotamine) 0.25 mg IM/MM q5min up to 1.25 mg; can be given as IV bolus of 0.125 mg (may exacerbate HTN)
- carboprost (Hemabate®), a synthetic PGF-1α analog 0.25 mg IM/MM q15min to max 2 mg (major prostaglandin side effects and contraindicated in cardiovascular, pulmonary, renal and hepatic dysfunction)

Local Control
- bimanual compression: elevate the uterus and massage through patient's abdomen
- uterine packing (mesh with antibiotic treatment)
- Bakri Balloon for tamponade: may slow hemorrhage enough to allow time for correction of coagulopathy or for preparation of an OR

Surgical Therapy (Intractable PPH)
- D&C (beware of vigorous scraping which can lead to Asherman's syndrome)
- embolization of uterine artery or internal iliac artery by interventional radiologist
- laparotomy with bilateral ligation of uterine artery (may be effective), internal iliac artery (not proven), ovarian artery, or hypogastric artery
- hysterectomy last option with angiographic embolization if post-hysterectomy bleeding

Retained Placenta

Definition
- placenta undelivered after 30 min postpartum

Etiology
- placenta separated but not delivered
- abnormal placental implantation (placenta accreta, placenta increta, placenta percreta)

Risk Factors
- placenta previa, prior C/S, post-pregnancy curettage, prior manual placental removal, uterine infection

Clinical Features
- incomplete placenta removed
- risk of postpartum hemorrhage and infection

Investigations
- explore uterus
- assess degree of blood loss

Management
- 2 large bore IVs, type and screen
- Brant maneuver (firm traction on umbilical cord with one hand applying suprapubic pressure to avoid uterine inversion by holding uterus in place)
- oxytocin 10 IU in 20 mL NS into umbilical vein
- manual removal if above fails
- D&C if required
**Uterine Inversion**

**Definition**
- inversion of the uterus through cervix ± vaginal introitus

**Etiology/Epidemiology**
- often iatrogenic (excess cord traction with fundal placenta)
- excessive use of uterine tocolytics
- more common in grand multiparous (lax uterine ligaments)
- 1/1500-1/2000 deliveries

**Clinical Features**
- can cause profound vasovagal response with vasodilation and hypovolemic shock
- shock may be disproportionate to maternal blood loss

**Management**
- urgent management essential, call anesthesia
- ABCs: initiate IV crystalloids
- can use tocolytic drug (see Management of Preterm Labour, OB38) or nitroglycerin IV to relax uterus and aid replacement
- replace uterus without removing placenta
- remove placenta manually and withdraw slowly
- IV oxytocin infusion (only after uterus replaced)
- re-explore uterus
- may require GA ± laparotomy

**Postpartum Pyrexia**

**Definition**
- fever >38°C on any 2 of the first 10 d postpartum, except the first day

**Etiology**
- endometritis
- wound infection secondary to C/S
- mastitis/engorgement
- UTE
- atelectasis
- pneumonia

**Investigations**
- detailed history and physical exam, relevant cultures
- for endometritis: blood and genital cultures

**Treatment**
- depends on etiology
  - infection: empiric antibiotics, adjust when sensitivities available
  - endometritis: clindamycin + gentamycin IV
  - mastitis: cefoxaxillin or cefazolin
  - wound infection: cephalaxin
  - DVT: anticoagulants
- prophylaxis against post-C/S endometritis: begin antibiotic immediately after cord clamping and administer only 1-3 doses – cefazolin is most common choice

**ENDOMETRITIS**
- definition: infection of uterine myometrium and parametrium
- clinical features: fever, chills, abdominal pain, uterine tenderness, foul-smelling discharge or lochia
- treatment: depends on infection severity; oral antibiotics if well, IV with hospitalization in moderate to severe cases

**VENOUS THROMBOEMBOLISM**
- see Venous Thromboembolism, OB21
Mastitis

- definition: inflammation of mammary glands
- must r/o inflammatory carcinoma, as indicated
- differentiate from mammary duct ectasia: mammary duct(s) beneath nipple clogged and dilated ± ductal inflammation ± nipple discharge (thick, grey to green), often postmenopausal women

| Table 26. Lactational versus Non-Lactational Mastitis |
|---------------------------------|------------------------|------------------------|
| **Lactational**                  | **Non-Lactational**    |
| Epidemiology                    | Periductal mastitis most common |
|                                 | Mean age 32 yr          |
| Etiology                        | S. aureus               |
|                                 | May be sterile          |
|                                 | May be infected with S. aureus or other anaerobes |
|                                 | Smoking is risk factor  |
|                                 | May be associated with mammary duct ectasia |
| Symptoms                        | Unilateral localized pain |
|                                 | Tenderness              |
|                                 | Erythema                |
| Treatment                       | Heat or ice packs       |
|                                 | Continued nursing/pumping |
|                                 | Antibiotics (dicloxacillin/cephalexin) |
|                                 | (Erythromycin if pen-allergic) |
| Abscess                         | Fluctuant mass          |
|                                 | Purulent nipple discharge |
|                                 | Fever, leukocytosis     |
|                                 | Discontinue nursing, IV antibiotics (nafcillin/oxacillin), I&D usually required |
|                                 | If mass does not resolve, FNA to exclude cancer and USS to assess presence of abscess |
|                                 | Treatment includes antibiotics, aspiration or I&D (tends to recur) |
|                                 | May develop mammary duct fistula |
|                                 | A minority of non-lactational abscesses may occur peripherally in breast with no associated periductal mastitis (usually S. aureus) |

Postpartum Mood Alterations

POSTPARTUM BLUES
- 85% of new mothers, onset day 3-10; extension of the “normal” hormonal changes and adjustment to a new baby
- self-limited, should resolve by 2 wk
- manifested by mood lability, depressed affect, increased sensitivity to criticism, tearfulness, fatigue, irritability, poor concentration/despondency

POSTPARTUM DEPRESSION
- definition: major depression occurring in a woman within 6 mo of childbirth (see Psychiatry, PS12)
- epidemiology: 10-20%, risk of recurrence 50%
- risk factors
  - personal or family history of depression (including PPD)
  - prenatal depression or anxiety
  - stressful life situation
  - poor support system
  - unwanted pregnancy
  - colicky or sick infant
- clinical features: suspect if the “blues” last beyond 2 wk, or if the symptoms in the first two wk are severe (e.g. extreme disinterest in the baby, suicidal or homicidal/infanticide ideation)
- assessment: Edinburgh Postnatal Depression Scale or other
- treatment: antidepressants, psychotherapy, supportive care, ECT if refractory
- prognosis: interferes with bonding and attachment between mother and baby so it can have long term effects

POSTPARTUM PSYCHOSIS
- definition: onset of psychotic symptoms over 24-72 h within first month postpartum, can present in the context of depression
- epidemiology: rare (0.2%)
Postpartum Care

Postpartum Office Visit at 6 Weeks

Care of Baby
- assess weight, feeding, immunization
- encourage breastfeeding if no contraindications

Care of Mother (The 10 Bs)
- Be careful: do not use douches or tampons for 4-6 wk post-delivery
- Be fit: encourage gradual increases in walking, Kegel exercises
- Birth control: assess for use of contraceptives; breastfeeding is NOT an effective method of birth control (see Gynecology, GY19 for more detail about different contraceptive options postpartum)
- Bladder: assess for urinary incontinence, maintain high fluid intake
- Bleeding: (see Lacerations, OB47), 300 µg of RhIG should be given if Rh+ fetus and Rh− mother or extensive bleeding at delivery
- Blood pressure: especially if gestational HTN
- Blood tests: glucose, CBC (for anemia as sign of hematomas, retained placenta)
- Blues: (see Postpartum Mood Alterations, OB51)
- Bowel: fluids and high-fibre foods, bulk laxatives; for hemorrhoids/perineal tenderness: pain meds, doughnut cushion, Sitz baths, ice compresses
- Breast and pelvic exam: watch for Staphylococcal or Streptococcal mastitis/abscess, ± Pap smear at 6 wk

Physiological Changes Postpartum
- uterus weight rapidly diminishes through catabolism, cervix loses its elasticity and regains firmness
  † should involute ~1 cm below umbilicus per day in first 4-5 d, reaches non-pregnant state in 4-6 wk postpartum
- ovulation resumes in ~45 d for non-lactating women and within 3-6 mo for lactating women
- lochia: normal vaginal discharge postpartum
  † decreases and changes in colour from red (lochia rubra; presence of erythrocytes) → yellow (lochia serosa) → white (lochia alba; residual leukorrhea) over 3-6 wk
  † foul smelling lochia suggests endometritis

Breastfeeding Problems
- inadequate milk: consider domperidone
- breast engorgement: cool compress, manual expression/pumping
- nipple pain: clean milk off nipple after feeds, moisture cream, topical steroid if needed
- mastitis: treat promptly (see Postpartum Pyrexia, OB50)
- inverted nipples: makes feeding difficult
- maternal medications: may require pediatric consultation (see Breastfeeding and Drugs, OB53)

Bladder Dysfunction
- pelvic floor prolapse can occur after vaginal delivery
- stress or urge urinary incontinence common
- increased risk with instrumental delivery or prolonged second stage
- conservative management: pelvic floor retraining with Kegel exercises, vaginal cones or pessaries, lifestyle modifications (e.g. limit fluid, caffeine intake)
- surgical management: minimally invasive procedures (tension-free vaginal tape, transobturator tape, midurethral sling) (see Gynecology, GY35)

Puerperal Pain
- “after pains” common in first 3 d due to uterine contractions; encourage simple analgesia
- ice packs can be used on perineum if painful
- encourage regular analgesia and stool softener

The acronym “BUBBLES” for what to ask about when rounding on postpartum care. Modify this for C/S or vaginal delivery

Baby care and breastfeeding (latch, amount)
Uterus – firm or boggy?
Bladder function – Voiding well? Dysuria?
Bowel function – Passing gas or stool? Constipated?
Lochia or discharge – Any blood?
Episiotomy/laceration/incision – Pain controlled?
Symptoms of VTE – Dyspnea? calf pain?
Breastfeeding and Drugs

Table 27. Drug Safety During Breastfeeding

<table>
<thead>
<tr>
<th>Safe During Breastfeeding</th>
<th>Contraindicated to Breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics (e.g. acetaminophen, NSAIDs)</td>
<td>Chloramphenicol (bone marrow suppression)</td>
</tr>
<tr>
<td>Anticoagulants (e.g. heparin)</td>
<td>Sulphotamides (in G6PD deficiency, can lead to hemolysis)</td>
</tr>
<tr>
<td>Antiepileptics (e.g. phenytoin, carbamazepine, valproic acid)</td>
<td>Nitrofurantoin (in G6PD deficiency, can lead to hemolysis)</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Antimicrobials (e.g. penicillins, aminoglycosides, cephalosporins)</td>
<td>Lithium</td>
</tr>
<tr>
<td>β-adrenergics (e.g. propanolol, labetalol)</td>
<td>Anti-neoplastics and immunosuppressants</td>
</tr>
<tr>
<td>Insulin</td>
<td>Psychotropic drugs (relative contraindication)</td>
</tr>
<tr>
<td>Steroids</td>
<td>OCP (low dose) – although may decrease breast milk production</td>
</tr>
</tbody>
</table>

Common Medications

Table 28. Common Medications

<table>
<thead>
<tr>
<th>Drug Name (Brand Name)</th>
<th>Dosing Schedule</th>
<th>Indications/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>betamethasone valerate (Celestone®)</td>
<td>12 mg IM q24h x 2 doses</td>
<td>Enhancement of fetal pulmonary maturity for PTL</td>
</tr>
<tr>
<td>carprofen (Hemabate®)</td>
<td>0.25 mg IM/MM q15min; max 2 mg</td>
<td>Treatment of uterine atony</td>
</tr>
<tr>
<td>cefazolin</td>
<td>2 g IV then 1 g q8h</td>
<td>GBS prophylaxis (penicillin allergic and not at risk for anaphylaxis)</td>
</tr>
<tr>
<td>clindamycin</td>
<td>900 mg IV q8h</td>
<td>GBS prophylaxis (penicillin allergic and at risk for anaphylaxis)</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>6 mg IM q12h x 4 doses</td>
<td>Enhancement of fetal pulmonary maturity for PTL</td>
</tr>
<tr>
<td>dinoprostone (Cervidil®; PGE2 impregnated thread)</td>
<td>10 mg PV (remove after 12h) max of 3 doses</td>
<td>Induction of labour</td>
</tr>
<tr>
<td>doxilamivam</td>
<td>2 tabs qhs + 1 tab qAM + 1 tab qPM max of 8 tabs/d</td>
<td>Each tablet contains 10 mg doxilamivam succinate with vitamin B6</td>
</tr>
<tr>
<td>erythromycin</td>
<td>500 mg IV q6h</td>
<td>GBS prophylaxis (penicillin allergic and at risk for anaphylaxis)</td>
</tr>
<tr>
<td>folic acid</td>
<td>0.4-1 mg PO OD x 1-3 mo; prepregnancy and T1</td>
<td>Prevention of oNTD</td>
</tr>
<tr>
<td>methotrexate</td>
<td>5 mg PO OD with past Hx of NTD</td>
<td>For ectopic pregnancy or medical abortion</td>
</tr>
<tr>
<td>methylfetamine (Ergotamine®)</td>
<td>0.075 mg IM/IMM q5min up to 1.25 mg IV or BOS 0.125 mg</td>
<td>Treatment of uterine atony</td>
</tr>
<tr>
<td>misoprostol (Cytotec®)</td>
<td>80-1000 µg PR x 1 dose 400 µg PO x 1 dose or 800 µg PV x 1 dose, 3 to 7 d after methotrexate</td>
<td>For treatment of PPH</td>
</tr>
<tr>
<td>oxytocin (Pitocin®)</td>
<td>0.5-2.0 mU/min F, or 10 U/L NS incr. by 1-2 mU/min q20-60min max of 36-48 mU/min 10 U IM at delivery of anterior shoulder and of placenta 20 U/L NS or RL IV continuous infusion</td>
<td>Augmentation of labour (also induction of labour)</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>5 million U IV then 2.5 million U IV q4h until delivery</td>
<td>Treatment of uterine atony</td>
</tr>
<tr>
<td>PGE2 gel (Prostin® gel)</td>
<td>0.5 mg PV q6-12h; max of 3 doses</td>
<td>Induction of labour</td>
</tr>
<tr>
<td>Rh IgG (Rhogam®)</td>
<td>300 µg IM x 1 dose</td>
<td>Given to Rh negative women</td>
</tr>
<tr>
<td>misoprostol (Cytotec®) is also indicated to protect against NSAID-induced gastric ulcers in non-pregnant individuals. The use of misoprostol for cytoprotection is contraindicated in pregnancy. Warn female patients of this contraindication.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acronyms ................................................................. 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic Anatomy Review .................................................. 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differential Diagnoses of Common Presentations ....................... 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of Vision                                      Diplopia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red Eye                                             Ocular Problems in the Elderly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular Pain                                         Ocular Problems in the Elderly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Floaters                                            Contact Lens Wearer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flashes of Light                                      Acute Painless Vision Loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular Emergencies ................................................... 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Ocular Examination ............................................... 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optics ........................................................................ 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging Modalities ...................................................... 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Orbit .................................................................. 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Globe Displacement                                    Orbital Cellulitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preseptal Cellulitis ................................................. 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacrimal Apparatus .................................................. 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry Eye Syndrome                                      Dacryocystitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epiphora (Tearing)                                    Dacryoadenitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lids and Lashes ........................................................ 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lid Swelling                                          Hordeolum (Stye)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ptosis                                               Chalazion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichiasis                                          Blepharitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entropion                                            Xanthelasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectropion                                            ........................................ 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctiva .............................................................. 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pinguecula                                           ........................................ 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pterygium                                             ........................................ 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subconjunctival Hemorrhage                            ........................................ 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis ........................................................... 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sclera .................................................................... 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episcleritis                                          Scleritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cornea .................................................................... 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foreign Body                                         Herpes Zoster</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal Abrasion                                     Keratoconus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent Erosions                                    Arcus Senilis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal Ulcer                                        Kayser-Fleischer Ring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes Simplex ......................................................... 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Uveal Tract ........................................................ 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uveitis ................................................................... 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lens .......................................................................... 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataracts                                            ........................................ 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dislocated Lens (Ectopia Lentsis) .............................. 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitreous .................................................................... 22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior Vitreous Detachment (PVD) ............................. 22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitreous Hemorrhage ............................................... 22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endophthalmitis and Vitritis ....................................... 22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retina ...................................................................... 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Retinal Artery Occlusion (CRAO) ......................... 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Branch Retinal Artery Occlusion (BRAO) .......................... 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central/Branch Retinal Vein Occlusion (CRVO/BRVO) ............. 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinal Detachment (RD) ............................................... 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinitis Pigmentosa .................................................. 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leber's Congenital Amaurosis ....................................... 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-Related Macular Degeneration (ARMD) ........................ 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glaucoma ................................................................ 27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Open Angle Glaucoma (POAG) ............................. 27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal Tension Glaucoma .............................................. 27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary Open Angle Glaucoma ..................................... 27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Angle-Closure Glaucoma ..................................... 27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary Angle-Closure Glaucoma ................................... 27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupils ...................................................................... 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupillary Light Reflex ............................................... 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupil Abnormalities ..................................................... 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated Pupil (Mydriasis) .............................................. 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constricted Pupil (Miosis) ............................................. 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative Afferent Pupillary Defect (RAPD) ......................... 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancies ................................................................ 34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lid Carcinoma .............................................................. 34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant Melanoma ...................................................... 34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastases .................................................................. 34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular Manifestations of Systemic Disease ....................... 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV/AIDS .................................................................. 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Systemic Infections ............................................. 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus (DM) .................................................. 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension ............................................................... 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Sclerosis (MS) ............................................... 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA/Amaurosis Fugax ..................................................... 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves' Disease ........................................................... 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connective Tissue Disorders ......................................... 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giant Cell Arteritis (GCA)/Temporal Arteritis ..................... 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis ................................................................. 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric Ophthalmology ............................................... 38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strabismus ................................................................. 38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amblyopia ................................................................. 38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocoria ................................................................. 38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinoblastoma ............................................................ 38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinopathy of Prematurity (ROP) .................................... 38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasolacrimal System Defects ......................................... 38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmia Neonatorum ............................................... 38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital Glaucoma ..................................................... 38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular Trauma .............................................................. 42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blunt Trauma ................................................................ 42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blow-Out Fracture ........................................................ 42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penetrating Trauma ....................................................... 42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical Burns ............................................................ 42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyphema ................................................................. 42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical Ophthalmology ................................................ 44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular Drug Toxicity ..................................................... 44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common Medications .................................................... 44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>References ................................................................. 46</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA</td>
<td>(best corrected) visual acuity</td>
</tr>
<tr>
<td>AION</td>
<td>anterior ischemic optic neuropathy</td>
</tr>
<tr>
<td>ARMD</td>
<td>age-related macular degeneration</td>
</tr>
<tr>
<td>BRAD</td>
<td>branch retinal artery occlusion</td>
</tr>
<tr>
<td>BRVO</td>
<td>branch retinal vein occlusion</td>
</tr>
<tr>
<td>C/D</td>
<td>cup to disc ratio</td>
</tr>
<tr>
<td>CMV</td>
<td>cytomegalovirus</td>
</tr>
<tr>
<td>CRAO</td>
<td>central retinal artery occlusion</td>
</tr>
<tr>
<td>D</td>
<td>diopter</td>
</tr>
<tr>
<td>DR</td>
<td>diabetic retinopathy</td>
</tr>
<tr>
<td>EDM</td>
<td>extraocular movement</td>
</tr>
<tr>
<td>FML</td>
<td>fluoromethalone</td>
</tr>
<tr>
<td>GAT</td>
<td>Goldmann applanation tonometry</td>
</tr>
<tr>
<td>GCA</td>
<td>giant cell arteritis</td>
</tr>
<tr>
<td>HE</td>
<td>Heidelberg retinal tomography</td>
</tr>
<tr>
<td>INO</td>
<td>internuclear ophthalmoplegia</td>
</tr>
<tr>
<td>IOL</td>
<td>intraocular lens</td>
</tr>
<tr>
<td>IOP</td>
<td>intraocular pressure</td>
</tr>
<tr>
<td>LASIK</td>
<td>laser-assisted in situ keratomileusis</td>
</tr>
<tr>
<td>OHT</td>
<td>ocular hypertension</td>
</tr>
<tr>
<td>PGCAD</td>
<td>primary angle-closure glaucoma</td>
</tr>
<tr>
<td>PDT</td>
<td>photodynamic therapy</td>
</tr>
<tr>
<td>PERLA</td>
<td>pupils equal, round, and reactive to light and accommodation</td>
</tr>
<tr>
<td>POAG</td>
<td>primary open angle glaucoma</td>
</tr>
<tr>
<td>PRK</td>
<td>photorefractive keratectomy</td>
</tr>
<tr>
<td>PVD</td>
<td>posterior vitreous detachment</td>
</tr>
<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>RAPD</td>
<td>relative afferent pupillary defect</td>
</tr>
<tr>
<td>RD</td>
<td>retinal detachment</td>
</tr>
<tr>
<td>RDG</td>
<td>retinopathy of prematurity</td>
</tr>
<tr>
<td>REPE</td>
<td>retinal pigment epithelium</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>SPIK</td>
<td>superficial punctate keratitis</td>
</tr>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
<tr>
<td>YAG</td>
<td>yttrium aluminium garnet</td>
</tr>
</tbody>
</table>

**Basic Anatomy Review**

**Lateral View**

- Tendon of superior rectus muscle
- Ciliary muscle and body
- Lens
- Conjunctival fornix

**Superior View**

- Anterior chamber iris
- Ciliary muscle and body
- Retina
- Tendon of lateral rectus muscle
- Sclera

**Figure 1. Anatomy of the eye**

**Figure 2. Layers of the retina**
### Differential Diagnoses of Common Presentations

#### Loss of Vision

- **Transient** (seconds to hours)
  - Cornea/Anterior Segment
    - Corneal edema
    - Hyphema
    - Acute angle-closure glaucoma
    - Trauma/foreign body
  - Vitreous/Retina/Optic Nerve
    - Vitreous hemorrhage
    - Retinal detachment
    - Retinal artery/vein occlusion
    - Acute macular lesion
    - Optic neuritis
    - Temporal arteritis
    - Anterior ischemic optic neuropathy (AION)
  - Cortical/Other
    - Occipital infarction/hemorrhage
    - Cortical blindness
    - Functional (non-organic, diagnosis of exclusion)

- **Acute** (seconds to days)
  - Cornea/Anterior Segment
    - Corneal dystrophy/scar/edema
    - Cataract
    - Glaucoma
  - Vitreous/Retina/Optic Nerve
    - Age-related macular degeneration (ARMD)
    - Diabetic retinopathy
    - Retinal vascular insufficiency
    - Compressive optic neuropathy (intracranial mass, orbital mass)
    - Intraocular neoplasm
    - Retinitis pigmentosa
  - Cortical/Other
    - Pituitary adenoma
    - Medication-induced (sildenafil, amiodarone)
    - Nutritional deficiency
    - Papilledema

- **Chronic** (weeks to months)
  - Cornea/Anterior Segment
    - Cataract
    - Refractive error
    - Corneal dystrophy
  - Vitreous/Retina/Optic Nerve
    - ARMD
    - Glaucoma
    - Diabetic retinopathy
  - Cortical/Other
    - Reversible
      - Trauma/foreign body
      - Retinal artery/vein occlusion
      - Retinal detachment
    - Irreversible
      - ARMD
      - Glaucoma
      - Diabetic retinopathy

Note: Anti-VEGF treatment for exudative ARMD and diabetic macular edema may reverse some vision loss.
Red Eye
- lids/orbit/lacrimal system
  - hordeolum/chalazion
  - blepharitis
  - entropion/ectropion
  - foreign body/laceration
  - dacryocystitis/dacryoadenitis
- conjunctiva/sclera
  - subconjunctival hemorrhage
  - conjunctivitis
  - dry eyes
  - pterygium
  - episcleritis/scleritis
  - preseptal/orbital cellulitis
- cornea
  - foreign body (including contact lens)
  - keratitis
  - abrasion, laceration
  - ulcer
- anterior chamber
  - anterior uveitis (iritis, iridocyclitis)
  - acute angle-closure glaucoma
  - hyphema (blood in anterior chamber)
  - hypopyon (pus in anterior chamber)
- other
  - trauma
  - post-operative
  - endophthalmitis

Ocular Pain
- differentiate from eye fatigue (asthenopia)
- herpes zoster prodrome
- trauma/foreign body
- keratitis
- corneal abrasion, corneal ulcer
- acute angle-closure glaucoma
- acute uveitis
- scleritis, episcleritis
- optic neuritis

Floaters
- age-related vitreous syneresis (shrinkage and collapse of vitreous gel)
- posterior vitreous detachment (PVD)
- vitreous hemorrhage
- retinal tear/detachment
- posterior uveitis

Flashes of Light (Photopsia)
- PVD
- retinal tear/detachment
- migraine with aura

Photophobia (Severe Light Sensitivity)
- corneal abrasion, corneal ulcer
- keratitis
- acute angle-closure glaucoma
- iritis
- meningitis, encephalitis
- migraine
- subarachnoid hemorrhage (SAH)

Diplopia (Double Vision)
- binocular diplopia (occurs with both eyes open, eliminated with occlusion of either eye)
  - strabismus, CN palsy (III, IV, VI) 2° to ischemia, diabetes, tumour, trauma, myasthenia gravis, muscle restriction/entrapment, thyroid ophthalmopathy, internuclear ophthalmoplegia (INO) 2° to multiple sclerosis, brainstem infarct
- monocular diplopia (occurs with one eye open, remains with occlusion of unaffected eye)
  - refractive error, strands of mucus in tear film, keratoconus, cataracts, dislocated lens, peripheral iridotomy

Ocular Problems in the Elderly
- blepharitis
- ptosis
- entropion, ectropion
- dry eyes, epiphora (excessive tearing)
- presbyopia
- cataracts
- glaucoma
- age-related macular degeneration
- retinal artery/vein occlusion
- temporal arteritis (arteritic ischemic optic neuropathy)

Ocular Problems in the Contact Lens Wearer
- superficial punctate keratitis (SPK) from dry eyes
- solution hypersensitivity
- tight lens syndrome
- corneal abrasion
- giant papillary conjunctivitis/contact lens allergy
- sterile corneal infiltrates (immunologic)
- infected ulcers (*Pseudomonas, Acanthamoeba*)

Acute Painless Vision Loss
- vitreous hemorrhage
- retinal artery/vein occlusion
- retinal detachment
- anterior ischemic optic neuropathy (AION)
- optic neuritis
- amaurosis fugax
Table 1. Common Differential Diagnoses of Red Eye

<table>
<thead>
<tr>
<th></th>
<th>Conjunctivitis</th>
<th>Acute Iritis</th>
<th>Acute Angle-Closure Glaucoma</th>
<th>Keratitis (Corneal Abrasion/Ulcer)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discharge</strong></td>
<td>Bacteria: purulent Virus: serous Allergy: mucous</td>
<td>No</td>
<td>No</td>
<td>Profuse tearing</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td>No</td>
<td>++ (tender globe)</td>
<td>+++ (nausea)</td>
<td>++ (on blinking)</td>
</tr>
<tr>
<td><strong>Photophobia</strong></td>
<td>No</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Blurred Vision</strong></td>
<td>No</td>
<td>+++</td>
<td>+++</td>
<td>Varies</td>
</tr>
<tr>
<td><strong>Pupil</strong></td>
<td>Normal</td>
<td>Smaller</td>
<td>Fixed in mid-dilation</td>
<td>Same or smaller</td>
</tr>
<tr>
<td><strong>Injection</strong></td>
<td>Conjunctiva with limbal pallor</td>
<td>Ciliary flush</td>
<td>Diffuse</td>
<td>Diffuse</td>
</tr>
<tr>
<td><strong>Cornea</strong></td>
<td>Normal</td>
<td>Keratic precipitates</td>
<td>Cloudy</td>
<td>Infiltrate, edema, epithelial defects</td>
</tr>
<tr>
<td><strong>Intraocular pressure</strong></td>
<td>Normal</td>
<td>Varies</td>
<td>Increased markedly</td>
<td>Normal or increased</td>
</tr>
<tr>
<td><strong>Anterior chamber</strong></td>
<td>Normal</td>
<td>+ + + Cells and flare</td>
<td>Shallow</td>
<td>Cells and flare or normal</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Large, tender pre-auricular node(s) if viral</td>
<td>Posterior synechiae</td>
<td>Coloured halos</td>
<td>Nausea and vomiting</td>
</tr>
</tbody>
</table>

Ocular Emergencies

These require urgent consultation to an ophthalmologist for management

**Sight Threatening**
- lid/globe lacerations
- chemical burn
- corneal ulcer
- gonococcal conjunctivitis
- acute iritis
- acute angle-closure glaucoma
- CRAO
- intraocular foreign body
- retinal detachment (especially when macula threatened)
- endophthalmitis

**Life Threatening**
- proptosis (r/o cavernous sinus fistula or thrombosis)
- CN III palsy with dilated pupil (intracranial aneurysm or neoplastic lesion)
- papilledema (must r/o intracranial mass lesion)
- orbital cellulitis
- temporal (giant cell) arteritis
- leukocoria: white reflex (absent red reflex, must rule out retinoblastoma)

The Ocular Examination

**Visual Acuity – Distance**
- Snellen Acuity (Figure 5) = testing distance (usually 20 feet or 6 metres)
  - smallest line patient can read on the chart
  - e.g. 20/40 = what the patient can see at 20 feet (numerator), what a “normal” person can see at 40 feet (denominator)
- testing hierarchy for low vision: Snellen acuity (20/x) → counting fingers at a given distance (CF) → hand motion (HM) → light perception with projection (LP with projection) → light perception (LP) → no light perception (NLP)
- legal blindness is BCVA that is ≤20/200 in best eye
- minimum visual requirements to operate a non-commercial automobile in Ontario are: with both eyes open and examined together, 20/50 BCVA

**Visual Acuity – Near**
- use pocket vision chart (Rosenbaum Pocket Vision Screener)
- record Jaeger (J) or Point number and testing distance (usually 30 cm) e.g. J2 @ 30 cm
- conversion to distance VA possible (e.g. immobile patient, no distance chart available)

Example 1
- SC 20/40 -1
- 20/80 +2 → 20/25 PH

Example 2
- CC CF 3’
- HM

Note: RIGHT EYE visual acuity always listed on top.

- V Vision
- SC Without correction
- CC With correction
- 20/40 +1 All except one letter of 20/40
- 20/80 +2 All of 20/80 plus two letters of 20/70
- PH Visual acuity with pinhole correction
- CF Counting fingers
- HM Hand motion

Figure 5. Ophthalmology nomenclature for VA

Normal Infant and Child Visual Acuity
- 6-12 mo: 20/120
- 1-2 yr: 20/80
- 2-4 yr: 20/20

Not every red eye has conjunctivitis.
Visual Acuity for Infants, Children, Non-English Speakers, and Dysphasics

- newborns
  - VA cannot be tested
- 3 mo-3 yr (can only assess visual function, not acuity)
  - test each eye for fixation symmetry using an interesting object
  - normal function noted as “CSM” = central, steady, and maintained
- 3 yr until alphabet known
  - pictures or letter cards/charts such as HOTV or Sheridan-Gardner test (children point to optotypes on a provided matching card)
  - tumbling “E” chart

Colour Vision

- test with Ishihara pseudoisochromatic plates
- record number of correctly identified plates presented to each eye, specify incorrect plates
- important for testing optic nerve function (e.g. optic neuritis, chloroquine use, thyroid ophthalmopathy)
- note: red-green colour blindness is sex-linked and occurs in 7-10% of males

VISUAL FIELDS

- test “visual fields by confrontation” (4 quadrants, each eye tested separately) for estimation of visual field loss (Figure 6)
- accurate, quantifiable assessment with automated visual field testing (Humphrey or Goldmann) or Tangent Screen
- use Amsler grid (each eye individually) to test for central or paracentral scotomas (island-like gaps in the vision) in patients with ARMD

PUPILS

- use reduced room illumination with patient focusing on distant object to prevent “near reflex”
- examine pupils for shape, size, symmetry, and reactivity to light (both direct and consensual response)
- test for relative afferent pupillary defect (RAPD) with swinging flashlight test
- test pupillary constriction portion of near reflex by bringing object close to patient’s nose
- “normal” pupil testing often noted as PERLA (pupils equal, round, and reactive to light and accommodation)

ANTERIOR CHAMBER DEPTH

- shine light tangentially from temporal side
- if >2/3 of nasal side of iris in shadow → shallow anterior chamber

The van Herick method

- shine thin angled slit beam onto the peripheral cornea of each eye
- estimate depth between the posterior surface of the cornea and the iris as a proportion of corneal thickness
- follow-up with gonioscopy for ratios ≤1/4

Gonioscopy

- allows direct visualization of the angle structures
- angle considered open if trabecular meshwork, scleral spur, and iris processes are visualized
- angle considered narrow (occludable) if only Schwalbe’s line or a small portion of the trabecular meshwork is seen

EXTRAOCULAR MUSCLES

Alignment

- Hirschberg corneal reflex test
  - examine in primary position of gaze (i.e. straight ahead) with patient focusing on distant object
  - shine light into patient’s eyes from ~30 cm away
  - corneal light reflex should be symmetric and at the same position on each cornea
- strabismus testing as indicated (cover test, cover-uncover test, prism testing) (see Strabismus, OP38)
Movement
- examine movement of eyeball through six cardinal positions of gaze (Figure 8)
- ask patient if diplopia is present in any position of gaze
- observe for horizontal, vertical, or rotatory nystagmus (rhythmic, oscillating movements of the eye)
- resolving horizontal nystagmus at end-gaze is usually normal
- see sidebar for cranial nerve innervation of extraocular muscles

Diplopia
- major symptom associated with dysfunction of extraocular muscles or abnormalities of the motor nerves innervating these muscles
- must determine whether diplopia is monocular or binocular
- determine whether diplopia was sudden onset (due to an acute event such as ischemia) or gradual (due to progressive process such as tumour or inflammation)
- with myasthenia gravis, diplopia and ptosis usually worsen on prolonged upgaze; can rule out with a Tensilon® test (see Neurology, N32)
- if suspect compressive lesion (most commonly seen with CN III palsy with a blown pupil), need MRI and angiography to rule out aneurysm or tumour
- new-onset diplopia that disappears with occlusion of either eye (binocular diplopia) needs urgent referral while chronic binocular diplopia and monocular diplopia should be referred non-urgently

Diplopia
- major symptom associated with dysfunction of extraocular muscles or abnormalities of the motor nerves innervating these muscles
- must determine whether diplopia is monocular or binocular
- determine whether diplopia was sudden onset (due to an acute event such as ischemia) or gradual (due to progressive process such as tumour or inflammation)
- with myasthenia gravis, diplopia and ptosis usually worsen on prolonged upgaze; can rule out with a Tensilon® test (see Neurology, N32)
- if suspect compressive lesion (most commonly seen with CN III palsy with a blown pupil), need MRI and angiography to rule out aneurysm or tumour
- new-onset diplopia that disappears with occlusion of either eye (binocular diplopia) needs urgent referral while chronic binocular diplopia and monocular diplopia should be referred non-urgently

Figure 8. Diagnostic positions of gaze for isolated primary actions of extraocular muscles

Figure 9. Diplopia

EXTERNAL EXAMINATION
- four Ls
  - lymph nodes (preauricular, submandibular)
  - lids
  - lashes
  - lacrimal system

SLIT-LAMP EXAMINATION
- systematically examine all structures of the anterior segment and anterior vitreous (for structures see Figure 1)
  - when necessary, use:
    - fluorescein dye: stains Bowman’s membrane in de-epithelialized cornea; dye appears green with cobalt blue filtered light
    - Rose Bengal dye: stains devitalized corneal epithelium
  - special lenses (78 or 90 D) used with the slit-lamp allow a binocular, stereoscopic view of the fundus and vitreous

Aqueous Flare
- resembles dust particles in a beam of light
- results from protein leaking from blood vessels
- distinguish from aqueous cells (individual cells in anterior chamber)

Note:
RIGHT EYE drawn on the left,
LEFT EYE drawn on the right
(as if looking at patient’s face).
TONOMETRY
- measurement of intraocular pressure (IOP) (Figure 11)
- normal range is 10-21 mmHg (average 15 mmHg)
- IOP has diurnal variation, so always record the time of day at which the measurement was taken
- commonly measured by:
  - Goldmann applanation tonometry (GAT): gold standard, performed using the slit-lamp with special tip (prism)
  - Tono-Pen®: benefit is portability and use of disposable probe tips. Use when cornea is scarred/asymmetric (GAT inaccurate)
  - air puff (non-contact and least reliable)
- use topical anesthetic for GAT and Tono-Pen®

OPHTHALMOSCOPY/FUNDOSCOPY
- performed with:
  - direct ophthalmoscope (monocular with small field of view, only posterior pole visualized)
  - slit-lamp with 78 or 90 D lens (binocular view, visualization to mid-periphery of retina)
  - indirect ophthalmoscopy with headlamp and 20 or 28 D lens (binocular view, visualization of entire retina to ora serrata/edge of retina)
- best performed with pupils dilated (see Table 11 for list of mydriatics and cycloplegics)
  1. assess red reflex
     - light reflected off the retina produces a “red reflex” when viewed from ~1 foot away
     - anything that interferes with the passage of light will diminish the red reflex (e.g. large vitreous hemorrhage, cataract)
  2. examine the posterior segment of the eye (Figure 10)
     - vitreous
     - optic disc (colour, C:D ratio, sharpness of disc margin)
     - macula (~2 disc diameters temporal to disc), fovea (foveal light reflex)
     - retinal vessels
     - retinal background
- contraindications to pupillary dilatation
  - shallow anterior chamber – can precipitate acute angle-closure glaucoma
  - iris-supported anterior chamber lens implant
  - potential neurologic abnormality requiring pupil evaluation
  - use caution with cardiovascular disease – mydriatics may cause tachycardia

REFRACITION
- two techniques used
  - flash/streak retinoscopy: refractive error determined objectively by the examiner using lenses and retinoscope
  - manifest: subjective trial using loose lenses or a phoropter (device the patient looks through that is equipped with lenses)
- a typical lens prescription would contain:
  - sphere power in D (measurement of refractive power of lens, equal to reciprocal of focal length in meters)
  - cylinder power in D to correct astigmatism (always positive value)
  - axis of cylinder in degrees
  - “add” (bifocal/progressive reading lens) for presbyopes
    - e.g. -1.50 + 1.00 x 120 degrees, add +2.00

REFRACTIVE EYE SURGERY
- permanently alters corneal refractive properties by ablating tissue to change curvature of the cornea
- used for correction of myopia, hyperopia, and astigmatism
- common types include PRK and LASIK (see Surgical Ophthalmology, OP44)
- potential risks/side-effects: infection, under/overcorrection, decreased night vision (nyctalopia), corneal haze, dry eyes, regression, complete sever of corneal flap (LASIK only)
Table 2. Optics

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Clinical Features</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emmetropia</strong></td>
<td>Image of distant objects focus exactly on the retina (Figure 12)</td>
<td>No refractive error</td>
<td></td>
</tr>
<tr>
<td><strong>Myopia</strong></td>
<td>Globe too long relative for refractive mechanisms, or refractive mechanisms too strong</td>
<td>“Nearsightedness”</td>
<td>Correct with negative diopter/concave/“negative” lenses to diverge light rays</td>
</tr>
<tr>
<td></td>
<td>Light rays from distant object focus in front of retina → blurring of (distance) vision (Figure 12)</td>
<td>Usually presents in 1st or 2nd decade, stabilizes in 2nd and 3rd decade; rarely begins after age 25 except in patients with diabetes or cataracts</td>
<td>Blurring of distance vision; near vision usually unaffected</td>
</tr>
<tr>
<td><strong>Hyperopia</strong></td>
<td>Globe too short relative to refractive mechanisms, or refractive mechanisms too weak</td>
<td>“Farsightedness”</td>
<td>When symptomatic, correct with positive diopter/convex/“plus” lenses to converge light rays</td>
</tr>
<tr>
<td></td>
<td>Light rays from distant object focus behind retina</td>
<td>“Nearsightedness”</td>
<td>When symptomatic, correct with positive diopter/convex/“plus” lenses to converge light rays</td>
</tr>
<tr>
<td></td>
<td>May be developmental or due to any etiology that shortens globe</td>
<td>May develop accommodative esotropia (see Strabismus; OP38)</td>
<td>Hyperopia corrected with positive converging lens</td>
</tr>
<tr>
<td><strong>Astigmatism</strong></td>
<td>Light rays not refracted uniformly in all meridians due to non-spherical surface of cornea or non-spherical lens (e.g. football-shaped)</td>
<td>Affects approximately 30% of population, with prevalence increasing with age</td>
<td>Correct with cylindrical lens (if regular), try contact lens (if irregular)</td>
</tr>
<tr>
<td></td>
<td>Two types:</td>
<td>Mild astigmatism unnoticeable</td>
<td>Refractive eye surgery</td>
</tr>
<tr>
<td></td>
<td>Regular—curvature uniformly different in meridians at right angles to each other</td>
<td>Higher amounts of astigmatism may cause blurring vision, squinting, asthenopia, or headaches</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irregular—distorted cornea caused by injury, keratoconus (cone-shaped cornea), corneal scar, or severe dry eye</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Presbyopia</strong></td>
<td>Normal aging process (&gt;40 yr)</td>
<td>If initially emmetropic, person begins to hold reading material farther away, but distance vision remains unaffected</td>
<td>Correct with positive diopter/convex/“plus” lenses for reading</td>
</tr>
<tr>
<td></td>
<td>Hardening/reduced deformability of lens results in decreased accommodative ability</td>
<td>If initially myopic, person removes distance glasses to read</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Accommodative power is 14D at age 10, diminishes to 3.5D by age 40</td>
<td>If initially hyperopic, symptoms of presbyopia occur earlier</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Near images cannot be focused onto the retina (focus is behind the retina as in hyperopia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anisometropia</strong></td>
<td>Difference in refractive errors between eyes</td>
<td></td>
<td>Second most common cause of amblyopia in children</td>
</tr>
</tbody>
</table>

### Imaging Modalities

- **Adaptive optics scanning laser ophthalmology** – optical coherence tomography (SLO-OCT)
  - combines the surface detail of confocal ophthalmoscopy with the internal detail of OCT
  - allows 3D OCT images, volume and area maps, and retinal thickness maps, at the resolution of living rods and cones
  - can visualize photoreceptors, nerve fibres and blood cells in retinal capillaries
- **CT, MRI**
  - orbital imaging, particularly in orbital trauma and neuro-ophthalmology
- **Fluorescein angiography**
  - non-invasive evaluation of vascular pattern of the fundus
  - commonly used in ARMD, DR, retinal vascular diseases
- **Indocyanine green angiography**
  - uses infra-red light and intravenous ICG dye for imaging of choroidal structure
  - particularly useful to detect polypoidal vasculopathy (variant of ARMD) more commonly present among Asian patients
• Heidelberg retinal tomograph (HRT)
  ▪ confocal scanning laser tomography of retinal nerve head and surrounding nerve fibre layer
  ▪ used to assess extent of structural glaucomatous changes
• optical coherence tomography (OCT)
  ▪ non-invasive, cross-sectional, high-resolution imaging of vitreous, retinal layers, optic nerve
  ▪ commonly used to assess macular edema/holes/cysts, ARMD progression, epi-retinal membrane, retinal detachment (RD)
• anterior segment optical coherence tomography (AS-OCT)
  ▪ non-invasive, cross-sectional, high-resolution imaging of cornea, aqueous, iris and lens
• perimetry
  ▪ quantitative evaluation of visual fields, used to screen for scotomas and monitor progression
    (e.g. in glaucoma)
• ultrasonography
  ▪ evaluation of orbit in real-time. A-scans (one-dimensional), B-scans (two-dimensional), and Doppler are all used (e.g. large RDs, foreign bodies, monitoring intraocular tumours)

### The Orbit

#### Globe Displacement

<table>
<thead>
<tr>
<th>Table 3. Exophthalmos (Proptosis) and Enophthalmos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exophthalmos (Proptosis)</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td><strong>Definition</strong></td>
</tr>
<tr>
<td>• Anterior displacement (protrusion) of the globe</td>
</tr>
<tr>
<td>• Exophthalmos generally refers to an endocrine etiology or protrusion of &gt;18 mm (as measured by a Hertel exophthalmometer)</td>
</tr>
<tr>
<td>• Proptosis generally refers to other etiologies (e.g. cellitis) or protrusion of &lt;18 mm</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
</tr>
<tr>
<td>• CT/MRI head/orbits, ultrasound orbits, thyroid function tests</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
</tr>
<tr>
<td>• Note: rule out pseudoexophthalmos (e.g. lid retraction)</td>
</tr>
<tr>
<td>• Graves’ disease (unilateral or bilateral, most common cause in adults)</td>
</tr>
<tr>
<td>• Orbital cellulitis (unilateral, most common cause in children)</td>
</tr>
<tr>
<td>• 1° or 2° orbital tumours</td>
</tr>
<tr>
<td>• Orbital/retrobulbar hemorrhage</td>
</tr>
<tr>
<td>• Cavernous sinus thrombosis or fistula</td>
</tr>
<tr>
<td><strong>Cranial nerve involvement</strong></td>
</tr>
<tr>
<td>• Orbital fat atrophy</td>
</tr>
<tr>
<td>• Congenital abnormality</td>
</tr>
<tr>
<td>• Metastatic disease</td>
</tr>
</tbody>
</table>

#### Preseptal Cellulitis

• infection of soft tissue anterior to orbital septum

**Etiology**
• usually follows periorbital trauma or dermal infection

**Clinical Features** (Table 4)

**Treatment**
• systemic antibiotics (suspect *H. influenzae* in children; *S. aureus* or *Streptococcus* in adults)
  ▪ e.g. amoxicillin-clavulanic acid
  ▪ if severe or child <1 yr, treat as orbital cellulitis

#### Orbital Cellulitis

• OCULAR and MEDICAL EMERGENCY
• inflammation of orbital contents posterior to orbital septum
• common in children, elderly, and immunocompromised

**Etiology**
• usually 2° to sinus/facial/tooth infections or trauma, can also arise from preseptal cellulitis

**Clinical Features** (Table 4)

**Treatment**
• admit, blood cultures x2, orbital CT, IV antibiotics (ceftriaxone + vancomycin) for 1 wk
• surgical drainage of abscess with close follow-up, especially in children

---

**Periorbital and Orbital Cellulitis Before and After the Advent of Haemophilus influenzae type B Vaccination**

*Ophthalmol 2000;107:1450-1453*

**Study:** Retrospective case series.

**Patients:** 315 pediatric inpatients in Massachusetts with a discharge diagnosis of periorbital or orbital cellulitis.

**Results:** Prior to the introduction of the Hib vaccine, 11.7% of cases were culture positive for Hib. After the vaccination program was initiated, the case rate dropped to 3.5% (P=0.028). All cases of orbital cellulitis were associated with sinusitis, and cases of periorbital cellulitis were most commonly associated with upper respiratory tract infections or sinusitis.
Complications
• optic nerve inflammation, cavernous sinus thrombosis, meningitis and brain abscess with possible loss of vision, death

Table 4. Clinical Features of Preseptal and Orbital Cellulitis

<table>
<thead>
<tr>
<th>Finding</th>
<th>Preseptal Cellulitis</th>
<th>Orbital Cellulitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>May be present</td>
<td>Present</td>
</tr>
<tr>
<td>Lid edema</td>
<td>Moderate to severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Conjunctival injection</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Chemosis</td>
<td>Absent or mild</td>
<td>Marked</td>
</tr>
<tr>
<td>Proptosis</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Pain on eye movement</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Ocular mobility</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Vision</td>
<td>Normal</td>
<td>Diminished ± diplopia</td>
</tr>
<tr>
<td>RAPD</td>
<td>Absent</td>
<td>May be seen</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>Moderate</td>
<td>Marked</td>
</tr>
<tr>
<td>ESR</td>
<td>Normal or elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Additional findings</td>
<td>Skin infection</td>
<td>Sinusitis, dental abscess</td>
</tr>
</tbody>
</table>

Lacrimal Apparatus
• tear film made up of three layers
  ▪ outer oily layer (reduces evaporation): secreted by the Meibomian glands
  ▪ middle watery layer (forms the bulk of the tear film): constant secretion from conjunctival glands and reflex secretion by lacrimal gland with ocular irritation or emotion
  ▪ inner mucinous layer (aids with tear adherence to cornea): secreted by conjunctival goblet cells
• tears drain from the eyes through the upper and lower lacrimal puncta → superior and inferior canaliculi → lacrimal sac → nasolacrimal duct → nasal cavity behind inferior concha (Figure 3)

Dry Eye Syndrome (Keratoconjunctivitis Sicca)

Etiology
• aqueous-deficient (lacrimal pathology)
  ▪ Sjögren Syndrome (autoimmune etiology e.g. rheumatoid arthritis, SLE)
  ▪ non-Sjögren Syndrome (idiopathic age-related disease; lacrimal gland scarring e.g. trachoma; decreased secretion e.g. contact lenses, CN VII palsy; anticholinergics, antihistamines, diuretics, β-blockers)
• evaporative (normal lacrimal function, excessive evaporation of aqueous layer)
  ▪ Meibomian gland dysfunction (posterior blepharitis)
  ▪ vitamin A deficiency (xerophthalmia with goblet cell dysgenesis)
  ▪ eyelid abnormalities e.g. ectropion, CN VII palsy (decreased blinking)
  ▪ preserved topical ocular medications
  ▪ contact lenses, allergic conjunctivitis
• overlap of mixed etiologies common

Clinical Features
• dry eyes, red eyes, foreign body sensation, blurred vision, tearing
• slit-lamp exam: decreased tear meniscus, decreased tear break up time (normally should be 10 s), SPK
• surface damage observed with fluorescein/Rose Bengal staining
• decreased distance in Schirmer’s test

Complications
• erosions and scarring of cornea

Treatment
• medical: preservative-free artificial tears up to q1h and ointment at bedtime (preservative toxicity becomes significant if used more than q1h PRN)
  ▪ for severe cases, cyclosporine ophthalmic emulsion 0.05% (Restasis®) can be used
• procedural: punctal occlusion (punctal plug insertion), lid taping, tarsorrhaphy (sew lids together) if severe
• treat underlying cause

Long term use of artificial tears with preservatives should be avoided when treating dry eyes.
**Epiphora (Excessive Tearing)**

**Etiology**
- emotion, pain
- environmental stressor (cold, wind, pollen, sleep deprivation)
- lid/lash malposition: ectropion, entropion, trichiasis
- inflammatory: conjunctivitis, uveitis, keratitis, corneal foreign body
- dry eyes (reflex tearing)
- lacrimal drainage obstruction (congenital failure of canalization, aging, rhinitis, dacryocystitis)
- paradoxical gustatory lacrimation reflex (crocodile tears)

**Investigations**
- using fluorescein dye, examine for punctal reflux by pressing on canaliculi
- Jones dye test: fluorescein placed in conjunctival cul-de-sac, and cotton applicator placed in nose to detect flow (i.e. rule out lacrimal drainage obstruction)

**Treatment**
- lid repair for ectropion or entropion
- eyelash removal for trichiasis
- punctal irrigation
- nasolacrimal duct probing (infants)
- tube placement: temporary (Crawford) or permanent (Jones)
- surgical: dacryocystorhinostomy (see Surgical Ophthalmology, OP44) – forming a new connection between the lacrimal sac and the nasal cavity

**Dacryocystitis**
- acute or chronic infection of the lacrimal sac
- most commonly due to obstruction of the nasolacrimal duct
- commonly associated with *S. aureus*, *S. pneumoniae*, *Pseudomonas* species

**Clinical Features**
- pain, swelling, redness over lacrimal sac at medial canthus
- epiphora, crusting, ± fever
- digital pressure on the lacrimal sac may extrude pus through the punctum
- in the chronic form, epiphora may be the only symptom

**Treatment**
- warm compresses, nasal decongestants, systemic and topical antibiotics
- if chronic, obtain cultures by aspiration
- once infection resolves, consider dacryocystorhinostomy (see Surgical Ophthalmology, OP44)

**Dacryoadenitis**
- inflammation of the lacrimal gland (outer third of upper eyelid)
- acute causes: *S. aureus*, mumps, EBV, herpes zoster, *N. gonorrhoeae*
- chronic causes (often bilateral): lymphoma, leukemia, sarcoidosis, tuberculosis, thyroid ophthalmopathy

**Clinical Features**
- pain, swelling, tearing, discharge, redness of the outer region of the upper eyelid
- chronic form is more common and may present as painless enlargement of the lacrimal gland

**Treatment**
- supportive: warm compresses, oral NSAIDs
- systemic antibiotics if bacterial cause
- if chronic, treat underlying disorder

**Lids and Lashes**

**Lid Swelling**

**Etiology**
- commonly due to allergy, with shriveling of skin between episodes
- dependent edema on awakening (e.g. CHF, renal or hepatic failure)
- orbital venous congestion due to mass or cavernous sinus fistula
- dermatochalasis (loose skin due to aging or heredity)
- lid cellulitis, thyroid disease (e.g. myxedema), trauma, chemosis
Ptosis

- drooping of upper eyelid

Etiology

- aponeurotic: disinsertion or dehiscence of levator aponeurosis (most common)
  - associated with advancing age, trauma, surgery, pregnancy, chronic lid swelling
- mechanical
  - incomplete opening of eyelid due to mass or scarring
- neuromuscular
  - myasthenia gravis (neuromuscular palsy), myotonic dystrophy
  - CN III palsy
  - Horner’s syndrome (see Constricted Pupil, Horner’s Syndrome, OP32)
- congenital
- pseudoptosis (e.g. dermatochalasis, enophthalmos, contralateral exophthalmos)

Treatment

- surgery

Trichiasis

- eyelashes turned inwards
- may result from chronic inflammatory lid diseases (e.g. blepharitis), Stevens-Johnson syndrome, trauma, burns
- patient complains of red eye, foreign body sensation, tearing
- may result in corneal ulceration and scarring

Treatment

- topical lubrication, eyelash plucking, electrolysis, cryotherapy

Entropion

- lid margin turns in towards globe causing tearing, foreign body sensation, and red eye
- most commonly affects lower lid
- may cause abrasions with 2nd corneal scarring

Etiology

- involutional (aging)
- cicatricial (herpes zoster, surgery, trauma, burns)
- orbicularis oculi muscle spasm
- congenital

Treatment

- lubricants, evert lid with tape, surgery

Ectropion

- lid margin turns outward from globe causing tearing and possibly exposure keratitis

Etiology

- involutional (aging)
- paralytic (CN VII palsy)
- cicatricial (burns, trauma, surgery)
- mechanical (lid edema, tumour, herniated fat)
- congenital

Treatment

- topical lubrication, surgery

Hordeolum (Stye)

- acute inflammation of eyelid gland: either Meibomian glands (internal lid) or glands of Zeis (modified sweat gland) or Moll (modified sebaceous gland in external lid)
- infectious agent is usually S. aureus
- painful, red swelling of lid

Treatment

- warm compresses, lid care, gentle massage
- topical antibiotics (e.g. erythromycin ointment bid)
- usually resolves in 2-5 d
**Chalazion**

- chronic granulomatous inflammation of Meibomian gland often preceded by an internal hordeolum
- acute inflammatory signs are usually absent
- differential diagnosis: basal cell carcinoma, sebaceous cell adenoma, Meibomian gland carcinoma

**Treatment**

- warm compresses
- if no improvement after 1 mo, consider incision and curettage
- chronic recurrent lesion must be biopsied to rule out malignancy

---

**Blepharitis**

- inflammation of lid margins

**Etiology**

- two main types
  - staphylococcal (S. aureus): ulcerative, dry scales
  - seborrheic: no ulcers, greasy scales

**Clinical Features**

- itching, tearing, foreign body sensation
- thickened, red lid margins, crusting, discharge with pressure on lids ("toothpaste sign")

**Complications**

- recurrent chalazia
- conjunctivitis
- keratitis (from poor tear film)
- corneal ulceration and neovascularization

**Treatment**

- warm compresses and lid scrubs with diluted "baby shampoo"
- topical or systemic antibiotics as needed
- if severe, ophthalmologist may prescribe a short course of topical corticosteroids

---

**Xanthelasma**

- eyelid xanthoma (lipid deposits in dermis of lids)
- appear as pale, slightly elevated yellowish plaques or streaks
- most commonly on the medial upper lids, often bilateral
- associated with hyperlipidemia (approximately 50% of patients)
- common in the elderly, more concerning in the young

**Treatment**

- excision for cosmesis only, commonly recurs

---

**Conjunctiva**

- thin, vascular mucous membrane/epithelium
- bulbar conjunctiva: lines sclera to limbus (junction between cornea and sclera)
- palpebral (tarsal) conjunctiva: lines inner surface of eyelid

---

**Pinguecula**

- yellow-white subepithelial deposit of hyaline and elastic tissue adjacent to the nasal or temporal limbus, sparing the cornea
- associated with sun and wind exposure, aging
- common, benign, sometimes enlarges slowly
- may be irritating due to abnormal tear film formation over the deposits
- surgery for cosmesis only
- irritative symptoms may be treated with lubricating drops
**Pterygium**
- fibrovascular triangular encroachment of epithelial tissue onto the cornea, usually nasally
- may induce astigmatism, decrease vision
- excision for chronic inflammation, threat to visual axis, cosmesis
- irritative symptoms may be treated with lubricating drops
- one-third recur after excision, lower recurrence with conjunctival autograft (5%)

**Subconjunctival Hemorrhage**
- blood beneath the conjunctiva, otherwise asymptomatic
- idiopathic or associated with trauma, Valsalva maneuver, bleeding disorders, hypertension
- give reassurance if no other ocular findings, resolves spontaneously in 2-3 wk
- if recurrent, consider medical/hematologic work-up

**Conjunctivitis**

**Etiology**
- infectious
  - bacterial, viral, chlamydial, fungal, parasitic
- non-infectious
  - allergic: atopic, seasonal, giant papillary conjunctivitis (contact lens wearers)
  - toxic: irritants, dust, smoke, irradiation
  - 2nd to another disorder: dacryocystitis, dacryoadenitis, cellulitis, Kawasaki's disease

**Clinical Features**
- red eye (conjunctival injection often with limbal pallor), chemosis, subepithelial infiltrates
- itching, foreign body sensation, tearing, discharge, crusting of lashes in the morning, lid edema
- preauricular and/or submandibular nodes
- follicles: pale lymphoid elevations of the conjunctiva
- papillae: fibrovascular elevations of the conjunctiva with central network of finely branching vessels (cobblestone appearance)

**ALLERGIC CONJUNCTIVITIS**

**Atopic**
- associated with rhinitis, asthma, dermatitis, hay fever
- small papillae, chemosis, thickened and erythematous lids, corneal neovascularization
- seasonal (pollen, grasses, plant allergens)
- treatment: cool compresses, antihistamine, mast cell stabilizer (e.g. ketotifen, olopatadine)

**Giant Papillary Conjunctivitis**
- immune reaction to mucus debris on lenses in contact lens wearers
- large papillae form on superior palpebral conjunctiva
- treatment: clean, change or discontinue use of contact lens

**Vernal Conjunctivitis**
- large papillae (cobblestones) form on superior palpebral conjunctiva with corneal ulcers and keratitis
- seasonal (warm weather)
- occurs in children, lasts for 5-10 yr then resolves
- treatment: consider topical steroid, topical cyclosporine (by ophthalmologist)

**VIRAL CONJUNCTIVITIS**
- serous discharge, lid edema, follicles
- subepithelial corneal infiltrates
- may be associated with rhinorrhea
- preauricular node often palpable and tender
- initially unilateral, often progresses to the other eye
- mainly due to adenovirus – highly contagious for up to 12 d

**Treatment**
- cool compresses, topical lubrication
- usually self-limiting (7-12 d)
- proper hygiene is very important
**BACTERIAL CONJUNCTIVITIS**
- purulent discharge, lid swelling, papillae, conjunctival injection, chemosis
- common agents include *S. aureus, S. pneumoniae, H. influenzae* and *M. catarrhalis*
- in neonates or if sexually active must consider *N. gonorrhoeae* (invades cornea to cause keratitis)
- *Chlamydia trachomatis* is the most common cause in neonates (see *Chlamydial Conjunctivitis*, below)

**Treatment**
- topical broad-spectrum antibiotic
- systemic antibiotics if indicated, especially in neonates and children
- usually a self-limited course of 10-14 d if no treatment, 1-3 d with treatment

**CHLAMYDIAL CONJUNCTIVITIS**
- caused by *Chlamydia trachomatis*
- affects neonates (ophthalmia neonatorum) on day 3-5, sexually active individuals
- causes trachoma and inclusion conjunctivitis

**Trachoma**
- leading infectious cause of blindness in the world
- severe keratoconjunctivitis leads to corneal abrasion, ulceration, and scarring
- initially, follicles on superior palpebral conjunctiva
- treatment: topical and systemic tetracycline

**Inclusion Conjunctivitis**
- chronic conjunctivitis with follicles and subepithelial infiltrates
- most common cause of conjunctivitis in newborns
- prevention: topical erythromycin at birth
- treatment: topical and systemic tetracycline, doxycycline or erythromycin

**Sclera**
- white fibrous outer protective coat of the eye, composed of irregularly distributed collagen bundles
- continuous with the cornea anteriorly and the dura of the optic nerve posteriorly
- episclera is a thin layer of vascularized tissue between the sclera and conjunctiva

**Episcleritis**
- immunologically mediated inflammation of episclera
- 1/3 bilateral; simple (80%) or nodular (20%)
- more frequent in women than men (3:1)

**Etiology**
- mostly idiopathic
- in 1/3 of cases, associated with collagen vascular diseases, infections (herpes zoster, herpes simplex, syphilis), inflammatory bowel disease, rosacea, atopy

**Clinical Features**
- usually asymptomatic; may have discomfort, heat sensation, red eye (often interpalpebral), rarely pain
- sectoral or diffuse injection of radially-directed vessels, chemosis, small mobile nodules
- blanches with topical phenylephrine (constricts superficial conjunctival vessels)

**Treatment**
- generally self-limited, recurrent in 2/3 of cases
- topical steroid for 3-5 d if painful (prescribed and monitored by ophthalmologist)

**Scleritis**
- usually bilateral: diffuse, nodular, or necrotizing
- anterior scleritis: pain radiating to face, may cause scleral thinning, in some cases necrotizing
- posterior scleritis: rapidly progressive blindness, may cause exudative RD
- more common in women and elderly

---

**Antibiotics versus Placebo for Acute Bacterial Conjunctivitis**
Cochrane DB Syst Rev 2006;2:CD001211

**Study:** Cochrane systemic review and meta-analysis of 5 heterogeneous trials investigating the efficacy of topical antibiotic treatment for bacterial conjunctivitis.

**Patients:** 1034 participants randomized to topical antibiotic treatment or placebo.

**Results:** Topical antibiotics are beneficial in improving early (days 2 to 5) clinical and microbiological remission rates, with respective risk ratios (RR) of 1.24 and 1.77, respectively. Later (days 6 to 10) cure rates are lower than earlier values, with a clinical RR of 1.11 and a microbiological RR of 1.56. Most cases would, however, clinically resolve spontaneously on days 2-5 with placebo treatment only (85%). There were no reported serious outcomes in either group.

**Conclusion:** Topical antibiotic treatment of acute bacterial conjunctivitis is associated with a significantly improved rate of early clinical and microbiological remission, although most cases are self-limiting, and serious sight-threatening complications are rare.
Etiology
- may be a manifestation of systemic disease
- collagen vascular disease, e.g. SLE, rheumatoid arthritis, ankylosing spondylitis
- granulomatous, e.g. tuberculosis, sarcoidosis, syphilis
- metabolic, e.g. gout, thyrotoxicosis
- infectious, e.g. S. aureus, S. pneumoniae, P. aeruginosa, herpes zoster
- chemical or physical agents (e.g. thermal, alkali, or acid burns)
- idiopathic

Clinical Features
- severe pain, photophobia, red eye, decreased vision
- pain is best indicator of disease progression
- inflammation of scleral, episcleral, and conjunctival vessels
- may have anterior chamber cells and flare, corneal infiltrate, scleral thinning
- sclera may have a blue hue (best seen in natural light), due to rearranged scleral fibres
- scleral edema or thinning
- failure to blanch with topical phenylephrine

Treatment
- systemic NSAID or steroid (topical steroids are not effective)
- treat underlying etiology

Cornea

- function
  - transmission of light
  - refraction of light (2/3 of total refractive power of eye)
  - barrier against infection, foreign bodies
- transparency due to avascularity, uniform structure and deturgescence (relative dehydration)
- 5 layers (anterior to posterior): epithelium, Bowman’s membrane, stroma, Descemet’s membrane, endothelium (dehydrates the cornea; dysfunction leads to corneal edema)
- extensive sensory fibre network (V1 distribution); therefore abrasions and inflammation (keratitis) are very painful

Foreign Body
- foreign material in or on cornea
- may have associated rust ring if metallic
- patients may note tearing, photophobia, foreign body sensation, red eye
- signs include foreign body, conjunctival injection, epithelial defect that stains with fluorescein, corneal edema, anterior chamber cells/flare

Complications
- abrasion, infection, scarring, rust ring, 2° iritis

Treatment
- remove under magnification using local anesthetic and sterile needle or refer to ophthalmology (depending on depth and location)
- treat as per corneal abrasion

Corneal Abrasion

- epithelial defect usually due to trauma (e.g. fingernails, paper, twigs), contact lens (Figure 14)

Clinical Features (Table 5)
- pain, redness, tearing, photophobia, foreign body sensation
- de-epithelialized area stains with fluorescein dye
- pain relieved with topical anesthetic

Complications
- infection, ulceration, recurrent erosion, 2° iritis

Treatment
- topical antibiotic (drops or ointment)
- consider topical NSAID, cycloplegic (relieves pain and photophobia by paralyzing ciliary muscle), patch
- most abrasions clear spontaneously within 24-48 h
Recurrent Erosions

- recurrent episodes of pain, photophobia, foreign body sensation with a spontaneous corneal epithelial defect
- usually occurs upon awakening
- associated with improper adherence of epithelial cells to the underlying basement membrane

Etiology

- previous traumatic corneal abrasion
- corneal dystrophy
- idiopathic

Treatment

- as for corneal abrasion until re-epithelialization occurs
- topical hypertonic saline ointment at bedtime for 3 mo, topical lubrication
- bandage contact lens, anterior stromal puncture or phototherapeutic keratectomy for chronic recurrences

Corneal Ulcer

Etiology

- local necrosis of corneal tissue due to infection
- infection is usually bacterial, rarely viral, fungal or protozoan (Acanthamoeba)
- 2° to corneal exposure, abrasion, foreign body, contact lens use (50% of ulcers)
- also associated with conjunctivitis, blepharitis, keratitis, vitamin A deficiency

Clinical Features

- pain, photophobia, tearing, foreign body sensation, decreased VA (if central ulcer)
- corneal opacity that necroses and forms an excavated ulcer with infiltrative base
- overlying corneal epithelial defect that stains with fluorescein
- may develop corneal edema, conjunctival injection, anterior chamber cells/flare, hypopyon, corneal hypoesthesia (in viral keratitis)
- bacterial ulcers may have purulent discharge, viral ulcers may have watery discharge

Complications

- decreased vision, corneal perforation, iritis, endophthalmitis

Investigations

- Seidel test: fluorescein drop on the cornea under cobalt blue filter is used to detect penetrating lesions. Any aqueous leakage will change dark orange dye to bright yellow-green at site of wound

Treatment

- urgent referral to ophthalmology
- culture prior to treatment
- topical antibiotics every hour
- must treat vigorously to avoid complications

<table>
<thead>
<tr>
<th>Table 5. Corneal Abrasion vs. Corneal Ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abra</strong></td>
</tr>
<tr>
<td><strong>Time Course</strong></td>
</tr>
<tr>
<td><strong>History of Trauma</strong></td>
</tr>
<tr>
<td><strong>Cornea</strong></td>
</tr>
<tr>
<td><strong>Iris Detail</strong></td>
</tr>
<tr>
<td><strong>Corneal Thickness</strong></td>
</tr>
<tr>
<td><strong>Extent of Lesion</strong></td>
</tr>
</tbody>
</table>

Herpes Simplex Keratitis

- usually HSV type 1 (90% of population are carriers)
- may be triggered by stress, fever, sun exposure, immunosuppression

Clinical Features

- pain, tearing, foreign body sensation, red eye, may have decreased vision, eyelid edema
- corneal hypoesthesia
- dendritic (thin and branching) lesion in epithelium that stains with fluorescein

Antiviral Treatment and other Therapeutic Interventions for Herpes Simplex Virus Epithelial Keratitis

Cochrane DB Syst Rev 2010;12:CD002898

Rates of corneal re-epithelialization after acute HSV corneal epithelial keratitis are similar after treatment with trifluridine or acyclovir, and significantly better than after treatment with idoxuridine or vidarabine. Brivudine and ganciclovir are not inferior to acyclovir. Combining an antiviral agent with Interferon or corneal epithelial debridement did not improve outcomes overall, but did hasten corneal healing. Debridement with concomitant antiviral treatment was more effective than debridement alone.

Patching for corneal abrasion.

Cochrane DB Syst Rev 2006;2:CD004764

Patching is not indicated for simple corneal abrasions, measuring less than 10 mm. There is no improvement in healing rates on days 1-3, no changes in reported pain and no difference in the use of antibiotics between the patch and non-patch groups.

Figure 14. Corneal abrasion vs. ulcer

Abrasion vs. Ulcer on Slit Lamp

An abrasion appears clear while an ulcer is more opaque.

Figure 14. Corneal abrasion vs. ulcer
Complications
- corneal scarring (can lead to loss of vision)
- chronic interstitial keratitis due to penetration of virus into stroma
- 2° iritis, 2° glaucoma

Treatment
- topical antiviral such as trifluridine, consider systemic antiviral such as acyclovir
- dendritic debridement
- NO STEROIDS initially – may exacerbate condition
- ophthalmologist must exercise caution if adding topical steroids for chronic keratitis or iritis

Herpes Zoster
- dermatitis of the forehead (CN V1 territory) may involve globe
- Hutchinson's sign: if tip of nose is involved (nasociliary branch of V1) then eye will be involved in approximately 75% of cases
- if no nasal involvement, eye is involved in 1/3 of patients

Clinical Features
- pain, tearing, photophobia, red eye
- corneal edema, pseudodendrite, superficial punctate keratitis
- corneal hypoesthesia

Complications
- corneal keratitis, ulceration, perforation and scarring
- 2° iritis, 2° glaucoma, cataract
- muscle palsies (rare) due to CNS involvement
- occasionally severe post-herpetic neuralgia

Treatment
- oral antiviral (acyclovir, valcyclovir, or famciclovir) immediately
- topical steroids, cycloplegia as indicated for keratitis, iritis
- erythromycin ointment if conjunctival involvement

Keratoconus
- bilateral paracentral thinning and bulging (ectasia) of the cornea to form a conical shape
- usually sporadic, but associated with Down's syndrome, atopy, contact lens use (theorized to be related to chronic vigorous eye rubbing)
- associated with breaks in Descemet's and Bowman's membrane
- results in irregular astigmatism, scarring, stromal edema

Treatment
- attempt correction with spectacles or contact lens
- cross-linking treatment may halt or slow disease progression
- intrastromal corneal ring segments can help flatten the corneal cone
- penetrating keratoplasty (corneal transplant) 90% successful
- post-operative complications: endophthalmitis, graft rejection, graft failure, graft dehiscence

Arcus Senilis
- hazy white ring in peripheral cornea, <2 mm wide, clearly separated from limbus
- common, bilateral, benign corneal degeneration due to lipid deposition, part of the aging process
- may be associated with hypercholesterolemia if age <40 yr, check lipid profile
- no associated visual symptoms, no complications, no treatment necessary

Kayser-Fleischer Ring
- brown-yellow-green pigmented ring in peripheral cornea, starting inferiorly
- due to deposition of copper pigment in Descemet's membrane
- associated with Wilson's disease
- no associated symptoms or complications of ring
- treat underlying disease
The Uveal Tract

- uveal tract (from anterior to posterior) = iris, ciliary body, choroid
- vascularized, pigmented middle layer of the eye, between the sclera and the retina

Uveitis

- uveal inflammation which may involve one or all three parts of the tract
- idiopathic or associated with autoimmune, infectious, granulomatous, malignant causes
- should be managed by an optometrist or ophthalmologist
- anatomically classified as anterior uveitis, intermediate uveitis, posterior uveitis or panuveitis based on primary site of inflammation

Table 6. Anatomic Classification of Uveitis

<table>
<thead>
<tr>
<th>Location</th>
<th>Anterior Uveitis (Irisitis)</th>
<th>Intermediate Uveitis</th>
<th>Posterior Uveitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Usually idiopathic</td>
<td>Mostly idiopathic, 2° causes include sarcoidosis, Lyme disease and multiple sclerosis</td>
<td>Bacterial: syphilis, tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Connective tissue diseases (see Rheumatology, RH8)</td>
<td></td>
<td>Viral: herpes simplex virus, cytomegalovirus in AIDS</td>
</tr>
<tr>
<td></td>
<td>HLA-B27: reactive arthritis, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease</td>
<td></td>
<td>Fungal: histoplasmosis, candidiasis</td>
</tr>
<tr>
<td></td>
<td>Non-HLA-B27: juvenile idiopathic arthritis</td>
<td></td>
<td>Parasitic: toxoplasmosis (most common cause), toxocara</td>
</tr>
<tr>
<td></td>
<td>Infectious: syphilis, Lyme disease, toxoplasmosis, TB, HSV, herpes zoster</td>
<td></td>
<td>Immunosuppression may predispose to any of the above infections</td>
</tr>
<tr>
<td></td>
<td>Other: sarcoidosis, trauma, large abrasion, post ocular surgery</td>
<td></td>
<td>Autoimmune: Behçet’s disease (triad of oral ulcers, genital ulcers, and posterior uveitis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Malignancies (masquerade syndrome): metastatic lesions, malignant melanoma</td>
</tr>
</tbody>
</table>

Clinical Features

- Photophobia (due to reactive spasm of inflamed iris muscle), ocular pain, tenderness of the globe, brow ache (ciliary muscle spasm), decreased VA (in severe cases with hydropopy), lacrimation
- Ciliary flush (perilimbal conjunctival injection), miosis (spasm of sphincter muscle)
- Anterior chamber “cells” (WBC in anterior chamber), decreased VA, episcleral injection, keratic precipitates, corneal neovascularization
- Iris typically reduces IOP because ciliary body inflammation causes decreased aqueous production; however, severe iritis, or iritis from herpes simplex and zoster may cause an inflammatory glaucoma (trabeclitis)
- Insidious onset of blurred vision, accompanied by vitreous floaters
- Initial symptoms are usually unilateral but inflammatory changes are usually bilateral and asymmetric
- Associated with anterior uveitis, most severe cases of 2° intermediate uveitis
- Vitreous cells, condensations, and snowballs (vitreous aggregates of inflammatory cells)
- Posterior segment ‘snowbank’ = grey-white fibrovascular plaque at the pars plana
- Painless as choroid has no sensory innervation
- Often no conjunctival or scleral injection present
- Decreased VA
- Floaters (debris and inflammatory cells)
- Vitreous cells and opacities
- Hypopyon formation

Complications

- Inflammatory glaucoma
- Posterior synechiae
  - Adhesions of posterior iris to anterior lens capsule
  - Indicated by an irregularly shaped pupil
  - If occurs 360° entraps aqueous in posterior chamber, iris bows forward “iris bombé” → angle closure glaucoma
- Peripheral anterior synechiae (rare); adhesions of iris to cornea → secondary angle closure glaucoma
- Cataracts
- Band keratopathy (with chronic iritis)
- Superficial corneal calcification keratopathy
- Macular edema with chronic iritis
- Cystoid macular edema (30% of cases), cataract, and glaucoma
- Macular edema
- Vitritis
- Neovascularization
- Visual field loss/scotoma

Treatment

- Mydriatics: dilate pupil to prevent formation of posterior synechiae and to decrease pain from ciliary spasm
- Steroids: topical, sub-tenon or systemic
- Systemic analgesia
- Extensive medical workup may be indicated to rule out 2° causes
- Systemic or sub-tenon/intravitreal steroids and immunosuppressive agents
- Vitrectomy, cryotherapy or laser photoagulation to the “snowbank”
- Steroids: sub-tenon, intravitreal or systemic if indicated (e.g. threat of vision loss)
Lens

- consists of an outer capsule surrounding a soft cortex and a firm inner nucleus

Cataracts

- any opacity of the lens, regardless of etiology
- most common cause of reversible blindness worldwide
- types: nuclear sclerosis, cortical, posterior subcapsular

Etiology

- acquired
  - age-related (over 90% of all cataracts)
  - cataract associated with systemic disease (may have juvenile onset)
    - diabetes mellitus
    - metabolic disorders (e.g. Wilson's disease, galactosemia, homocystinuria)
    - hypocalcemia
    - traumatic (may be rosette shaped)
    - intraocular inflammation (e.g. uveitis)
    - toxic (steroids, phenothiazines)
    - radiation
  - congenital
    - high myopia
    - present with altered red reflex or leukocoria
    - treat promptly to prevent amblyopia

Clinical Features

- gradual, painless, progressive decrease in VA
- glare, dimness, halos around lights at night, monocular diplopia
- "second sight" phenomenon: patient is more myopic than previously noted, due to increased refractive power of the lens (in nuclear sclerosis only)
  - patient may read without previously needed reading glasses
- diagnose by slit-lamp exam, and by noting changes in red reflex using ophthalmoscope
- may impair view of retina during fundoscopy

Treatment

- medical: attempt correction of refractive error, no strong evidence suggesting benefit of vitamin supplementation
- surgical: definitive treatment
  - indications for surgery
    - to improve visual function in patients whose visual loss leads to functional impairment (no need to wait for "ripe" cataract, may postpone surgery as long as one eye has sufficient vision)
    - to aid management of other ocular disease (e.g. cataract that prevents adequate retinal exam or laser treatment of DR)
  - congenital or traumatic cataracts
  - phacoemulsification (phaco = lens)
  - most commonly used surgical technique (see Surgical Ophthalmology, OP44)
  - post-operative complications
    - RD, endophthalmitis, dislocated IOL, macular edema, glaucoma
    - with new foldable IOLs that have truncated edges, <10% of patients get posterior capsular opacification, which should be treated with YAG laser

Prognosis

- excellent if not complicated by other ocular disease

Dislocated Lens (Ectopia Lentis)

Etiology

- associated with Marfan's Syndrome, Ehlers-Danlos type VI, homocystinuria, syphilis, lens coloboma (congenital cleft due to failure of ocular adnexa to complete growth)
- traumatic
Clinical Features
- decreased VA
- may get unilateral diplopia
- iridodenesis (quivering of iris with movement)
- direct ophthalmoscopy may elicit abnormal red reflex

Complications
- cataract, glaucoma, uveitis

Treatment
- surgical correction ± lens replacement

Vitreous
- clear gel (99% water plus collagen fibrils, glycosaminoglycans, and hyaluronic acid) that fills the posterior segment of eye
- normally adherent to optic disc, pars plana, and along major retinal blood vessels

Posterior Vitreous Detachment (PVD)

Etiology
- central vitreous commonly shrinks and liquefies with age (syneresis)
- during syneresis, molecules that hold water condense causing vitreous floaters
- liquid vitreous moves between posterior vitreous gel and retina
- vitreous is peeled away and separates from the internal limiting membrane of the neurosensory retina posterior to the vitreous base

Clinical Features
- floaters, flashes of light

Complications
- traction at areas of abnormal vitreoretinal adhesions may cause retinal tears/detachment
- retinal tears/detachment may cause vitreous hemorrhage if bridging retinal blood vessel is torn
- complications more common in high myopes and following ocular trauma (blunt or perforating)

Treatment
- acute onset of PVD requires a dilated fundus exam to r/o retinal tears/detachment
- no specific treatment available for floaters/flashes of light

Vitreous Hemorrhage
- bleeding into the vitreous cavity

Etiology
- proliferative diabetic retinopathy (PDR)
- retinal tear/detachment
- PVD
- retinal vein occlusion
- trauma

Clinical Features
- sudden loss of VA
- may be preceded by many floaters and/or flashes of light
- ophthalmoscopy: no red reflex if large hemorrhage, retina not visible due to blood in vitreous

Treatment
- ultrasound (B-scan) to r/o retinal detachment
- expectant: in non-urgent cases (e.g. no retinal detachment), blood usually resorbs in 3-6 mo
- surgical: vitrectomy ± retinal detachment repair ± retinal endolaser to possible bleeding sites/vessels
**Endophthalmitis and Vitritis**

- intraocular infection: acute, subacute, or chronic

**Etiology**
- most commonly a postoperative complication; risk following cataract surgery is <0.1%
- also due to penetrating injury to eye (risk is 3-7%), endogenous spread, and intravitreal injections
- etiology usually bacterial, may be fungal

**Clinical Features**
- painful, red eye, photophobia, discharge
- severely reduced VA, lid edema, proptosis, corneal edema, anterior chamber cells/flare, hypopyon, reduced red reflex
- may have signs of a ruptured globe (severe subconjunctival hemorrhage, hyphema, decreased IOP, etc.)

**Treatment** (see Ocular Trauma, OP42)
- **OCULAR EMERGENCY:** presenting vision best indicates prognosis
  - LP or worse: admission, immediate vitrectomy and intravitreal antibiotics to prevent loss of vision
  - HM or better: vitreous tap for culture and intravitreal antibiotics
  - topical fortified antibiotics

**Retina**

- composed of two parts (Figure 2)
  - neurosensory retina: comprises 9 of the 10 retinal layers, including the photoreceptors and the ganglion cell layer
  - retinal pigmented epithelium (RPE) layer: external to neurosensory retina
  - macula: rich in cones (for colour vision); most sensitive area of retina; looks darker due to lack of retinal vessels and thinning of retina in this region; 15° temporal and slightly below the optic disc
  - fovea: centre of macula; responsible for acute, fine vision
  - optic disc: slightly oval vertically, pinkish colour with centrally depressed yellow cup (normal cup:disc ratio is <0.5), retinal artery and vein pass through cup
  - ora serrata: irregularly-shaped, anterior margin of the retina (can only be visualized with indirect ophthalmoscopy of the far peripheral retina, or through a Goldmann 3 mirror lens)

**Central Retinal Artery Occlusion (CRAO)**

**Etiology**
- emboli from carotid arteries or heart (e.g. arrhythmia, endocarditis, valvular disease)
- thrombus
- temporal arteritis

**Clinical Features**
- sudden, painless (except in GCA), severe monocular loss of vision
- RAPD
- patient may have experienced transient episodes in the past (amaurosis fugax)
- fundoscopy
  - “cherry-red spot”
  - retinal pallor
  - narrowed arterioles, boxcarring (segmentation of blood in arteries)
  - cotton-wool spots (retinal infarcts)
  - cholesterol emboli (Hollenhorst plaques) – usually located at arteriole bifurcations
  - after ~6 wk cherry-red spot recedes and optic disc pallor becomes evident

**Treatment**
- **OCULAR EMERGENCY:** attempt to restore blood flow within 2 h
  - the sooner the treatment = better prognosis (irreversible retinal damage if >90 min of complete CRAO)
  - massage the globe (compress eye with heel of hand for 10 s, release for 10 s, repeat for 5 min) to dislodge embolus
  - decrease intraocular pressure
    - topical β-blockers
    - inhaled oxygen-carbon dioxide mixture
    - IV acetazolamide
    - IV mannitol (draws fluid from eye)
  - drain aqueous fluid – anterior chamber paracentesis (carries risk of endophthalmitis)
  - treat underlying cause to prevent CRAO in other eye

**Endophthalmitis Vitrectomy Study**

For treatment of post-cataract surgery endophthalmitis:
- Intravitreal antibiotics preferred over systemic antibiotics
- Vitrectomy indicated only if vision LP or worse

**Figure 18. Retina**

**Hallmark of CRAO**
“Cherry-red spot” located at centre of macula (visualisation of unaffected highly vascular choroid through the thin fovea).

**Treatment for a central retinal artery occlusion (CRAO) must be initiated within 2 h of symptom onset for any hope of restoring vision.**
Branch Retinal Artery Occlusion (BRAO)
- only part of the retina becomes ischemic resulting in a visual field loss
- more likely to be of embolic etiology than CRAO; need to search for source
- management: ocular massage to dislodge embolus if VA is affected

Central/Branch Retinal Vein Occlusion (CRVO/BRVO)
- second most frequent "vascular" retinal disorder after DR
- usually a manifestation of a systemic disease (e.g. hypertension, diabetes mellitus)
- thrombus occurs within the lumen of the blood vessel

Predisposing Factors
- arteriosclerotic vascular disease
- hypertension
- diabetes mellitus
- glaucoma
- hyperviscosity (e.g. polycythemia rubra vera, sickle-cell disease, lymphoma, leukemia)
- drugs (e.g. oral contraceptive pill, diuretics)

Clinical Features
- painless, monocular, gradual or sudden visual loss
- ± RAPD
- fundoscopy
  - "blood and thunder" appearance
  - diffuse retinal hemorrhages, cotton-wool spots, venous engorgement, swollen optic disc, macular edema
- two fairly distinct groups
  - venous stasis/non-ischemic retinopathy
    - no RAPD, VA approximately 20/80
    - mild hemorrhage, few cotton wool spots
    - resolves spontaneously over weeks to months
    - may regain normal vision if macula intact
  - hemorrhagic/ischemic retinopathy
    - usually older patient with deficient arterial supply
    - RAPD, VA approximately 20/200, reduced peripheral vision
    - more hemorrhages, cotton wool spots, congestion
    - poor visual prognosis

Complications
- degeneration of retinal pigment epithelium
- neovascularization of retina and iris (2° rubeosis), leading to 2° glaucoma
- vitreous hemorrhage
- macular edema

Treatment
- no treatment available to restore vision in CRVO/BRVO
- treat underlying cause/contributing factor
- fluorescein angiography to determine extent of retinal non-perfusion (risk of neovascularization)
- retinal laser photocoagulation, or intravitreal anti-VEGF injection to reduce retinal or iris neovascularization and prevent neovascular glaucoma
- macular grid laser photocoagulation for the treatment of macular edema in BRVO, not CRVO, intravitreal or slow-release biodegradable corticosteroid, or anti-VEGF injection is effective in the treatment of macular edema in both CRVO and BRVO

Retinal Detachment (RD)
- cleavage in the plane between the neurosensory retina and the retinal pigment epithelium (RPE)
- three types
  - rhegmatogenous (most common)
    - caused by a tear or hole in the neurosensory retina, allowing fluid from the vitreous to pass into the subretinal space
    - tears may be caused by posterior vitreous detachment (PVD), degenerative retinal changes, trauma or iatrogenically
    - incidence increases with advancing age, in high myopes and after ocular surgery/trauma
  - tractional
    - caused by traction (due to vitreal, epiretinal, or subretinal membrane) pulling the neurosensory retina away from the underlying RPE
    - found in conditions such as DR, CRVO, sickle cell disease, ROP, and ocular trauma
  - exudative
    - caused by damage to the RPE resulting in fluid accumulation in the subretinal space
    - main causes are intraocular tumours, posterior uveitis, central serous retinopathy
Clinical Features
- sudden onset
- flashes of light
- due to mechanical stimulation of the retinal photoreceptors
- floaters
- hazy spots in the line of vision which move with eye position, due to drops of blood from torn vessels bleeding into the vitreous
- curtain of blackness/portal field loss
- darkness in one field of vision when the retina detaches in that area
- loss of central vision (if macula “off”)
- decreased IOP (usually 4-5 mmHg lower than the other, normal eye)
- ophthalmoscopy: detached retina is grey-white with surface blood vessels, loss of red reflex
- ± RAPD

Treatment
- prophylactic: symptomatic tear (flashes or floaters) can be sealed off with laser/cryotherapy, with the goal of preventing progression to detachment
- therapeutic
  - rhegmatogenous
    - scleral buckle procedure (see Surgical Ophthalmology, OP44)
  - pneumatic retinopexy (see Surgical Ophthalmology, OP44)
  - both treatments above are used in combination with localization of retinal tears/holes and subsequent treatment with cryotherapy or laser to create adhesions between the RPE and the neurosensory retina
  - vitrectomy plus injection of gas or silicone oil in cases of recurrent detachment
  - tractional
    - vitrectomy ± membrane removal/scleral buckling/injection of intraocular gas or silicone oil as necessary
    - exudative
    - treat underlying cause

Complications
- loss of vision, vitreous hemorrhage, recurrent retinal detachment
- a retinal detachment is an emergency, especially if the macula is still attached (macula "on")
- prognosis for visual recovery varies inversely with the amount of time the retina is detached and whether the macula is attached or not

Retinitis Pigmentosa
- worldwide incidence between 1/3500 and 1/7000 people
- many forms of inheritance, most commonly autosomal recessive (60%)
- hereditary degenerative disease of the retina manifested by rod > cone photoreceptor degeneration and retinal atrophy

Clinical Features
- night blindness, decreased peripheral vision ("tunnel vision"), decreased central vision (macular changes), glare (from cataract)

Investigations
- fundoscopy: areas of “bone-spicule” pigment clumping in mid-periphery of retina, narrowed retinal arterioles, pale optic disc
- electrophysiological tests: electroretinography (ERG) and electrooculography (EOG) assist in diagnosis

Treatment
- no treatments available to reverse the condition; cataract extraction improves visual function; vitamin A and vitamin E supplementation can reduce progression of disease in some patients

Leber’s Congenital Amaurosis
- worldwide incidence 1/80,000
- inherited degeneration, autosomal recessive
- symptoms: resting nystagmus, sluggish or no papillary response, severe vision loss/blindness
- diagnosis: 11 types, confirmed by genetic testing
- management: no treatments available to reverse the conditions for most forms; one form (LCAS) shown to be successfully treatable by gene replacement using adeno-associated virus
Age-Related Macular Degeneration (ARMD)

- leading cause of irreversible blindness in the western world, associated with increasing age, usually bilateral
- 10% of people >65 yr old have some degree of ARMD
- female > male
degenerative changes are concentrated at the macula, thus only central vision is lost; peripheral vision (important for navigation) is maintained so patients can usually maintain an independent lifestyle

Classification
- Non-Exudative/“Dry” (Non-Neovascular) ARMD
  - most common type of ARMD (90% of cases)
  - slowly progressive loss of visual function
  - drusen: yellow-white deposits between the retinal pigment epithelium (RPE) and Bruch’s membrane (area separating inner choroidal vessels from RPE)
  - RPE atrophy: coalescence of depigmented RPE, clumps of focal hyperpigmentation or hypopigmentation
  - may progress to neovascular ARMD

- Exudative/“Wet” (Neovascular) ARMD
  - 10% of ARMD, but 80% of ARMD that results in severe visual loss
  - choroidal neovascularization: drusen predisposes to breaks in Bruch’s membrane causing subsequent growth and proliferation of choroidal capillaries
  - may lead to serous detachment of overlying RPE and retina, hemorrhage and lipid precipitates into subretinal space
  - can also lead to an elevated subretinal mass due to fibrous metaplasia of hemorrhagic retinal detachment
  - leads to disciform scarring and severe central visual loss

Risk Factors
- female
- increased age
- family history
- smoking
- Caucasian race
- blue irides

Clinical Features
- variable degree of progressive central visual loss
- metamorphopsia (distorted vision characterized by straight parallel lines appearing convergent or wavy) due to macular edema

Investigations
- Amsler grid: held at normal reading distance with glasses on, assesses macular function
- fluorescein angiography: assess degree of neovascularization – pathologic new vessels leak dye

Treatment
- non-neovascular “dry” ARMD
  - monitor, Amsler grid allows patients to check for metamorphopsia
  - low vision aids (e.g. magnifiers, closed-circuit television)
  - anti-oxidants, green leafy vegetables
  - sunglasses/visors
  - see Age-related Eye Disease Study (AREDS) sidebar
- neovascular “wet” ARMD
  - see Common Medications, OP44
  - laser photocoagulation for neovascularization
  - 50% of choroidal neovascularization cannot be treated initially
  - no definitive treatment for disciform scarring
  - PDT with verteporfin (Visudyne®)
  - IV injection of verteporfin followed by low intensity laser to area of choroidal neovascularization
  - intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF)
  - pegaptanib (Macugen®), ranibizumab (Lucentis®), bevacizumab (Avastin®) (see OP45)

Exudative ARMD
- Hard/Soft Exudates: lipid deposits in the retina associated with diabetic retinopathy and hypertension
- Drusen vs. Exudate
  - Drusen: hyaline material secreted by RPE seen frequently in ARMD typically in peri-macular region
  - Hard/Soft Exudates: lipid deposits in the retina associated with diabetic retinopathy and hypertension

Exudative ARMD Lesions on Fluorescein Angiography
- Classic: well-defined leakage
- Occult: mottled or ill-defined leakage

Classified ARMD Lesions on Fluorescein Angiography
- Classic: well-defined leakage
- Occult: mottled or ill-defined leakage

Common Medications
- Age-related Eye Disease Study (AREDS) Study: A multicentre, single-blind, randomized controlled trial comparing the effects of ranibizumab and bevacizumab on visual acuity in patients with age-related macular degeneration (ARMD).
- Patients: 1208 patients aged 50 or more with age-related macular degeneration (ARMD).
- Intervention: Intravitreal injections of ranibizumab vs. intravitreal injections of bevacizumab.
- Results: The monthly use of either bevacizumab or ranibizumab results in the same visual acuity outcome. This finding holds true for the mean visual acuity and the proportion of patients who gain 15 letters, lose 15 letters, or remain stable. Equivalent visual-acuity outcomes were observed with both the monthly and the as-needed regimens of ranibizumab.
- Conclusion: This study supports the use of either bevacizumab or ranibizumab for the treatment of neovascular ARMD. The continued-global use of intravitreal bevacizumab is an equally effective, low-cost alternative to ranibizumab.
**Glucoma**

**Definition**
- progressive optic neuropathy involving characteristic structural changes to optic nerve head with associated visual field changes
- commonly associated with high IOP, but not required for diagnosis

**Background**
- aqueous is produced by the ciliary body and flows from the posterior chamber to the anterior chamber through the pupil, and drains into the episcleral veins via the trabecular meshwork and the Canal of Schlemm (Figure 20)
- an isolated increase in IOP is termed ocular hypertension (or glaucoma suspect) and these patients should be followed for increased risk of developing glaucoma (10% if IOP 20-30 mmHg; 40% if IOP 30-40 mmHg; and most if IOP >40 mmHg)
- pressures >21 mmHg are more likely to be associated with glaucoma; however, up to 50% of patients with glaucoma do not have IOP >21 mmHg
- loss of peripheral vision most commonly precedes central loss
- sequence of events: gradual pressure rise → increased C:D ratio → visual field loss

**Investigations**
- medical and family history
- VA testing
- slit lamp exam to assess anterior chamber depth
- ophthalmoscopy to assess the disc features
- tonometry by applanation or indentation to measure IOP
- visual field testing
- pachymetry to measure corneal thickness
- future follow-up includes optic disc examination, IOP measurement, and visual field testing to monitor course of disease

---

**Figure 19. Glaucomatous damage**

**Figure 20. Aqueous flow and sites of potential resistance**

- 1. Ciliary body processes
- 2. Pupillary block
- 3. Pretrabecular
- 4. Trabecular and Canal of Schlemm
- 5. Post-trabecular

---

**Anti-angiogenic Therapy with Anti-vascular Endothelial Growth Factor Modalities for Neovascular Age-related Macular Degeneration**

**Cochrane DB Syst Rev** 2008;2:CD005139

**Study:** Cochrane systematic review of RCTs investigating the use of anti-VEGF (vascular endothelial growth factor) modalities for the treatment of wet age-related macular degeneration (ARMD).

**Patients:** Classic or occult wet type ARMD.

**Interventions:** Pegaptanib/Macugen® (aptamer comprised of ribonucleic acids that bind VEGF), ranibizumab/Lucentis® (anti VEGF fragment antibody) and verteporfin/Visudyne® photodynamic therapy (PDT).

**Results:** The MARINA trial showed that the pooled relative risk (RR) for a gain of 15 or more letters of visual acuity was 5.81 for ranibizumab versus placebo, while the FOCUS trial showed that the pooled RR for a gain of 15 or more letters at one year was 4.44 for a combination of ranibizumab + verteporfin PDT versus verteporfin PDT alone.

**Conclusion:** Ranibizumab offers significant benefit for the treatment of wet ARMD with significant improvements in best corrected visual acuity at one year.
Primary Open Angle Glaucoma (POAG)

- most common form, >95% of all glaucoma cases
- due to obstruction of aqueous drainage within the trabecular meshwork and its drainage into the Canal of Schlemm
- insidious and asymptomatic, screening is critical for early detection

Major Risk Factors

- elevated intraocular pressure (>21 mmHg)
- age: prevalence at 40 yr is 1-2% and at 80 yr is 10%
- ethnicity: African descent
- familial (2-3x increased risk); polygenic

Minor Risk Factors

- myopia
- hypertension
- diabetes
- hyperthyroidism (Graves’ disease)
- chronic topical ophthalmic steroid use in steroid responders – yearly eye exams recommended if >4 wk of steroid use
- previous ocular trauma
- anemia/hemodynamic crisis (ask about blood transfusions in past)

Clinical Features

- asymptomatic initially
- insidious, painless, gradual rise in IOP due to restriction of aqueous outflow
- bilateral, but usually asymmetric
- earliest signs are optic disc changes
  - increased C: D ratio (vertical C: D >0.6)
  - significant C: D asymmetry between eyes (>0.2 difference)
  - thinning, notching of the neuroretinal rim
  - flame shaped disc hemorrhage
  - 360º of peripapillary atrophy
  - nerve fibre layer defect
  - large vessels become nasally displaced
- visual field loss
  - slow, progressive, irreversable loss of peripheral vision
  - paracentral defects, arcuate scotoma and nasal step are characteristics (Figure 19)
- late loss of central vision if untreated

Treatment

- medical treatment: decrease IOP by increasing the drainage and/or decreasing the production of aqueous (see Glaucoma Medications, Table 12, OP45)
  - increase aqueous outflow
    * topical cholinergics
    * topical prostaglandin analogues
    * topical α-adrenergics
  - decrease aqueous production
    * topical β-blockers
    * topical and oral carbonic anhydrase inhibitor
    * topical α-adrenergics
- laser trabeculoplasty, cyclophotocoagulation in order to achieve selective destruction of ciliary body (for refractory cases)
- trabeculectomy (see Surgical Ophthalmology, OP44)
- serial optic nerve head examinations, IOP measurements, and visual field testing to monitor disease course

Normal Tension Glaucoma

- POAG with IOP in normal range
- often found in women >60 but may occur earlier
- damage to optic nerve may be due to vascular insufficiency

Treatment

- treat reversible causes
Secondary Open Angle Glaucoma

- increased IOP 2° to ocular/systemic disorders that obstruct the trabecular meshwork
  - steroid-induced glaucoma
  - traumatic glaucoma
  - pigmentary dispersion syndrome
  - pseudoexfoliation syndrome

Primary Angle-Closure Glaucoma

- 5% of all glaucoma cases
- peripheral iris bows forward in an already susceptible eye with a shallow anterior chamber obstructing aqueous access to the trabecular meshwork
- sudden forward shift of the lens-iris diaphragm causes pupillary block, and results in inability of the aqueous to flow from the posterior chamber to the anterior chamber resulting in a sudden rise in IOP

Risk Factors

- hyperopia: small eye, big lens – large lens crowds the angle
- age >70
- female
- family history
- more common in people of Asian and Inuit descent
- mature cataracts
- shallow anterior chamber
- pupil dilation (topical and systemic anticholinergics, stress, darkness)

Clinical Features

- red, painful eye = RED FLAG
- unilateral, but other eye increased risk
- decreased visual acuity, vision acutely blurred from corneal edema
- halos around lights
- nausea and vomiting, abdominal pain
- fixed, mid-dilated pupil
- corneal edema with conjunctival injection
- marked increase in IOP; may be noticeable even to palpation (>40 mmHg)
- shallow anterior chamber ± cells in anterior chamber

Complications

- irreversible loss of vision within hours to days if untreated
- permanent peripheral anterior synchiae, resulting in permanent angle closure

Treatment

- refer to ophthalmologist – acute angle closure glaucoma is an EMERGENCY
  - laser iridotomy
  - aqueous suppressants and hyperosmotic agents
- medical treatment (see Glaucoma Medications, Table 12, OP45)
  - miotic drops (pilocarpine) to reverse pupillary block
  - decrease IOP
    - topical β-blockers
    - topical adrenergics
    - topical cholinergics
      - pilocarpine 1-4% q15min, up to q5min
    - systemic carbonic anhydrase inhibitors
      - IV acetazolamide 250-500 mg
    - systemic hyperosmotic agents
      - oral glycerine 1 g/kg
      - IV mannitol 1 g/kg

Secondary Angle-Closure Glaucoma

Uveitis

- inflamed iris adheres to lens (posterior synchiae)

Neovascular Glaucoma

- abnormal blood vessels develop on surface of iris (rubeosis iridis), in the angle, and within the trabecular meshwork
- due to retinal ischemia associated with proliferative diabetic retinopathy or CRVO
- treatment with laser therapy to retina reduces neovascular stimulus to iris vessels
Pupils

- pupil size is determined by the balance between the sphincter muscle and the dilator muscle
- sphincter muscle is innervated by the parasympathetic nervous system
  - carried by CN III; pre- and post-ganglionic fibres synapse in ciliary ganglion, and use acetylcholine as the neurotransmitter
- dilator muscle is innervated by the sympathetic nervous system (SNS)
  - first order neuron = hypothalamus → brainstem → spinal cord
  - second order preganglionic neuron = spinal cord → sympathetic trunk via internal carotid artery → superior cervical ganglion in neck
  - third order postganglionic fibres originate in the superior cervical ganglion, neurotransmitter is noradrenaline
  - as a diagnostic test, 4-10% cocaine prevents the re-uptake of noradrenaline, and will cause dilation of normal pupil, but not one with loss of sympathetic innervation (Horner’s Syndrome)
  - see Figure 8 in Neurology, N6

Pupillary Light Reflex

- light shone directly into eye travels along optic nerve (CN II, afferent limb) → optic tracts → bilateral midbrain
- impulses enter bilaterally in midbrain via pretectal area and Edinger-Westphal nuclei
- nerve impulses then travel down CN III (efferent limb) bilaterally to reach the ciliary ganglia, and finally to the iris sphincter muscle, which results in the direct and consensual light reflexes

Pupil Abnormalities

Denervation Hypersensitivity
- when post-ganglionic fibres are damaged, the understimulated end-organ develops an excess of neuroreceptors and becomes hypersensitive
- postganglionic parasympathetic lesions (i.e. Adie’s pupil)
  - pupil will constrict with 0.125% pilocarpine (cholinergic agonist), normal pupil will not
- postganglionic sympathetic lesions (this test is used to differentiate between pre- and post-ganglionic lesions in Horner’s syndrome)
  - pupil will dilate with 0.125% adrenaline, normal pupil will not

Local Disorders of Iris
- posterior synechiae (adhesions between iris and lens) due to iritis can present as an abnormally shaped pupil
- ischemic damage (e.g. post-acute angle-closure glaucoma) usually occurs at 3 and 9 o'clock positions resulting in a vertically oval pupil that reacts poorly to light
- trauma (e.g. post-intraocular surgery)

Anisocoria
- unequal pupil size
- idiopathic/physiologic anisocoria
  - 20% of population
  - round, regular, <1 mm difference
  - pupils reactive to light and accommodation
  - responds normally to mydriatics/miotics
- post eye surgery
- see Table 7 for other causes of anisocoria
**Patient with Anisocoria**

Relevant history and examination with specific attention to:
- History of ocular trauma
- Check old photographs (ptosis, ocular deviation, long standing anisocoria)
- Use of topical medications
- Exposure to toxins and drugs
- Associated ocular and neurologic symptoms/signs

**Which pupil is abnormal?**
Examine pupils in light and dark

- Anisocoria accentuated by darkness (small pupil abnormal)
  - Dilation lag
  - Ptosis
  - Test with 10% cocaine
  - Small pupil does not dilate
  - Horner’s syndrome
- Anisocoria equal in light and dark
  - Brisk reaction to light
  - Large pupil constricts
  - Large pupil does not constrict
  - Adie’s tonic pupil
  - Physiologic anisocoria
- Anisocoria accentuated by light (large pupil is abnormal)
  - Isolated sluggish to light
  - Light near dissociation
  - Use of 0.1% pilocarpine
  - Minimal/no constriction
  - Use of 0.1% pilocarpine
  - Pharmacologic anisocoria
  - Third nerve palsy

**Patient Must Fixate on Distant Target**

Figure 22. Approach to anisocoria

**Table 7. Summary of Conditions Causing Anisocoria**

<table>
<thead>
<tr>
<th>Features</th>
<th>Site of Lesion</th>
<th>Light and Accommodation</th>
<th>Anisocoria</th>
<th>Mydriatics/Miotics</th>
<th>Effect of Pilocarpine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anisocoria accentuated by darkness (small pupil abnormal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anisocoria equal in light and dark</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anisocoria accentuated by light (large pupil is abnormal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABNORMAL MIOTIC PUPIL (impaired pupillary dilation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argyll-Robertson Pupil</td>
<td>Irregular, usually bilateral</td>
<td>Midbrain</td>
<td>Poor in light; better to accommodation</td>
<td>Dilates/Constricts</td>
<td></td>
</tr>
<tr>
<td>Horner’s Syndrome</td>
<td>Round, unilateral, ptosis, anhidrosis, pseudoenophthalmos</td>
<td>Sympathetic system</td>
<td>Both brisk</td>
<td>Greater in dark</td>
<td>Dilates/Constricts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABNORMAL MYDRIATIC PUPIL (impaired pupillary constriction)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adie’s Tonic Pupil</td>
<td>Irregular, larger in bright light</td>
<td>Ciliary ganglion</td>
<td>Poor in light, better to accommodation</td>
<td>Greater in light</td>
<td>Dilates/Constricts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CN III Palsy</td>
<td>Round</td>
<td>Superficial CN III</td>
<td>± fixed (acutely) at 7-9 mm</td>
<td>Greater in light</td>
<td>Dilates/Constricts</td>
</tr>
<tr>
<td>Mydriatic Pupil</td>
<td>Round, uni- or bilateral</td>
<td>Iris sphincter</td>
<td>Fixed at 7-8 mm</td>
<td>Greater in light</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Will not constrict</td>
</tr>
</tbody>
</table>
Dilated Pupil (Mydriasis)

Sympathetic Stimulation
- fight or flight response
- mydriatic drugs: epinephrine, dipivefrin (Propine®), phenylephrine

Parasympathetic Understimulation
- cycloplegics/mydriatics: atropine, tropicamide, cyclopentolate (parasympatholytic)
- CN III palsy
  - eye deviated down and out with ptosis present
  - etiology includes stroke, neoplasm, aneurysm, acute rise in ICP, diabetes mellitus (may spare pupil), trauma
  - CN III palsy will respond to drugs (e.g. pilocarpine), unlike a pupil dilated from medication (mydriatics)

Acute Angle-Closure Glaucoma
- fixed, mid-dilated pupil

Adie's Tonic Pupil
- 80% unilateral, females > males
- pupil is tonic or reacts poorly to light (both direct and consensual) but constricts with accommodation
- if decreased deep tendon reflexes may be Adie's syndrome
- caused by benign lesion in ciliary ganglion; results in denervation hypersensitivity of parasympathetically innervated constrictor muscle
  - dilute (0.125%) solution of pilocarpine will constrict tonic pupil but have no effect on normal pupil
  - long-standing Adie's pupils are smaller than unaffected eye

Trauma
- damage to iris sphincter from blunt or penetrating trauma
- iris transillumination defects may be apparent using ophthalmoscope or slit lamp
- pupil may be dilated (traumatic mydriasis) or irregularly shaped from tiny sphincter ruptures

Constricted Pupil (Miosis)

Senile Miosis
- decreased sympathetic stimulation with age

Parasympathetic Stimulation
- local or systemic medications such as:
  - cholinergic agents: pilocarpine, carbachol
  - cholinesterase inhibitor: phospholine iodide
  - opiates, barbiturates

Horner's Syndrome
- lesion in sympathetic pathway
- difference in pupil size greater in dim light, due to decreased innervation of adrenergics to iris dilator muscle
- associated with ptosis, anhydrosis of ipsilateral face/neck
- application of cocaine 4-10% (blocks reuptake of noradrenaline) to eye does not result in pupil dilation (vs. physiologic anisocoria), therefore confirms diagnosis
- hydroxyamphetamine 1% (stimulates noradrenaline release) will dilate pupil if central or preganglionic lesion, not postganglionic lesion
- postganglionic lesions result in denervation hypersensitivity, which will cause pupil to dilate with 0.125% adrenaline, whereas normal pupil will not
- causes: carotid or subclavian aneurysm, brainstem infarct, demyelinating disease, cervical or mediastinal tumour, Pancoast tumour, goiter, cervical lymphadenopathy, surgical sympathectomy, Lyme disease, cervical ribs, tabes dorsalis, cervical vertebral fractures

Iritis
- miotic pupil initially
- later, may be irregularly shaped pupil due to posterior synechiae
- later stages non-reactive to light
Argyll-Robertson Pupil
- both pupils irregular and <3 mm in diameter, ± ptosis
- does not respond to light stimulation
- responds to accommodation (light-near dissociation)
- suggestive of neurosyphilis or other conditions (DM, encephalitis, MS, chronic alcoholism, CNS degenerative diseases)

Other Causes
- optic neuritis, retinal lesions

Relative Afferent Pupillary Defect (RAPD)

- also known as Marcus Gunn pupil
- impairment of direct pupillary response to light, caused by a lesion in visual afferent (sensory) pathway anterior to optic chiasm
- DDx: large retinal detachment, BRAO, CRAO, CRVO, advanced glaucoma, optic nerve compression, optic neuritis (most common)
- does not occur with media opacity (e.g. corneal edema, cataracts)
- pupil reacts poorly to light and better to accommodation
- test: swinging flashlight
  - if light is shone in the affected eye, direct and consensual response to light is decreased
  - if light is shone in the unaffected eye, direct and consensual response to light is normal
  - if the light is moved quickly from the unaffected eye to the affected eye, “paradoxical” dilation of both pupils occurs
  - observe red reflex, especially in patients with dark irides
- if the defect is bilateral there is no RAPD, as dilation is measured relative to the other eye

Cataracts never produce an RAPD.

It is possible to have RAPD and normal vision at the same time, e.g. in damaged superior colliculus caused by thalamic hemorrhage.

Differentiate RAPD from physiologic pupillary athetosis (“hippus”), which is rapid, rhythmic fluctuations of the pupil, with equal amplitude in both eyes.
Malignancies

• uncommon site for 1° malignancies
• eye usually affected secondarily by cancer or cancer treatments
• see Retinoblastoma, OP41

Lid Carcinoma

Etiology
• basal cell carcinoma (rodent ulcer) (90%)
  ▪ spread via local invasion, rarely metastasizes
  ▪ ulcerated centre, indurated base with pearly rolled edges, telangiectasia
• squamous cell carcinoma (<5%)
  ▪ spread via local invasion, may also spread to nodes and metastasize
  ▪ ulceration, keratosis of lesion
• sebaceous cell carcinoma (1-5%)
  ▪ often masquerades as chronic blepharitis or recurrent chalazion
  ▪ highly invasive, metastasize
• Kaposi’s sarcoma, malignant melanoma, Merkel cell tumour, metastatic tumour

Treatment
• incisional or excisional biopsies
• may require cryotherapy, radiotherapy, chemotherapy, immunotherapy
• surgical reconstruction

Malignant Melanoma

• most common 1° intraocular malignancy in adults
• more prevalent in Caucasians
• arise from uveal tract, 90% choroidal melanoma
• hepatic metastases predominate

Treatment
• imaging to investigate spread
• depending on the size of the tumour, either radiotherapy, enucleation, limited surgery

Metastases

• most common intraocular malignancy in adults
• most commonly from breast and lung in adults, neuroblastoma in children
• usually infiltrate the choroid, but may also affect the optic nerve or extraocular muscles
• may present with decreased or distorted vision, irregularly shaped pupil, iritis, hyphema

Treatment
• local radiation, chemotherapy
• enucleation if blind, painful eye

Ocular Manifestations of Systemic Disease

HIV/AIDS

• up to 75% of patients with AIDS have ocular manifestations

External Ocular Signs
• Kaposi’s sarcoma
  ▪ 2° to human herpes virus 8 (HHV-8), affects conjunctiva of lid or globe
  ▪ numerous vascular skin malignancies
  ▪ DDx: subconjunctival hemorrhage (non-clearing), hemangioma
• multiple molluscum contagiosum
• herpes simplex keratitis
• herpes zoster keratitis
Retina
- HIV retinopathy (most common)
  - cotton wool spots in >50% of HIV patients
  - intraretinal hemorrhage
- CMV retinitis
  - ocular opportunistic infection that develops in late stages of HIV when severely
    immunocompromised (CD4 count ≤50)
  - a necrotizing retinitis, with retinal hemorrhage and vasculitis, “brushfire” or “pizza pie”
    appearance
  - presents with scotomas (macular involvement and retinal detachment), blurred vision, and
    floaters
  - untreated infection will progress to other eye in 4-6 wk
- treatment: virostatic agents (e.g. gancyclovir or foscarnet) via IV or intravitreal injection
- necrotizing retinitis
  - from herpes simplex virus, herpes zoster, toxoplasmosis
- disseminated choroiditis
- Pneumocystis carinii, Mycobacterium avium intracellulare, Candida

Other Systemic Infections
- herpes zoster
  - see Herpes Zoster, OP19
- candidal endophthalmitis
  - fluffy, yellow-white, superficial retinal infiltrate that may eventually result in vitritis
  - may present with inflammation of the anterior chamber
- treatment: systemic amphotericin B, oral fluconazole
- toxoplasmosis
  - focal, grey-yellow-white, chorioretinal lesions with surrounding vasculitis and vitreous
    infiltration (vitreous cells)
  - can be congenital (transplacental) or acquired (caused by Toxoplasma gondii protozoa
    transmitted through raw meat and cat feces)
  - congenital form more often causes visual impairment (more likely to involve the macula)
  - treatment: pyrimethamine, sulfonamide, folinic acid, or clindamycin. Consider adding
    steroids if severe inflammation (vitrinitis, macular or optic nerve involvement)

Diabetes Mellitus (DM)
- see Endocrinology, E6
- most common cause of blindness in young people in North America
- consider DM if unexplained retinopathy, cataract, extraocular muscle palsy, optic neuropathy,
  sudden change in refractive error
- loss of vision due to:
  - progressive microangiopathy leading to macular edema
  - progressive diabetic retinopathy → neovascularization → traction → retinal detachment
  - vitreous hemorrhage
  - rubeosis iridis (neovascularization of the iris) leading to neovascular glaucoma (poor prognosis)
  - macular ischemia

DIABETIC RETINOPATHY (DR)

Background
- altered vascular permeability (loss of pericytes, breakdown of blood-retinal barrier, thickening
  of basement membrane)
- predisposition to retinal vessel obstruction (CRAO, CRVO, and BRVO)

Classification
- non-proliferative: increased vascular permeability and retinal ischemia
  - microaneurysms
  - dot and blot hemorrhages
  - hard exudates (lipid deposits), non-specific for DR
  - macular edema
- advanced non-proliferative (or pre-proliferative):
  - non-proliferative findings plus:
    - venous beading (in ≥2 of 4 retinal quadrants)
    - intraretinal microvascular anomalies (IRMA) in 1 of 4 retinal quadrants
      - IRMA: dilated, leaky vessels within the retina
    - cotton wool spots (nerve fibre layer infarcts)

Diabetes Mellitus (DM)
- see Endocrinology, E6
- most common cause of blindness in young people in North America
- consider DM if unexplained retinopathy, cataract, extraocular muscle palsy, optic neuropathy,
  sudden change in refractive error
- loss of vision due to:
  - progressive microangiopathy leading to macular edema
  - progressive diabetic retinopathy → neovascularization → traction → retinal detachment
  - vitreous hemorrhage
  - rubeosis iridis (neovascularization of the iris) leading to neovascular glaucoma (poor prognosis)
  - macular ischemia

DIABETIC RETINOPATHY (DR)

Background
- altered vascular permeability (loss of pericytes, breakdown of blood-retinal barrier, thickening
  of basement membrane)
- predisposition to retinal vessel obstruction (CRAO, CRVO, and BRVO)

Classification
- non-proliferative: increased vascular permeability and retinal ischemia
  - microaneurysms
  - dot and blot hemorrhages
  - hard exudates (lipid deposits), non-specific for DR
  - macular edema
- advanced non-proliferative (or pre-proliferative):
  - non-proliferative findings plus:
    - venous beading (in ≥2 of 4 retinal quadrants)
    - intraretinal microvascular anomalies (IRMA) in 1 of 4 retinal quadrants
      - IRMA: dilated, leaky vessels within the retina
    - cotton wool spots (nerve fibre layer infarcts)
• proliferative:
  ▪ 5% of patients with diabetes will reach this stage
  ▪ neovascularization of iris, disc, retina to vitreous
  ▪ neovascularization of iris (rubeosis iridis) can lead to neovascular glaucoma
  ▪ vitreous hemorrhage from bleeding, fragile new vessels, fibrous tissue can contract causing tractional retinal detachment
  ▪ high risk of severe visual loss 2° to vitreous hemorrhage, retinal detachment

Screening Guidelines for Diabetic Retinopathy
• type 1 DM
  ▪ screen for retinopathy beginning annually 5 yr after disease onset
  ▪ annual screening indicated for all patients over 12 yr and/or entering puberty
• type 2 DM
  ▪ initial examination at time of diagnosis, then annually
• pregnancy
  ▪ oculary exam in 1st trimester, close follow-up throughout as pregnancy can exacerbate DR
  ▪ gestational diabetics are not at risk for diabetic retinopathy

Treatment
• Diabetic Control and Complications Trial (DCCT)
  ▪ tight control of blood sugar decreases frequency and severity of microvascular complications
  ▪ blood pressure control
  ▪ focal laser for clinically significant macular edema, intravitreal injection of corticosteroid or anti-VEGF for focal involved diabetic macular edema
• panretinal laser photocoagulation for proliferative diabetic retinopathy; reduces neovascularization, hence reducing the angiogenic stimulus from ischemic retina by decreasing retinal metabolic demand → reduces risk of blindness
  ▪ vitrectomy for non-clearing vitreous hemorrhage and retinal detachment in proliferative diabetic retinopathy
  ▪ vitrectomy before vitreous hemorrhage does not improve the visual prognosis

Lens Changes
• earlier onset of senile nuclear sclerosis and cortical cataract
• may get hyperglycemic cataract, due to sorbitol accumulation (rare)
• changes in blood glucose levels (poor control) can suddenly cause refractive changes by 3–4 diopters

Extraocular Muscle Palsy
• usually CN III infarct
• pupil usually spared in diabetic CN III palsy, but ptosis is observed
• may involve CN IV and VI
• usually recover within few months

Optic Neuropathy
• visual acuity loss due to infarction of optic disc/nerve

---

*Figure 25. DM vs. HTN retinopathy*
Hypertension

- retinopathy is the most common ocular manifestation
- chronic HTN retinopathy: arteriovenous (AV) nicking, blot retinal hemorrhages, microaneurysms, cotton wool spots
- acute HTN retinopathy: retinal arteriolar spasm, superficial retinal hemorrhage, cotton wool spots, optic disc edema

Table 8. Keith-Wagener-Barker Classification

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Mild arterial narrowing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2</td>
<td>Obvious arterial narrowing with focal irregularities</td>
</tr>
<tr>
<td>Group 3</td>
<td>Group 2 characteristics plus: Cotton-wool spots, Hemorrhage and/or exudate</td>
</tr>
<tr>
<td>Group 4</td>
<td>Group 3 plus papilledema</td>
</tr>
</tbody>
</table>

Multiple Sclerosis (MS)

- see Neurology, N46

Clinical Features

- blurred vision and decreased colour vision: 2° to optic neuritis
- central scotoma: due to damage to papillomacular bundle of retinal nerve fibres
- diplopia: 2° to INO
- RAPD, ptosis, nystagmus, uveitis, optic atrophy, optic neuritis
- white matter demyelinating lesions of optic nerve on MRI

Treatment

- IV steroids with taper to oral form for optic neuritis
  - DO NOT treat with oral steroids in isolation as this increases likelihood of eventual development of MS

TIA/Amaurosis Fugax

- sudden, transient blindness from intermittent vascular compromise
- ipsilateral carotid most frequent embolic source
- typically monocular, lasting <5-10 min
- Hollenhorst plaques (glistening microemboli seen at branch points of retinal arterioles)

Graves’ Disease

- ophthalmopathy occurs despite control of thyroid gland status
- ocular manifestations occur 2° to sympathetic overdrive and/or specific inflammatory infiltrate of the orbital tissue

Clinical

- initial inflammatory phase is followed by a quiescent cicatricial phase

Treatment

- treat hyperthyroidism
- monitor for corneal exposure and maintain corneal hydration
- manage diplopia, proptosis and compressive optic neuropathy with one or a combination of:
  - steroids (during acute phase)
  - orbital bony decompression
  - external beam radiation of the orbit
- consider strabismus and/or eyelid surgical procedures once acute phase subsides

Connective Tissue Disorders

- RA, juvenile idiopathic arthritis, SLE, Sjogren's syndrome, ankylosing spondylitis, polyarteritis nodosa
- most common ocular manifestation: dry eyes (keratoconjunctivitis sicca)
Giant Cell Arteritis (GCA)/Temporal Arteritis

- see Rheumatology, RH20

Clinical
- more common in women >60 yr
- abrupt monocular loss of vision, pain over the temporal artery, jaw claudication, scalp tenderness, constitutional symptoms, and past medical history of polymyalgia rheumatica
- ischemic optic atrophy
  - 50% lose vision in other eye if untreated

Diagnosis
- temporal artery biopsy + increased ESR (ESR can be normal, but likely 80-100 in first hour), CRP
- if biopsy of one side is negative, biopsy the other side

Treatment
- high dose corticosteroid to relieve pain and prevent further ischemic episodes
- if diagnosis of GCA is suspected clinically: start treatment + perform temporal artery biopsy to confirm diagnosis within 2 wk of initial presentation (DO NOT WAIT TO TREAT)

Sarcoidosis
- granulomatous uveitis with large “mutton fat” keratitic precipitates and posterior synechiae
- neurosarcoidosis: optic neuropathy, oculomotor abnormalities, visual field loss

Treatment
- steroids and mydriatics

Pediatric Ophthalmology

Strabismus
- ocular misalignment in one or both eyes, found in 3% of children
- object not visualized simultaneously by fovea of each eye
- terms used to describe strabismus depend upon:
  - direction of deviation relative to the fixating eye
  - conditions under which it presents: ‘latent’, ‘manifest’ misalignment
  - change with the position of gaze: ‘comitant’ (usually nonparalytic), ‘incomitant’ (usually occurs with paralytic or restrictive strabismus)
- often presents with parental concern about a wandering eye, crossing eye, or poor vision
- elicit a detailed family history of strabismus, amblyopia, type of eyeglasses and history of wear, extraocular muscle surgery or other eye surgery, and genetic diseases to identify children at higher risk
- distinguish from pseudostrabismus (prominent epicanthal folds, hypertelorism, markedly positive or negative angle κ)
- complications: amblyopia, cosmesis

HETEROTROPIA
- manifest deviation
- deviation not corrected by the fusion mechanism (i.e. deviation is apparent when the patient is using both eyes)

Types
- exo- (lateral deviation), eso- (medial deviation)
- hyper- (upward deviation), hypo- (downward deviation)
- esotropia = “crossed-eyes”; exotropia = “wall-eyed”

Differentiate from Pseudostrabismus
- prominent epicanthal folds: give appearance of esotropia but Hirschberg test is normal, more common in Asians
- markedly elevated angle κ (the angle formed by the pupillary axis and the visual axis at the centre of the pupil)
  - caused by the failure of optical axis of the eye and the visual axis to coincide
  - a small positive (up to 5°) angle κ is physiologic
  - a large positive angle κ (nasally deviated fovea) simulates eso-appearance
  - a large negative angle κ (temporally deviated fovea) gives an exo-appearance

ESR in Temporal Arteritis
- Males > age/2
- Females > (age + 10)/2

Does this Patient have Temporal Arteritis?
JAMA 2002;287:92-101
Rule in: jaw claudication and diplopia on history, temporal artery beading, prominence of the artery and tenderness over the artery on exam.
Rule out: no temporal artery abnormalities on exam, normal ESR.

Strabismus in children under 4 mo of age sometimes resolves, particularly if the deviation is intermittent, variable or measures less than 40 prism diopters
Tests

- Hirschberg test (corneal light reflex): positive if the light reflex on both corneas is asymmetrical
  - light reflex lateral to central cornea indicates esodeviation; light reflex medial to central cornea indicates exodeviation
  - false positives occur if visual axis and anatomic pupillary axis of the eye are not aligned (angle κ)
- cover test (Figure 26)
- the deviation can be quantified using prisms

HETEROPHORIA

- latent deviation
- deviation corrected in the binocular state by the fusion mechanism (i.e. deviation not seen when patient is focusing with both eyes)
- Hirschberg test will be normal (light reflexes symmetrical)
- very common – majority are asymptomatic
- may be exacerbated or become manifest with asthenopia (eye strain, fatigue)

Tests

- cover-uncover test
- alternate cover test
  - alternating the cover between both eyes reveals the total deviation, both latent and manifest
  - maintain cover over one eye for 2-3 s before rapidly shifting to other eye

Figure 26. Cover and cover-uncover tests for detection of tropias and phorias

Table 9. Paralytic vs. Non-Paralytic Strabismus

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Paralytic Strabismus</th>
<th>Nonparalytic Strabismus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Incomitant strabismus</td>
<td>Concomitant strabismus</td>
</tr>
<tr>
<td>Onset</td>
<td>Often sudden but may be gradual or congenital</td>
<td>Usually gradual or shortly after birth; rarely sudden</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Any age; most often acquired</td>
<td>Usually during infancy</td>
</tr>
<tr>
<td>Etiology</td>
<td>Reduction or restriction in range of eye movements due to:</td>
<td>No restriction in range of eye movements</td>
</tr>
<tr>
<td></td>
<td>• Neural (CN III, IV, VII): ischemia (e.g. DM, MS, aneurysm, brain tumour, trauma)</td>
<td>Develops early in childhood</td>
</tr>
<tr>
<td></td>
<td>• Muscular: myasthenia gravis (neuromuscular junction pathology), Graves’ disease</td>
<td>No restriction in range of eye movements</td>
</tr>
<tr>
<td></td>
<td>• Structural: restriction or entrapment of extraocular muscles due to orbital inflammation, tumour, fracture of the orbital wall</td>
<td>Monocular, alternating, or intermittent</td>
</tr>
<tr>
<td>Diplopia</td>
<td>Common</td>
<td>Uncommon; image from the misaligned eye is suppressed (see Amblyopia, OP40)</td>
</tr>
<tr>
<td>Visual acuity in other eye</td>
<td>Usually unaffected in the other eye, unless CN II is involved</td>
<td>Deviated eye may become amblyopic if not treated when the child is young</td>
</tr>
<tr>
<td></td>
<td>Amblyopia usually does not develop if child has alternating strabismus or intermittency, which allows neural pathways for both eyes to develop</td>
<td></td>
</tr>
<tr>
<td>Possibility of amblyopia</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Neurologic findings or systemic disease</td>
<td>May be present</td>
<td>Usually absent</td>
</tr>
</tbody>
</table>
Accommodative Esotropia

- normal response to approaching object is the triad of the near reflex: convergence, accommodation and miosis
- hyperopes must constantly accommodate – excessive accommodation can lead to esotropia in young children via over-activation of the near reflex
- average age of onset is 2.5 yr
- usually reversible with correction of refractive error

Non-accommodative Esotropia

- accounts for 50% of childhood strabismus
- most are idiopathic
- may be due to monocular visual impairment (e.g. cataract, corneal scarring, anisometropia, retinoblastoma) or divergence insufficiency (ocular misalignment that is greater at distance fixation than at near fixation)

Amblyopia

Definition

- a neurodevelopmental visual disorder with unilateral (or less commonly, bilateral) reduction of best corrected visual acuity that cannot be attributed only and directly to the effect of a structural abnormality of the eye. It is caused by abnormal visual experience early in life and cannot be remedied immediately by spectacle glasses alone
- in approximately half of the cases, amblyopia is secondary to strabismus (mainly esotropia). Other causes may include uncorrected refractive errors, anisometropia (asymmetric refractive errors), and concomitant structural ocular problems

Detection

- “Holler Test”: young child upset if good eye is covered
- quantitative visual acuity by age 3-4 yr using picture charts and/or matching game (Sheridan-Gardiner), testing each eye separately
- amblyopia treatment less successful after age 8-10 yr, but a trial should be given no matter what age
- prognosis: 90% will have good vision restored and maintained if treated <4 yr old

Etiology and Management

- strabismus
  - correct with glasses for accommodative esotropia (50% of children experience relief of their esotropia with glasses and will not require surgery)
  - occlusion of unaffected eye forces brain to use previously strabismic eye; aims to bring vision in previously suppressed eye to normal before surgery
  - surgery: recession (weakening) – moving muscle insertion further back on the globe; or resection (strengthening) – shortening the muscle
  - botulinum toxin for single muscle weakening
  - after ocular alignment is restored (glasses, surgery, botulinum toxin), patching is frequently necessary to maintain vision until approximately age 8 yr
- anisometropia
  - amblyopia usually in the more hyperopic eye
  - the more emmetropic (normal refraction) eye receives a clear image while the less emmetropic eye receives a blurred image; input from the blurred eye is cortically suppressed and visual pathway fails to develop normally
  - treat with glasses to correct refractive error
  - patching is required if visual acuity difference persists after 4-8 wk of using glasses
- deprivation amblyopia
  - occlusion due to ptosis, cataract, retinoblastoma, corneal opacity
  - occlusion amblyopia: prolonged patching of good eye may cause it to become amblyopic

Oclusion Therapy

- patching the good eye to force the brain to use the non-dominant eye and redevelop its vision
- atropine cycloplegic drops to impair accommodation and blur vision of the better seeing eye

Risks

- permanent loss of vision in the affected eye
- possibility of injury to ‘remaining’ good eye
  - safety glasses or polycarbonate lenses recommended if visual acuity in worse eye is less than 20/50
- loss of stereopsis
Leukocoria

- white reflex (red reflex is absent)

Differential Diagnosis
- cataract
- retinoblastoma
- retinal coloboma
- ROP
- persistent hyperplastic primary vitreous
- Coats' disease (exudative retinal telangiectasis)
- toxocariasis
- retinal detachment

Retinoblastoma

- most common primary intraocular malignancy in children
- incidence: 1/15,000; sporadic or genetic transmission; screening of siblings/offspring essential
- unilateral or bilateral (in 1/3 of cases)
- malignant – direct or hematogenous spread
- diagnosis
  - often presents with leukocoria or strabismus
  - U/S or CT scan may demonstrate calcified mass (present in most cases)

Treatment
- radiotherapy, chemotherapy combined with laser, cryopexy, and/or enucleation

Retinopathy of Prematurity (ROP)

- vasoproliferative retinopathy that is a major cause of blindness in the developed world

Risk Factors
- non-black race (black infants have lower risk of developing ROP)
- low gestational age, birth weight <1500 g
- high oxygen exposure after birth

Classification (ROP Staging)
- stage 1: faint demarcation line at the junction between the vascularized and avascular retina
- stage 2: elevated ridge
- stage 3: extra-retinal fibrovascular tissue extending into vitreous
- stage 4: partial retinal detachment (4A: macula "on", 4B: macula "off")
- stage 5: total retinal detachment
- plus (+) disease: dilatation and tortuosity of retinal vessels
- threshold disease: stage 3+ in zones 1 or 2 with 5 continuous or 8 cumulative clock hours of ROP involvement

Treatment
- threshold disease is treated with cryotherapy or laser (laser is now the standard treatment, with better refractive outcome), off label anti-VEGF intravitreal injections (see sidebar)
- ROP beyond threshold level is either watched carefully (usually stage 4A) or treated with vitrectomy/scleral buckle

Prognosis
- higher incidence of myopia among ROP infants, even if treated successfully
- stage 4B and 5 have poor prognosis for visual outcome despite treatment

Nasolacrimal System Defects

- congenital obstruction of the nasolacrimal duct (failure of canalization), usually occurs at 1-2 mo of age
- epiphora, crusting, discharge, recurrent conjunctivitis
- can have reflux of mucopurulent material from lacrimal punctum when pressure is applied over lacrimal sac
- treatment: massage over lacrimal sac at medial corner of eyelid
- vast majority spontaneously resolve in 9-12 mo, otherwise consider referral for duct probing
Ophthalmia Neonatorum

- newborn conjunctivitis in first month of life
- causes:
  - toxic: silver nitrate, erythromycin
  - infectious: bacterial (e.g. *Neisseria gonorrhoeae* – most common, *Chlamydia trachomatis*), herpes simplex virus
- diagnose using stains and cultures
- treatment: systemic antibiotics with possible hospitalization if infectious etiology
- topical prophylaxis, most commonly with erythromycin (or silver nitrate), is required by law at birth

Congenital Glaucoma

- due to inadequate development of the filtering mechanism of the anterior chamber angle

Clinical Features

- cloudy cornea, increased IOP
- photophobia, epiphora
- buphthalmos (large cornea, "ox eye", 2" to increased IOP), blepharospasm

Treatment

- filtration surgery is required soon after birth to prevent blindness

Ocular Trauma

Blunt Trauma

- caused by blunt object such as fist, squash ball
- history: injury, ocular history, drug allergy, tetanus status
- exam: VA first, pupil size and reaction, EOM (diplopia), external and slit lamp exam, ophthalmoscopy
- if VA normal or slightly reduced, globe less likely to be perforated
- if VA reduced may be perforated globe, corneal abrasion, lens dislocation, retinal tear
- bone fractures
  - blow out fracture: restricted EOM, diplopia, enophthalmos (sunken eye)
  - ethmoid fracture: subcutaneous emphysema of lid
- lids: swelling, laceration, emphysema
- conjunctiva: subconjunctival hemorrhage
- cornea: abrasion – detect with fluorescein staining and cobalt blue filter using slit lamp or ophthalmoscope
- anterior chamber: assess depth, hyphema, hypopyon
- iris: prolapse, iritis
- lens: cataract, dislocation
- retinal tear/detachment

Penetrating Trauma

- include ruptured globe ± prolapsed iris, intraocular foreign body
- rule out intraocular foreign body, especially if history of "metal striking metal", orbit CT
- initial management: REFER IMMEDIATELY
  - ABCs
  - don’t press on eye globe!
  - don’t check IOP if possibility of globe rupture
  - check vision, diplopia
  - apply rigid eye shield to minimize further trauma
  - keep head elevated 30-45° to keep IOP down
  - keep NPO
  - tetanus status
  - give IV antibiotics
  - selecting appropriate agents depends on the mechanism of injury. Gram positive bacteria are more commonly involved than gram negatives. Retained intraocular foreign objects increase the risk of infections with Bacillus species, whereas exposure to vegetable matter increased the risk of a fungal etiology
Hyphema

- blood in anterior chamber often due to damage to root of the iris
- may occur with blunt trauma

Treatment
- refer to ophthalmology
  - shield and bedrest x 5 d or as determined by ophthalmologist
  - sleep with head upright
- may need surgical drainage if hyphema persists or if re-bleed

Complications
- risk of re-bleed highest on days 2-5, resulting in 2° glaucoma, corneal staining, and iris necrosis
- never prescribe Aspirin®, as it increases the risk of a re-bleed

Blow-Out Fracture

- see Plastic Surgery, PL31
- blunt trauma causing fracture of orbital floor and herniation of orbital contents into maxillary sinus
- orbital rim remains intact
- inferior rectus and/or inferior oblique muscles may be incarcerated at fracture site
- infraorbital nerve courses along the floor of the orbit and may be damaged

Clinical Features
- pain and nausea at time of injury
- diplopia, restriction of EOM
- infraorbital and upper lip paresthesia (CN V2)
- enophthalmos (sunken eye), periorbital ecchymoses

Investigations
- plain films: Waters’ view and lateral
- CT: anteroposterior and coronal view of orbits

Treatment
- refrain from coughing, blowing nose
- systemic antibiotics may be indicated
- surgery if fracture >50% orbital floor, diplopia not improving, or enophthalmos >2 mm
- may delay surgery if the diplopia improves

Chemical Burns

- alkali burns have a worse prognosis than acid burns because acids coagulate tissue and inhibit further corneal penetration
- poor prognosis if cornea opaque, likely irreversible stromal damage
- even with a clear cornea initially, alkali burns can progress for weeks (thus, very guarded prognosis)

Treatment
- immediately irrigate at site of accident with water or buffered solution
  - IV drip for at least 20-30 min with eyelids retracted in emergency department
  - swab upper and lower fornices to remove possible particulate matter
- do not attempt to neutralize because the heat produced by the reaction will damage the cornea
- cycloplegic drops to decrease iris spasm (pain) and prevent 2° glaucoma (due to posterior synechiae formation)
- topical antibiotics and patching
- topical steroids (by ophthalmologist) to decrease inflammation, use for less than 2 wk (in the case of a persistent epithelial defect)

Fluorescein lights up alkali so you can detect it and assess whether it has been removed.

Shaken Baby Syndrome

- Syndrome of findings characterized by absence of external signs of abuse with respiratory arrest, seizures, or coma. Ocular exam findings are important diagnostically for Shaken Baby Syndrome. These findings include extensive retinal and vitreous hemorrhages that occur during the shaking process and are extremely rare in accidental trauma. A detailed fundoscopic exam or an ophthalmology referral should be conducted for all infants in whom abuse is suspected.

Classic Signs of Blow-Out
- Enophthalmos
- Decreased upgaze (IR trapped)
- Cheek anesthetized (infraorbital nerve trapped)
Surgical Ophthalmology

- **dacrocystorhinostomy (DCR):** excision of bone covering the nasolacrimal sac to restore tear drainage
- **LASIK (laser-assisted in-situ keratomileusis):** a microkeratome is used to create a corneal flap followed by laser remodeling of the stroma to correct refractive error
- ** trabeculectomy:** creation of a new outflow tract from anterior chamber to under conjunctiva; fibrosis prevented with mitomycin C or 5-FU injection during surgery
- **phacoemulsification (cataract extraction):** the use of ultrasonic waves to break up and aspirate a cataract followed by replacement with an artificial lens implant
- **vitrectomy:** the use of small trochars to enter the posterior segment and remove vitreous; commonly used to treat vitreous hemorrhage and retinal detachment
- **pneumatic retinopexy:** intraocular injection of air or an expandable gas in order to tamponade a retinal break for repair of retinal detachment
- **scleral buckle:** a band is secured on the outside of the globe that indents the eye wall, thereby relieving vitreous traction on the retina around any tears/holes and allowing the tears/holes to remain sealed

Ocular Drug Toxicity

Table 10. Drugs with Ocular Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Corneal microdeposits and superficial keratopathy (vortex keratopathy)</td>
</tr>
<tr>
<td></td>
<td>Rare: ischemic optic neuropathy</td>
</tr>
<tr>
<td>Atropine, benztropine</td>
<td>Pupillary dilation (risk of angle closure glaucoma)</td>
</tr>
<tr>
<td>Bisphosphonates (Fosamax®, Actonel®)</td>
<td>Inflammatory eye disease (iritis, scleritis, episcleritis)</td>
</tr>
<tr>
<td>Chloroquine, hydroxychloroquine</td>
<td>Bull’s eye maculopathy</td>
</tr>
<tr>
<td></td>
<td>Vortex keratopathy</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Anterior subcapsular cataract</td>
</tr>
<tr>
<td>Contraceptive pills</td>
<td>Decreased tolerance to contact lenses</td>
</tr>
<tr>
<td></td>
<td>Migraine</td>
</tr>
<tr>
<td></td>
<td>Optic neuritis</td>
</tr>
<tr>
<td></td>
<td>Central vein occlusion</td>
</tr>
<tr>
<td>Digitalis</td>
<td>Yellow vision</td>
</tr>
<tr>
<td></td>
<td>Blurred vision</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Optic neuropathy</td>
</tr>
<tr>
<td>Haloperidol (Haldol®)</td>
<td>Oculogyic crises</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Superficial keratopathy</td>
</tr>
<tr>
<td>Interferon</td>
<td>Retinal hemorrhages and cotton wool spots</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Optic neuropathy</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>Papilledema</td>
</tr>
<tr>
<td>Steroids</td>
<td>Posterior subcapsular cataracts</td>
</tr>
<tr>
<td></td>
<td>Glaucoma</td>
</tr>
<tr>
<td></td>
<td>Papilledema (systemic steroids)</td>
</tr>
<tr>
<td></td>
<td>Increased severity of HSV infections (geographic ulcers)</td>
</tr>
<tr>
<td></td>
<td>Predisposition to fungal infections</td>
</tr>
<tr>
<td>Sulphonamides, NSAIDs</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Tamsulosin (Flomax®)</td>
<td>Intraoperative Floppy Iris Syndrome, which can complicate cataract surgery</td>
</tr>
<tr>
<td>Tetraacycline</td>
<td>Papilledema (associated with pseudotumour cerebri)</td>
</tr>
<tr>
<td>Thiouracine</td>
<td>Pigmentary degeneration of retina</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Retinal deposition with macular sparing, peripheral visual field loss</td>
</tr>
<tr>
<td>Vitamin A intoxication</td>
<td>Papilledema</td>
</tr>
<tr>
<td>Vitamin D intoxication</td>
<td>Band keratopathy</td>
</tr>
</tbody>
</table>

Common Medications

**TOPICAL OCULAR DIAGNOSTIC DRUGS**

**Fluorescein Dye**
- water soluble orange-yellow dye
- green under cobalt blue light (ophthalmoscope or slit lamp)
- absorbed in areas of epithelial loss (ulcer or abrasion)
- also stains mucus and contact lenses

**Rose Bengal Stain**
- stains devitalized epithelial cells and mucus
Anesthetics
- e.g. proparacaine HCl 0.5%, tetracaine 0.5%
- indications: removal of foreign body and sutures, tonometry, examination of painful cornea
- toxic to corneal epithelium (inhibit mitosis and migration) and can lead to corneal ulceration and scarring with prolonged use, therefore NEVER prescribe

Mydriatics
- dilate pupils
- two classes
  - cholinergic blocking (e.g. tropicamide – Mydriacyl®)
    - dilation plus cycloplegia (loss of accommodation) by paralysis of iris sphincter and the ciliary body
    - indications: refraction, ophthalmoscopy, therapy for iritis
  - adrenergic stimulating (e.g. phenylephrine HCl 2.5%)
    - stimulate pupillary dilator muscles, no effect on accommodation
    - usually used with tropicamide for additive effects
- side effects: hypertension, tachycardia, arrhythmias

<table>
<thead>
<tr>
<th>Table 11. Mydriatic Cycloplegic Drugs and Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
</tr>
<tr>
<td>Tropicamide (Mydriacyl®) 0.5%, 1%</td>
</tr>
<tr>
<td>Cyclopentolate HCl 0.5%, 1%</td>
</tr>
<tr>
<td>Homatropine HBr 1%, 2%</td>
</tr>
<tr>
<td>Atropine sulfate 0.5%, 1%</td>
</tr>
<tr>
<td>Scopolamine HBr 0.25%, 5%</td>
</tr>
</tbody>
</table>

GLAUCOMA MEDICATIONS

<table>
<thead>
<tr>
<th>Table 12. Glaucoma Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Category</strong></td>
</tr>
<tr>
<td>α-Agonist Non-selective</td>
</tr>
<tr>
<td>• epinephrine HCl 1% (Epifrin®)</td>
</tr>
<tr>
<td>• dipivalyl epinephrine 0.1% (Propine®)</td>
</tr>
<tr>
<td>• brimonidine 0.2% (Alphagan®)</td>
</tr>
<tr>
<td>• apraclonidine 0.5% (Lopidine®)</td>
</tr>
<tr>
<td>β-Blocker Non-selective</td>
</tr>
<tr>
<td>• timolol (Timoptic®)</td>
</tr>
<tr>
<td>• levobunolol (Betagan®)</td>
</tr>
<tr>
<td>• betaxolol (Betoptic®)</td>
</tr>
<tr>
<td>Carbonic Anhydrase Inhibitor</td>
</tr>
<tr>
<td>• dorzolamide (Trusopt®)</td>
</tr>
<tr>
<td>• brinzolamide (Azopt®)</td>
</tr>
<tr>
<td>• oral: acetazolamide (Diamox®)</td>
</tr>
<tr>
<td>Parasympathomimetic (cholinergic stimulating)</td>
</tr>
<tr>
<td>• pilocarpine (Pilopine®)</td>
</tr>
<tr>
<td>• carbachol (Isopto Carbachol®)</td>
</tr>
<tr>
<td>Prostaglandin Analogues</td>
</tr>
<tr>
<td>• latanoprost (Xalatan®)</td>
</tr>
<tr>
<td>• travaprost (Travatan®)</td>
</tr>
<tr>
<td>• bimatoprost (Lumigan®)</td>
</tr>
</tbody>
</table>

WET AGE-RELATED MACULAR DEGENERATION MEDICATIONS

Vascular Endothelial Growth Factors (VEGF) Inhibitors
- block vascular endothelial growth factor which prevents ocular angiogenesis and further development of choroidal neovascularization
- administered via intravitreal injections
- pegaptanib (Macugen®) is a selective anti-VEGF targeting VEGF isoform 165 (no longer widely used)
- ranibizumab (Lucentis®) is a non-selective anti-VEGF agent
- bevacizumab (Avastin®) is another non-selective anti-VEGF agent but is only FDA approved for metastatic breast cancer, colorectal cancer and non-small cell lung cancer. Therefore, its ophthalmologic use is off-label
TOPICAL OCULAR THERAPEUTIC DRUGS

NSAIDs
- used for less serious chronic inflammatory conditions
- e.g. ketorolac (Acular®), diclofenac (Voltaren®), nepafenac (Nevanac®) drops

Anti-Histamines
- used to relieve red and itchy eye, often in combination with decongestants
- sodium cromoglycate – stabilizes membranes

Decongestants
- weak adrenergic stimulating drugs (vasoconstrictor)
- e.g. naphazoline, phenylephrine ( Isopto Frin®)
- rebound vasodilation with overuse; rarely can precipitate angle closure glaucoma

Antibiotics
- indications: bacterial conjunctivitis, keratitis, or blepharitis
- commonly as topical drops or ointments, may give systemically
- e.g. sulfonamide (sodium sulfacetamide, sulfisoxazole), gentamicin (Garamycin®), erythromycin, tetracycline, bacitracin, polymyxin B, fluoroquinolones (ciprofloxacin [Ciloxan®], ofloxacin [ Ocuflox®], moxifloxacin [Vigamox®], gatifloxacin [Zymar®])

Corticosteroids
- e.g. fluorometholone (FML®), betamethasone, dexamethasone (Maxidex®), prednisolone ( Predsol® 0.5%, Pred Forte® 1%), rimexolone (Vexol®), loteprednol etabonate 0.5% (Lotamax®)
- primary care physicians should avoid prescribing topical corticosteroids due to risk of glaucoma, cataracts, and reactivation of HSV keratitis
- complications
  ▪ potentiates HSV keratitis and fungal keratitis as well as mask symptoms
  ▪ increased IOP, more rapidly in steroid responders (within weeks)
  ▪ posterior subcapsular cataract (within months)

References

Books

Images

Journal Articles

Lectures/Cases
# Orthopedics

Jonny Elserafi, Michael Neufeld, Kajeandra Ravichandiran and David Stockton, chapter editors  
Jieun Kim and Daniel Soong, associate editors  
Jeff Martin, EBM editor  
Dr. Paul Kuzyk, Dr. Markku T. Nousiainen and Dr. Herbert P. von Schroeder, staff editors

## Acronyms
- OR

## Basic Anatomy Review
- ...2

## Differential Diagnosis of Joint Pain
- ...4

## Fractures – General Principles
- ...5

## Fracture Description

## Management of Fractures

## Fracture Healing

## General Fracture Complications

## Orthopedic X-Ray Imaging
- ...6

## Orthopedic Emergencies
- ...7

## Trauma Patient Work-Up

## Open Fractures

## Cauda Equina Syndrome

## Compartment Syndrome

## Articular Cartilage
- ...9

## Osteomyelitis

## Septic Joint

## Shoulder
- ...10

## Shoulder Dislocation

## Rotator Cuff Disease

## Acromioclavicular Joint Pathology

## Clavicle Fracture

## Frozen Shoulder

## Humerus
- ...15

## Proximal Humeral Fracture

## Humeral Shaft Fracture

## Elbow
- ...16

## Supracondylar Fracture

## Radial Head Fracture

## Olecranon Fracture

## Elbow Dislocation

## Epicondylitis

## Forearm
- ...18

## Radius and Ulna Fracture

## Monteggia Fracture

## Nightstick Fracture

## Galeazzi Fracture

## Wrist
- ...19

## Colles’ Fracture

## Smith’s Fracture

## Complications of Wrist Fractures

## Scaphoid Fracture

## Hand
- ...PL22

## Spine
- ...21

## Fractures of the Spine

## Cervical Spine

## Thoracolumbar Spine

## Pelvis
- ...25

## Pelvic Fracture

## Hip
- ...26

## Hip Dislocation

## Hip Fracture

## Arthritis of the Hip

## Hip Dislocation after Total Hip Arthroplasty

## Femur
- ...28

## Femoral Diaphysis Fracture

## Distal Femoral Fracture

## Knee
- ...29

## Evaluation of Knee

## Cruciate Ligament Tears

## Collateral Ligament Tears

## Meniscal Tears

## Quadriceps/Patellar Tendon Rupture

## Dislocated Knee

## Patella
- ...32

## Patellar Fracture

## Patellar Dislocation

## Patellofemoral Syndrome

## Tibia
- ...34

## Tibial Plateau Fracture

## Tibial Shaft Fracture

## Ankle
- ...35

## Evaluation of Ankle and Foot Complaints

## Ankle Fracture

## Ligamentous Injuries

## Foot
- ...36

## Talar Fracture

## Calcaneal Fracture

## Achilles Tendonitis

## Achilles Tendon Rupture

## Plantar Fasciitis (Heel Spur Syndrome)

## Bunions (Hallux Valgus)

## Metatarsal Fracture

## Pediatric Orthopedics
- ...38

## Fractures in Children

## Stress Fractures

## Evaluation of the Limping Child

## Epiphyseal Injury

## Slipped Capital Femoral Epiphysis

## Developmental Dysplasia of the Hip

## Legg-Calvé-Perthes Disease (Coxa Plana)

## Osgood-Schlatter Disease

## Congenital Talipes Equinovarus (Club Foot)

## Scoliosis

## Bone Tumours
- ...42

## Benign Active Bone Tumours

## Benign Aggressive Bone Tumours

## Malignant Bone Tumours

## Common Medications
- ...45

## References
- ...46
Acronyms

AC  acromioclavicular
ACL  anterior cruciate ligament
AIN  anterior interosseous nerve
ARDS acute respiratory distress syndrome
AVN  avascular necrosis
CA  coracoclavicular
CC  coracoclavicular
CRPS complex regional pain syndrome
DDH  developmental dysplasia of the hip
DRUJ  distal radioulnar joint
DVT  deep vein thrombosis
EtOH  ethanol/alcohol

FOOSH fall on outstretched hand
GA  general anesthetic
HD  heterotopic ossification
IBD  incision and drainage
IM  intramedullary
LCL  lateral collateral ligament
MCL  medial collateral ligament
MT  metatarsal
MTP  metatarsal phalangeal
MVC  motor vehicle collision
NVS  neurovascular status
NWB  non-weight bearing

OA  osteoarthritis
ORIF  open reduction internal fixation
PCL  posterior cruciate ligament
PE  pulmonary embolism
PIN  posterior interosseous nerve
RA  rheumatoid arthritis
RGI  range of motion
RSI  reflex sympathetic dystrophy
SCFE  slipped capital femoral epiphysis
SLAP  superior lateral, anterior posterior
SN  sensitivity
THA  total hip arthroplasty

Basic Anatomy Review

Figure 1. Median, musculocutaneous, and ulnar nerves: innervation of upper limb muscles

ANTERIOR VIEW
Figure 2. (Left) Blood supply to the upper limb
(Right) Axillary and radial nerves: innervation of the upper limb

Table 1. Sensory and Motor Innervation of the Nerves in the Upper and Lower Extremities

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Motor</th>
<th>Sensory</th>
<th>Nerve Roots</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary</td>
<td>Deltoid/Teres Minor</td>
<td>Lateral Upper Arm (Sergeant’s Patch)</td>
<td>C5, C6</td>
</tr>
<tr>
<td>Musculocutaneous</td>
<td>Biceps/Brachialis</td>
<td>Lateral Forearm</td>
<td>C5, C6</td>
</tr>
<tr>
<td>Radial</td>
<td>Triceps Wrist/Thumb/Finger Extensors</td>
<td>Lateral Dorsum of the Hand</td>
<td>C5, C6, C7, C8</td>
</tr>
<tr>
<td>Median</td>
<td>Wrist Flexors and Adductors</td>
<td>Volar Thumb to Radial ½ of Ring Finger</td>
<td>C6, C7</td>
</tr>
<tr>
<td>Ulnar</td>
<td>Wrist Flexors and Adductors</td>
<td>Medial Forearm</td>
<td>C8, T1</td>
</tr>
<tr>
<td>Tibial</td>
<td>Ankle Plantar Flexion</td>
<td>Sole of Foot</td>
<td>L5, S1</td>
</tr>
<tr>
<td>Superficial Peroneal</td>
<td>Ankle Eversion</td>
<td>Dorsum of Foot</td>
<td>L5, S1</td>
</tr>
<tr>
<td>Deep Peroneal</td>
<td>Ankle Dorsiflexion and Inversion</td>
<td>1st Web Space</td>
<td>L5, S1</td>
</tr>
<tr>
<td>Sural</td>
<td>Lateral Foot</td>
<td></td>
<td>S1, S2</td>
</tr>
<tr>
<td>Saphenous</td>
<td>Anteromedial Ankle</td>
<td></td>
<td>L3, L4</td>
</tr>
</tbody>
</table>
Differential Diagnosis of Joint Pain

**Figure 3. Nerves and arteries of lower limbs**

**Figure 4. Intrinsic vs. extrinsic joint pain**
Fractures – General Principles

Fracture Description

1. Integrity of Skin/Soft Tissue
   - closed: skin/soft tissue over and near fracture is intact
   - open: skin/soft tissue over and near fracture is lacerated or abraded, fracture exposed to outside environment
     - signs: continuous bleeding from puncture site or fat droplets in blood are suggestive of an open fracture

2. Location (Figure 5)
   - epiphyseal: end of bone, forming part of the adjacent joint
   - metaphyseal: the flared portion of the bone at the ends of the shaft
   - diaphyseal: the shaft of a long bone (proximal, middle, distal)
   - physis: growth plate

3. Orientation/Fracture Pattern (Figure 6)
   - transverse: fracture line perpendicular to long axis of bone; direct high energy force
   - oblique: angular fracture line; angular or rotational force
   - butterfly: fracture site fragment which looks like a butterfly
   - segmental: a separate segment of bone bordered by fracture lines; high energy
   - spiral: complex, multi-planar fracture line; rotational force, low energy
   - comminuted/multi-fragmentary: more than 2 fracture fragments
   - intra-articular: fracture line crosses articular cartilage and enters joint
   - avulsion: tendon or ligament tears/pulls fragment off bone; often in children, high energy
   - torus: a buckle fracture of one cortex, often in children (Figure 51, OR38)
   - green-stick: an incomplete fracture of one cortex, often in children (Figure 51, OR38)
   - pathologic: fracture through bone weakened by disease/tumour

4. Displacement (Figure 6)
   - nondisplaced: fracture fragments are in anatomic alignment
   - displaced: fracture fragments are not in anatomic alignment
   - distracted: fracture fragments are separated by a gap
   - angulated: direction of fracture apex, e.g. varus/valgus
   - translated: percentage of overlapping bone at fracture site
   - rotated: fracture fragment rotated about long axis of bone

Management of Fractures

- ABCs, primary survey and secondary survey (ATLS protocol)
  - rule out other fractures/injuries
  - rule out open fracture (see sidebar on OR8)
- AMPLE history: Allergies, Medications, Past medical history, Last meal, Events surrounding injury
  - consider pathologic fracture with history of only minor trauma
- analgesia
- imaging
- splint extremity

Figure 5. Schematic diagram of the long bone

X-Ray Rule of 2s
2 sides = bilateral
2 views = AP + lateral
2 joints = joint above + below
2 times = before + after reduction

Varus/Valgus Angulation
Varus = Apex away from midline
Valgus = Apex toward midline

Displacement
Refers to position of the distal fragment relative to the proximal fragment.

Quick Nerve Exam
"Thumbs Up": PIN (Radial Nerve)  
"OK Sign": AIN (Median Nerve) 
"Spread Fingers": Ulnar Nerve

Reasons for Splinting
- Pain control
- Reduces further damage to vessels, nerves, and skin
- Reduces risk of inadvertently converting closed to open fracture
- Facilitates patient transport
1. obtain the reduction (refer to Table 27 for appropriate IV sedation)
   - closed reduction
   - apply traction in the long axis of the limb
   - reverse the mechanism that produced the fracture
   - reduce with IV sedation and muscle relaxation (fluoroscopy can be used if available)
   - indications for open reduction:
     - NO CAST
     - other indications include:
       - failed closed reduction
       - not able to cast or apply traction due to site (e.g. hip fracture)
       - pathologic fractures
       - potential for improved function with ORIF
   - re-check neurovascular status after reduction and obtain post-reduction x-ray

2. maintain the reduction
   - external stabilization: splints, casts, traction, external fixator
   - internal stabilization: percutaneous pinning, extramedullary fixation (screws, plates, wires), intramedullary fixation (rods)
   - follow-up: evaluate bone healing

3. rehabilitate to regain function and avoid joint stiffness

Fracture Healing

Normal Healing

<table>
<thead>
<tr>
<th>Time</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 0-3</td>
<td>Hematoma, macrophages surround fracture site</td>
</tr>
<tr>
<td>Weeks 3-6</td>
<td>Osteoclasts remove sharp edges, callus forms within hematoma</td>
</tr>
<tr>
<td>Weeks 6-12</td>
<td>Bone forms within the callus, bridging fragments</td>
</tr>
<tr>
<td>Months 6-12</td>
<td>Cortical gap is bridged by bone</td>
</tr>
<tr>
<td>Years 1-2</td>
<td>Normal architecture is achieved through remodelling</td>
</tr>
</tbody>
</table>

Figure 8. Stages of Bone Healing

Evaluation of Healing: Tests of Union

- clinical: no longer tender to palpation or stressing on physical exam
- x-ray: trabeculae cross fracture site, visible callus bridging site on at least 3 of 4 cortices

General Fracture Complications

<table>
<thead>
<tr>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td></td>
</tr>
<tr>
<td>Compartment syndrome</td>
<td>Mal/non-union</td>
</tr>
<tr>
<td>Neurological injury</td>
<td>AVN</td>
</tr>
<tr>
<td>Vascular injury</td>
<td>Osteomyelitis</td>
</tr>
<tr>
<td>Infection</td>
<td>HD</td>
</tr>
<tr>
<td>Implant failure</td>
<td>Post-traumatic osteoarthritis</td>
</tr>
<tr>
<td>Fracture blisters</td>
<td>Joint stiffness/adhesive capsulitis</td>
</tr>
<tr>
<td>Systemic</td>
<td>CRPS type RSD</td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td></td>
</tr>
<tr>
<td>ARDS secondary to fat embolism</td>
<td>Hemorrhagic shock</td>
</tr>
</tbody>
</table>

Orthopedic X-Ray Imaging

General Principles

- x-ray 1 joint above and 1 below
- obtain at least 2 orthogonal views ± specialized views
Table 3. Orthopedic X-Ray Imaging

<table>
<thead>
<tr>
<th>Site</th>
<th>Injury</th>
<th>X-Ray views</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder</td>
<td>Anterior dislocation</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Posterior dislocation</td>
<td>Axillary ± stress view with 10lb in hand</td>
</tr>
<tr>
<td></td>
<td>Acromioclavicular</td>
<td>Trans-scapular</td>
</tr>
<tr>
<td></td>
<td>Frozen shoulder</td>
<td>Zanca view (10-15 cephalic tilt)</td>
</tr>
<tr>
<td>Arm</td>
<td>Humerus #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trans-scapular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Axillary</td>
</tr>
<tr>
<td>Elbow/Forearm</td>
<td>Supracondylar #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Radial head #</td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td>Monteggia #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Night stick #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Galeazzi #</td>
<td></td>
</tr>
<tr>
<td>Wrist</td>
<td>Colles’ #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Smith #</td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td>Scaphoid #</td>
<td>Scaphoid (wrist extension and ulnar deviation x 2wk)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>Pelvic #</td>
<td>AP pelvis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inlet and outlet views</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Judet views (obturator and iliac oblique for acetabular fracture)</td>
</tr>
<tr>
<td></td>
<td>Femoral head/neck #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Intertrochanteric #</td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>Frog-leg</td>
</tr>
<tr>
<td>Hip</td>
<td>SCFE</td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>Knee Dislocation</td>
<td>AP standing, lateral</td>
</tr>
<tr>
<td></td>
<td>Femur/tibia #</td>
<td>Skyline – tangential view with knees flexed at 45° to see patellofemoral</td>
</tr>
<tr>
<td></td>
<td>Patella #</td>
<td>joint</td>
</tr>
<tr>
<td></td>
<td>Patella dislocation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patella femoral syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tibia shaft #</td>
<td></td>
</tr>
<tr>
<td>Ankle</td>
<td>Ankle #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortise view: ankle at 15° of internal rotation</td>
</tr>
<tr>
<td>Foot</td>
<td>Talar #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Calcanial #</td>
<td>Lateral</td>
</tr>
<tr>
<td>Spine</td>
<td>Compression #</td>
<td>AP spine</td>
</tr>
<tr>
<td></td>
<td>Burst #</td>
<td>AP odontoid</td>
</tr>
<tr>
<td></td>
<td>Cervical spine #</td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oblique</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Swimmer’s view: lateral view with arm abducted 180° to evaluate C7-T1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>junction if lateral view is inadequate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lateral flexion/extension view: evaluate subluxation of cervical vertebrae</td>
</tr>
</tbody>
</table>

Orthopedic Emergencies

Trauma Patient Work-Up

Etiology
- high energy trauma e.g. motor vehicle accident, fall from height
- may be associated with spinal injuries or life-threatening visceral injuries

Clinical Presentation
- local swelling, tenderness, deformity of the limbs, and instability of the pelvis or spine
- decreased level of consciousness, hypotension/hypovolemia
- consider involvement of alcohol or other substances

Investigations
- trauma survey (see Emergency Medicine, ER2)
- x-rays: lateral cervical spine, AP chest, AP pelvis, AP and lateral of all bones suspected to be injured
- other views of pelvis: AP, inlet and outlet; Judet views for acetabular fracture (see Table 18 for classification of pelvic fractures)
**Treatment**
- ABCDEs and initiate resuscitation for life threatening injuries
- assess genitourinary injury (rectal exam/vaginal exam mandatory)
- external or internal fixation of all fractures
- DVT prophylaxis

**Complications**
- hemorrhage – life threatening (may produce signs and symptoms of hypovolemic shock)
- fat embolism syndrome (SOB, hypoxemia, petechial rash, thrombocytopenia and neurological symptoms)
- venous thrombosis – DVT and PE
- bladder/bowel injury
- neurological damage
- persistent pain/stiffness/limp/weakness in affected extremities
- post-traumatic osteoarthritis of joints with intra-articular fractures
- sepsis if missed open fracture

**Open Fractures**

**Definition**
- fractured bone and hematoma in communication with the external environment

**Emergency Measures**
- removal of obvious foreign material
- irrigate with normal saline if grossly contaminated
- cover wound with sterile dressings
- immediate IV antibiotics (see Table 4)
- tetanus toxoid or immunoglobulin as needed
- reduce and splint fracture
- NPO and prepare for OR (bloodwork, consent, ECG, CXR)
- operative irrigation and debridement within 6-8 h to decrease risk of infection
- traumatic wound often left open to drain but vacuum-assisted closure dressing may be used
- re-examine with repeat I&D in 48 h

**Table 4. Gustilo Classification of Open Fractures**

<table>
<thead>
<tr>
<th>Gustilo Grade</th>
<th>Length of Open Wound</th>
<th>Description</th>
<th>Prophylactic Antibiotic Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;1 cm</td>
<td>Minimal contamination and soft tissue injury Simple or minimally comminuted fracture</td>
<td>First generation cephalosporin (cefazolin) for 3 d If allergy use fluoroquinolone If MRSA +ve use vancomycin</td>
</tr>
<tr>
<td>II</td>
<td>1-10 cm</td>
<td>Moderate contamination Soft tissue injury</td>
<td>First generation cephalosporin (cefazolin) for 3 d plus Gram-negative coverage (gentamicin) for at least 3 d</td>
</tr>
<tr>
<td>III*</td>
<td>&gt;10 cm</td>
<td>IIIA: Extensive soft tissue injury with adequate ability of soft tissue to cover wound IIB: Extensive soft tissue injury with periosteal stripping and bone exposure; inadequate soft tissue to cover wound IIIc: Vascular injury/compromise</td>
<td>As per Grade II For soil contamination, penicillin is added for clostridial coverage</td>
</tr>
</tbody>
</table>

*Any high energy, comminuted fracture, shot gun, farmyard/soil/water contamination, exposure to oral flora, or fracture more than 8 h old is immediately classified as Grade III

**Cauda Equina Syndrome**
- see Neurosurgery, NS26

**Compartment Syndrome**

**Definition**
- increased interstitial pressure in an anatomical compartment (forearm, calf) where muscle and tissue are bounded by fascia and bone (fibro-osseous compartment) with little room for expansion
- interstitial pressure exceeds capillary perfusion pressure leading to muscle necrosis (in 4-6 h) and eventually nerve necrosis

**Etiology**
- intracompartamental: fracture (particularly tibial shaft fractures, pediatric supracondylar fractures, and forearm fractures), crush injury, ischemia-reperfusion injury
- extracompartamental: constrictive dressing (circumferential cast, poor positioning during surgery), circumferential burn
Figure 9. Pathogenesis of compartment syndrome

Clinical Features
- pain with active contraction of compartment
- pain with passive stretch
- swollen, tense compartment
- suspicious history
- 5 Ps: late sign (see sidebar) – do not wait for these to develop to make the diagnosis!

Investigations
- usually not necessary as compartment syndrome is a clinical diagnosis
- in children or unconscious patients where clinical exam is unreliable, compartment pressure monitoring with catheter AFTER clinical diagnosis is made (normal = 0 mmHg; elevated ≥30 mmHg or ≤30 mmHg of diastolic BP)

Treatment
- non-operative
  - remove constrictive dressings (casts, splints), elevate limb at the level of the heart
- operative
  - urgent fasciotomy
  - 48-72 h post-op: wound closure ± necrotic tissue debridement

Complications
- rhabdomyolysis, renal failure secondary to myoglobinuria
- Volkmann's ischemic contracture: ischemic necrosis of muscle, followed by secondary fibrosis and finally calcification; especially following supracondylar fracture of humerus

Articular Cartilage

Properties
- 2-4 mm layer covering ends of articulating bones, provides nearly frictionless surface
- avascular (nutrition from synovial fluid), aneural, alymphatic
- composed of: collagen (90% is type II; gives tensile strength), water, proteoglycans (gives compressive strength), and chondrocytes

ARTICULAR CARTILAGE DEFECTS

Etiology
- overt trauma, repetitive minor trauma (such as patellar maltracking); common sports injury
- degenerative conditions such as early stage osteoarthritis or osteochondritis dissecans

Clinical Features
- similar to symptoms of osteoarthritis (joint line pain with possible effusion, etc.)
- often have predisposing factors, such as ligament injury, malalignment of the joint (varus/valgus), obesity, bone deficiency (avascular necrosis, osteochondritis dissecans, ganglion bone cysts), inflammatory arthropathy, and familial osteoarthropathy
- may have symptoms of locking or catching related to the torn/displaced cartilage

Investigations
- x-ray (to rule out bony defects and check alignment)
- MRI
- diagnostic arthroscopy (treatment is often guided by what is seen during arthroscopy)
Table 5. Outerbridge Classification of Chondral Defects

<table>
<thead>
<tr>
<th>Grade</th>
<th>Chondral Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Softening and swelling of cartilage</td>
</tr>
<tr>
<td>II</td>
<td>Fragmentation and fissuring &lt;1/2 inch in diameter</td>
</tr>
<tr>
<td>III</td>
<td>Fragmentation and fissuring &gt;1/2 inch in diameter</td>
</tr>
<tr>
<td>IV</td>
<td>Erosion of cartilage down to bone</td>
</tr>
</tbody>
</table>

**Treatment**
- individualized; must take into account patient factors (age, skeletal maturity, activity level, etc.) and defect factors (Outerbridge classification, subchondral bone involvement, etc.)
- non-operative: rest, NSAIDs, bracing
- operative: microfracture, osteochondral grafting (autograft or allograft), autologous chondrocyte implantation

**Osteomyelitis**

**Treatment**

<table>
<thead>
<tr>
<th>Acute Osteomyelitis</th>
<th>Chronic Osteomyelitis</th>
</tr>
</thead>
</table>
| IV antibiotics; started empirically and adjusted after obtaining blood and aspirate cultures ± surgery for abscess | Surgical debridement
|                                                                                   | Antibiotics: both local (e.g. antibiotic beads) and systemic (IV)                      |

**Septic Joint**

**Etiology**
- most commonly caused by *Staphylococcus aureus* in adults
- consider coagulase-negative *Staphylococcus* in patients with prior joint replacement
- consider *Neisseria gonorrhoeae* in sexually active adults
- most common route of infection is hematogenous
- risk factors: age >80 yr, DM, RA, prosthetic joint, recent joint surgery, skin infection/ulcer, IV drug use, alcoholism, previous intra-articular corticosteroid injection

**Clinical Presentation**
- inability/refusal to bear weight, localized joint pain, erythema, warmth, swelling, pain on active and passive ROM, ± fever

**Investigations**
- x-ray (to rule out fracture, tumour, metabolic bone disease), ESR, CRP, WBC, blood cultures
- joint aspirate: WBC >80,000 with >90% neutrophils, protein level >4.4 mg/dL, joint glucose level < blood glucose level, no crystals, positive Gram stain results
- listen for heart murmur (to rule out infective endocarditis)

**Treatment**
- IV antibiotics, empiric therapy (based on age and risk factors), adjust following joint aspirate C&S results
- for small joints: needle aspiration, serial if necessary until sterile
- for major joints such as knee, hip, or shoulder: urgent decompression and surgical drainage

**Shoulder**

**Shoulder Dislocation**

**Prognosis**
- recurrence rate depends on age of 1st dislocation: <20 yr = 65-95%; 20-40 yr = 60-70%; >40 yr = 2-4%

**Specific Complications**
- rotator cuff or capsular tear, shoulder stiffness
- injury to axillary nerve/artery, brachial plexus
- recurrent/reduced dislocation (most common complication)

**Investigations**
- anterior dislocation x-rays (AP, trans-scapular, axillary views)
- posterior dislocation x-rays (AP, trans-scapular, axillary) or CT scan
## Table 6. Anterior and Posterior Shoulder Dislocation

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Anterior Shoulder Dislocation (&gt;90%)</th>
<th>Posterior Shoulder Dislocation (5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions</td>
<td>Abducted arm is externally rotated/hyperextended, or blow to posterior shoulder</td>
<td>Adducted, internally rotated, flexed arm</td>
</tr>
<tr>
<td>CLINICAL FEATURES</td>
<td>Pain, arm slightly abducted and externally rotated with inability to internally rotate</td>
<td>Pain, arm is held in adduction and internal rotation; external rotation is blocked</td>
</tr>
<tr>
<td>Shoulder Exam</td>
<td>&quot;Squared off&quot; shoulder + ve apprehension test: patient looks apprehensive with gentle shoulder abduction and external rotation to 90° since humeral head is pushed anteriorly and recreates feeling of anterior dislocation (Figure 13)</td>
<td>Anterior shoulder flattening, prominent coracoid, palpable mass posterior to shoulder + ve posterior apprehension (&quot;jerk&quot;) test: with patient supine, flex elbow 90° and adduct, internally rotate the arm while applying a posterior force to the shoulder; patient will &quot;jerk&quot; back with the sensation of subluxation (Figure 13)</td>
</tr>
<tr>
<td>Neurovascular Exam</td>
<td>Axillary nerve: sensory patch over deltoid and deltoit contraction</td>
<td>Full neurovascular exam as per anterior shoulder dislocation</td>
</tr>
<tr>
<td>RADIOGRAPHIC FINDINGS</td>
<td>Humeral head is anterior</td>
<td>Humeral head is posterior</td>
</tr>
<tr>
<td>Axillary View</td>
<td>Humerus head is anterior to the centre of the &quot;Mercedes-Benz sign&quot; (Figure 11)</td>
<td>Partial vacuum of glenoid fossa (vacant glenoid sign) and &gt;6 mm space between anterior glenoid rim and humeral head (positive rim sign), humeral head may resemble a lightbulb due to internal rotation (lightbulb sign)</td>
</tr>
<tr>
<td>Trans-scapular ‘Y’ View</td>
<td>Humerus head is posterior to centre of &quot;Mercedes-Benz sign&quot; (Figure 11)</td>
<td>± reverse Hil-Sachs lesion (75% of cases): divot in anterior humeral head ± reverse bony Bankart lesion: avulsion of the posterior glenoid labrum from the bony glenoid rim</td>
</tr>
<tr>
<td>AP View</td>
<td>Sub-coracoid lie of the humeral head is most common</td>
<td>± bony Bankart lesion: avulsion of the anterior glenoid labrum (with attached bone fragments) from the glenoid rim (Figure 12)</td>
</tr>
<tr>
<td>Hill-Sachs and Bony Bankart Lesions</td>
<td>± Hil-Sachs lesion: compression fracture of posterior humeral head due to forceful impaction of an anteriorly dislocacted humeral head against the glenoid rim (Figure 12)</td>
<td>± reverse Hil-Sachs lesion (75% of cases): divot in anterior humeral head ± reverse bony Bankart lesion: avulsion of the posterior glenoid labrum from the bony glenoid rim</td>
</tr>
<tr>
<td>TREATMENT</td>
<td>Closed reduction with IV sedation and muscle relaxation</td>
<td>Closed reduction with sedation and muscle relaxation</td>
</tr>
<tr>
<td></td>
<td>Traction-countertraction: assistant stabilizes torso with a folded sheet wrapped across the chest while the surgeon applies gentle steady traction (Figure 13)</td>
<td>Inferior traction on a flexed elbow with pressure on the back of the humeral head</td>
</tr>
<tr>
<td></td>
<td>Stimson: while patient lies prone with arm hanging over table edge, hang a 5 lb weight on wrist for 15-20 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hippocratic method: place heel into patient’s axilla and apply traction to arm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cunningham’s method: low risk, low pain; if not successful try above methods</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obtain post-reduction x-rays</td>
<td>Obtain post-reduction x-rays</td>
</tr>
<tr>
<td></td>
<td>Check post-reduction NVS</td>
<td>Check post-reduction NVS</td>
</tr>
<tr>
<td></td>
<td>Sling x 3 wk (avoid abduction and ext. rotation), followed by shoulder rehabilitation (dynamic stabilizer strengthening)</td>
<td>Sling in abduction and external rotation x 3 wk, followed by shoulder rehabilitation (dynamic stabilizer strengthening)</td>
</tr>
</tbody>
</table>

**Factors Causing Shoulder Instability**
- Shallow glenoid
- Loose capsule
- Ligamentous laxity

**Frequency of Dislocations:**
- Anterior shoulder > Posterior shoulder
- Posterior hip > Anterior hip

The glenohumeral joint is the most commonly dislocated joint in the body since stability is sacrificed for motion.
Rotator Cuff Disease

- rotator cuff consists of 4 muscles (Table 7) that act to stabilize humeral head within the glenoid fossa (see Figure 14)

Table 7. Rotator Cuff Muscles

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Muscle Attachments</th>
<th>Nerve Supply</th>
<th>Muscle Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraspinatus</td>
<td>Scapula Greater tuberosity of humerus</td>
<td>Suprascapular nerve</td>
<td>Abduction</td>
</tr>
<tr>
<td>Infraspinatus</td>
<td>Scapula Greater tuberosity of humerus</td>
<td>Suprascapular nerve</td>
<td>External rotation</td>
</tr>
<tr>
<td>Teres Minor</td>
<td>Scapula Greater tuberosity of humerus</td>
<td>Axillary nerve</td>
<td>External rotation</td>
</tr>
<tr>
<td>Subscapularis</td>
<td>Scapula Lesser tuberosity of humerus</td>
<td>Subscapular nerve</td>
<td>Internal rotation and adduction</td>
</tr>
</tbody>
</table>

SPECTRUM OF DISEASE: IMPINGEMENT, TENDONITIS, MICRO OR MACRO TEARS

Etiology
- impingement: “painful arc syndrome”, compression of rotator cuff tendons (primarily supraspinatus) and subacromial bursa between the head of the humerus and the undersurface of acromion, AC joint and CA ligament leads to bursitis, tendonitis and if left untreated, can lead to rotator cuff thinning and tear
- anything that leads to a narrow subacromial space
  - glenohumeral muscle weakness leading to abnormal motion of humeral head
  - scapular muscle weakness leading to abnormal motion of acromion
  - acromial abnormalities such as congenital narrow space or osteophyte formation

Clinical Features
- night pain and difficulty sleeping on affected side
- pain worse with active motion
- weakness and loss of range of motion especially between 90°-130° (e.g. trouble with overhead activities)
- tenderness to palpation over greater tuberosity
- rule out bicep tendinosis: Speed and Yergason’s tests; SLAP lesion: O’Brien’s test

Table 8. Rotator Cuff Special Tests (Figure 15)

<table>
<thead>
<tr>
<th>Test</th>
<th>Examination</th>
<th>Positive Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jobe’s Test</td>
<td>Supraspinatus: place the shoulder in 90° of abduction and 30° of forward flexion and internally rotate the arm so that the thumb is pointing toward the floor</td>
<td>Weakness with active resistance suggests a supraspinatus tear</td>
</tr>
<tr>
<td>Lift-off</td>
<td>Subscapularis: internally rotate arm so dorsal surface of hand rests on lower back. Patient instructed to actively lift hand away from back against examiner resistance. (use Belly Press Test if too painful)</td>
<td>Inability to actively lift hand away from back suggests a subscapularis tear</td>
</tr>
</tbody>
</table>
### Table 8. Rotator Cuff Special Tests (Figure 15) (continued)

<table>
<thead>
<tr>
<th>Test</th>
<th>Examination</th>
<th>Positive Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior-Cuff Test</td>
<td>Infraspinatus and teres minor: arm positioned at patient’s side in 90° of flexion. Patient instructed to externally rotate arm against the resistance of the examiner.</td>
<td>Weakness with active resistance suggests posterior cuff tear</td>
</tr>
<tr>
<td>Neer’s Test</td>
<td>Rotator cuff impingement: passive shoulder flexion</td>
<td>Pain elicited between 130-170° suggests impingement</td>
</tr>
<tr>
<td>Hawkins-Kennedy Test</td>
<td>Rotator cuff impingement: shoulder flexion to 90° and passive internal rotation</td>
<td>Pain with internal rotation suggests impingement</td>
</tr>
<tr>
<td>Painful Arc Test</td>
<td>Rotator cuff tendinopathy: patient instructed to actively abduct the shoulder</td>
<td>Pain with abduction greater than 90° suggests tendinopathy</td>
</tr>
</tbody>
</table>

**Figure 15. Rotator cuff tests**

**Investigations**
- x-rays: AP view may show high riding humerus relative to glenoid, evidence of chronic tendonitis
- MRI: coronal/sagittal oblique and axial orientations are useful for assessing full/partial tears and tendinopathy ± arthrogram: geyser sign (injected dye leaks out of joint through rotator cuff tear)
- arthrogram: see full thickness tear, difficult to assess partial thickness tears

**Treatment and Prognosis**
- mild (“wear”)
  - treatment is non-operative (physiotherapy, NSAIDs)
- moderate (“tear”)
  - non-operative treatment ± steroid injection
- severe (“repair”)
  - impingement that is refractory to 2-3 mo physio and 1-2 injections
  - may require arthroscopic or surgical repair, i.e. acromioplasty, rotator cuff repair

**Screening Out Rotator Cuff Tears**
- No night pain (SN 87.7%)
- No painful arc (SN 97.5%)
- No impingement signs (SN 97.2%)
- No weakness

Returning to the bedside: Using the history and physical examination to identify rotator cuff tears.
*JAM Geri Soc* 2000;48:1633-1637

**Ruling in Rotator Cuff Tears – 98% probability of rotator cuff tear if all 3 of the following are present:**
- Supraspinatus weakness
- External rotation weakness
- Positive impingement sign(s)

Acromioclavicular Joint Pathology

- 2 main ligaments attach clavicle to scapula: AC and CC ligaments

Mechanism
- fall onto shoulder with adducted arm (fall onto tip of shoulder)

Clinical Features
- palpate step deformity between distal clavicle and acromion (with dislocation)
- pain with adduction of shoulder and/or palpation over AC joint
- limited ROM

Investigations
- x-rays: AP, Zanca view (10-15° cephalic tilt), axillary ± stress views (10 lb weight in patient’s hand)

Treatment
- non-operative (most common): sling 1-3 wk, ice, analgesia, rehabilitation
- operative
  - indications: AC and CC ligaments are both torn and/or clavicle displaced posteriorly
  - procedure: excision of lateral clavicle with AC/CC ligament reconstruction

Table 9. Rockwood Classification of Acromioclavicular Joint Separation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Joint sprain, absence of complete tear of either ligament</td>
<td>Non-operative</td>
</tr>
<tr>
<td>II</td>
<td>Complete tear of AC ligament, incomplete tear of CC ligament, without marked elevation of lateral clavicular head</td>
<td>Non-operative</td>
</tr>
<tr>
<td>III</td>
<td>Complete tear of AC and CC ligaments, &gt;5 mm elevation at AC joint, superior aspect of acromion is below the inferior aspect of the clavicle</td>
<td>Most non-operative, operative as per indications above Will heal with step deformity, although most fully functional in 4-6 mo</td>
</tr>
<tr>
<td>IV/V</td>
<td>Based on the anatomical structure the displaced clavicle is in proximity with</td>
<td>Operative in most cases</td>
</tr>
</tbody>
</table>

Clavicle Fracture

- incidence: proximal (5%), middle (80%), or distal (15%) third of clavicle
- common in children (unites rapidly without complications)

Mechanism
- fall on shoulder (87%), direct trauma to clavicle (7%), FOOSH (6%)

Clinical Features
- pain and tenting of skin
- arm is clasped to chest to splint shoulder and prevent movement

Treatment
- evaluate neurovascular status of entire upper limb
- medial and middle third clavicle fractures
  - figure-of-eight sling x 1-2 wk
  - early ROM and strengthening once pain subsides
  - if ends overlap >2 cm consider ORIF
- distal third clavicle fractures
  - undisplaced (with ligaments intact): sling x 1-2 wk
  - displaced (CC ligament injury): ORIF

Specific Complications (see General Fracture Complications, OR6)
- cosmetic bump usually only complication
- shoulder stiffness, weakness with repetitive activity
- pneumothorax, brachial plexus injuries and subclavian vessel (all very rare)

Frozen Shoulder (Adhesive Capsulitis)

Definition
- disorder characterized by progressive pain and stiffness of the shoulder usually resolving spontaneously after 18 mo
Mechanism
- primary adhesive capsulitis
  - idiopathic, usually associated with diabetes mellitus
  - usually resolves spontaneously in 9-18 mo
- secondary adhesive capsulitis
  - due to prolonged immobilization
  - shoulder-hand syndrome: CRPS/RSD characterized by arm and shoulder pain, decreased motion, and diffuse swelling
  - following myocardial infarction, stroke, shoulder trauma
  - poorer outcomes

Clinical Features
- gradual onset (weeks to months) of diffuse shoulder pain with:
  - decreased active and passive ROM
  - pain worse at night and often prevents sleeping on affected side
  - increased stiffness as pain subsides: continues for 6-12 mo after pain has disappeared

Investigations
- x-rays may be normal, or may show demineralization from disease

Treatment
- Freezing Phase
  - active and passive ROM (physiotherapy)
  - NSAIDs and steroid injections if limited by pain
- Thawing Phase
  - manipulation under anaesthesia and early physiotherapy
  - arthroscopy for debridement/decompression

Humerus

Proximal Humeral Fracture

Mechanism
- young: high energy trauma (MVC)
- elderly: FOOSH from standing height in osteoporotic individuals

Clinical Features
- proximal humeral tenderness, deformity with severe fracture, swelling, painful ROM, bruising extends down arm later

Investigations
- test axillary nerve function (deltoid contraction and skin over deltoid)
- x-rays: AP, trans-scapular, axillary are essential
- CT scan: to evaluate for articular involvement and fracture displacement

Classification
- Neer classification is based on 4 fracture fragments (see Neer Classification sidebar)
  - displaced: displacement >1 cm and/or angulation >45°
  - the Neer system regards displacement, not the fracture line, as meeting criteria for a ‘part’ in the classification scheme
  - ± dislocated/subluxed: humeral head dislocated/subluxed from glenoid

Treatment
- treat osteoporosis if needed
- non-operative (nondisplaced or minimally displaced)
  - broad arm sling immobilization (nondisplaced): begin ROM in 7-10 d to prevent stiffness
  - closed reduction (minimally displaced) with sling immobilization x 2 wk, gentle ROM
- operative
  - ORIF (anatomic neck fractures, displaced, associated dislocated glenohumeral joint)
  - hemiarthroplasty may be necessary, especially in elderly

Specific Complications (see General Fracture Complications, OR6)
- AVN, axillary nerve palsy, malunion, post-traumatic arthritis

Conditions Associated with an Increased Incidence of Adhesive Capsulitis
- Prolonged immobilization (most significant)
- Female gender
- Age >49 yr
- Diabetes mellitus (5x)
- Cervical disc disease
- Hyperthyroidism
- Stroke
- Myocardial infarction
- Trauma and surgery

Anatomic neck fractures disrupt blood supply to the humeral head and AVN of the humeral head may ensue.
Humeral Shaft Fracture

Mechanism
- direct blows/MVC (most common), FOOSH, twisting injuries, metastases (in elderly)

Clinical Features
- pain, swelling, ± shortening, motion/crepitus at fracture site
- must test radial nerve function before and after treatment: look for drop wrist, sensory impairment dorsum of hand

Investigations
- x-rays: AP and lateral radiographs of the humerus including the shoulder and elbow joints

Treatment
- in general, humeral shaft fractures are treated non-operatively
- non-operative (most common)
  - ± reduction; can accept deformity due to compensatory range of motion of shoulder
  - hanging cast (weight of arm in cast provides traction across fracture site) with collar and cuff sling immobilization until swelling subsides, then Sarmiento functional brace, followed by ROM
- operative
  - indications: open fracture, neurovascular injury, unacceptable fracture alignment, polytrauma, segmental fracture, pathological fracture, “floating elbow” (simultaneous unstable humeral and forearm fractures), intra-articular
  - ORIF: plating (most common), intramedullary rod insertion, external fixation

Specific Complications (see General Fracture Complications, OR6)
- radial nerve palsy: expect spontaneous recovery in 3-4 mo, otherwise send for EMG
- non-union: most frequently seen in middle 1/3
- decreased ROM
- compartment syndrome

Elbow

Supracondylar Fracture

- most common in pediatric population (peak age ~7 yr old), rarely seen in adults
- fracture of the distal 1/3 of humerus just proximal to capitulum and trochlea, usually transverse
- AIN injury commonly associated with extension type

Mechanism
- >96% are extension injuries via FOOSH (e.g. fall off monkey bars); <4% are flexion injuries

Clinical Features
- pain, swelling, point tenderness
- neurovascular injury: assess median and radial nerve, radial artery (check radial pulse)

Investigations
- x-rays: AP, lateral of elbow (Figure 17)
  - assess for anterior fat pad (‘sail sign’) or the presence of a posterior fat pad representative of an occult fracture (Figure 18)

Treatment
- reduction indications: evidence of arterial obstruction, unacceptable angulation, displaced (>50%)
- non-operative
  - nondisplaced: long arm plaster slab in 90° flexion x 3 wk
- operative
  - indications: displaced, vascular injury, open fracture
  - requires percutaneous pinning followed by limb cast with elbow flexed >90°
  - in adults, ORIF is necessary

Specific Complications (see General Fracture Complications, OR6)
- stiffness is most common
- brachial artery injury (kinking can occur if displaced fracture), median or ulnar nerve injury, compartment syndrome (leads to Volkman’s ischemic contracture), malalignment cubitus varus (distal fragment tilted into varus)
### Radial Head Fracture

- a common fracture of the upper limb in young adults

**Mechanism**
- FOOSH with elbow extended and forearm pronated

**Clinical Features**
- marked local tenderness on palpation over radial head (lateral elbow)
- decreased ROM at elbow, mechanical block to forearm pronation and supination
- pain on pronation/supination

**Investigations**
- x-ray: enlarged anterior fat pad (“sail sign”) or the presence of a posterior fat pad indicates occult radial head fractures (Figure 18)

**Table 10. Classification and Treatment of Radial Head Fractures**

<table>
<thead>
<tr>
<th>Mason Class</th>
<th>Radiographic Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Undisplaced fracture</td>
<td>Elbow slab or sling x 3–5 d with early ROM</td>
</tr>
<tr>
<td>2</td>
<td>Displaced fracture</td>
<td>ORIF if: angulation &gt; 30°, involves ≥1/3 of the radial head, or if ≥3 mm of joint incongruity exists</td>
</tr>
<tr>
<td>3</td>
<td>Comminuted fracture</td>
<td>Radial head excision ± prosthesis</td>
</tr>
<tr>
<td>4</td>
<td>Comminuted fracture with posterior elbow dislocation</td>
<td>Radial head excision ± prosthesis</td>
</tr>
</tbody>
</table>

**Specific Complications** (see General Fracture Complications, OR6)
- myositis ossificans
- recurrent instability (if medial collateral ligament injured and radial head excised)

### Olecranon Fracture

**Mechanism**
- direct trauma to posterior aspect of elbow (fall onto the point of the elbow)

**Clinical Features**
- ± loss of active extension due to avulsion of triceps tendon

**Treatment**
- undisplaced (<2 mm, stable): cast x 10–14 d (elbow in 90° flexion) then gentle ROM
- displaced: ORIF (plate and screws or tension band wiring) and early ROM if stable

### Elbow Dislocation

- third most common joint dislocation after shoulder and patella
- usually the radius and ulna are dislocated together, or the radius head dislocates and the ulna remains (“Monteggia”)
- anterior capsule and collateral ligaments disrupted

**Mechanism**
- elbow hyperextension via FOOSH or valgus/supination stress during elbow flexion
- most commonly occurs in young people (5–25 yr) in sporting events or high speed MVCs
- 90% are posterior/posterolateral, anterior are rare and usually devastating

**Clinical Features**
- elbow pain, swelling, deformity
- flexion contracture
- ± absent radial or ulnar pulses

**Treatment**
- assess neurovascular status before reduction: brachial artery, median and ulnar nerves (can become entrapped during manipulation)
- closed reduction under conscious sedation (post-reduction x-rays required)
- Parvini’s method: patient lies prone with arm hanging down; apply gentle traction downwards on wrist, as olecranon slips distally, gently lift up the arm at elbow to reduce joint
- long-arm splint with forearm in neutral rotation and elbow in 90° flexion
- early ROM (<2 wk)

**Specific Complications** (see General Fracture Complications, OR6)
- stiffness (loss of extension), intra-articular loose body, neurovascular injury (ulnar nerve, median nerve, brachial artery), radial head fracture
- recurrent instability uncommon

---

Terrible Triad
- Radial head fracture
- Coronoid fracture
- Elbow dislocation

To avoid stiffness do not immobilize elbow joint >2-3 wk.

Anterior fat pad

Posterior fat pad

Terrible Triad
- Radial head fracture
- Coronoid fracture
- Elbow dislocation

Anterior Humeral Line
Radio-Capitellar Line
Capitellum
Radial Head

Figure 19. Lateral view of elbow

Elbow Dislocation
The radio-capitellar line refers to an imaginary line along the longitudinal axis of the radius that passes through the centre of the capitellum regardless of the degree of elbow flexion. If the radio-capitellar line does not pass through the centre of the capitellum a dislocation should be suspected.

The anterior humeral line refers to an imaginary line drawn along the anterior surface of the humeral cortex that passes through the middle third of the capitellum when extended inferiorly. In sublux supracondylar fractures the anterior humeral line is disrupted, typically passing through the anterior third of the capitellum.
**Epicondylitis**

- lateral epicondylitis = "tennis elbow", inflammation of the common extensor tendon as it inserts into the lateral epicondyte
- medial epicondylitis = "golfer's elbow", inflammation of the common flexor tendon as it inserts into the medial epicondyte

**Mechanism**
- repeated or sustained contraction of the forearm muscles

**Clinical Features**
- point tenderness over humeral epicondyle and/or distal to it
- pain upon resisted wrist extension (lateral epicondylitis) or wrist flexion (medial epicondylitis)
- generally a self-limited condition, but may take 6-18 mo to resolve

**Treatment**
- rest, ice, NSAIDs
- use brace/strap
- physiotherapy, stretching and strengthening
- corticosteroid injection
- surgery: percutaneous or open release of common tendon from epicondyle (only after 6-12 mo of conservative therapy)

---

**Radius and Ulna Fracture**

**Mechanism**
- commonly a FOOSH or high-energy direct blow
- fractures usually accompanied by displacement due to high force

**Investigations**
- x-ray: 1) AP and lateral of forearm; 2) AP, lateral, oblique of elbow and wrist
- CT if fracture is close to joint

**Treatment**
- goal is anatomic reduction since imperfect alignment significantly limits forearm pronation and supination
- ORIF with plates and screws; closed reduction with immobilization usually yields poor results for displaced forearm fractures (except in children)

**Complications** (see General Fracture Complications, OR6)
- soft tissue contracture resulting in limited forearm rotation – surgical release of tissue may be warranted

---

**Monteggia Fracture**

- more common and better prognosis in the pediatric age group when compared to adults

**Definition**
- fracture of the proximal ulna with radial head dislocation and proximal radioulnar joint injury (Figure 20)

**Mechanism**
- direct blow on the posterior aspect of the forearm
- hyperpronation
- fall on the hyperextended elbow

**Clinical Features**
- decreased rotation of forearm ± palpable lump at the radial head
- ulna angled apex anterior and radial head dislocated anteriorly (rarely the reverse deformity occurs)

**Treatment**
- adults: ORIF of ulna with indirect radius reduction in 90% of patients
- splint and early post-op ROM if elbow completely stable, otherwise immobilization in plaster with elbow flexed for 6 wk
- pediatrics: attempt closed reduction and immobilization in plaster with elbow flexed for Bado Type I-III, surgery for Type IV

---

**Figure 20. Monteggia fracture**

In all isolated ulna fractures, assess proximal radius to rule out a Monteggia fracture.
Specific Complications (see General Fracture Complications, OR6)
- PIN: most common nerve injury, especially with posterior approach to the radius fixation
- radial head instability/redislocation
- radioulnar synostosis

Nightstick Fracture

Definition
- isolated fracture of ulna without dislocation of radial head

Mechanism
- direct blow to forearm (e.g. holding arm up to protect face)

Treatment
- non-displaced: below elbow cast (x 10 d) followed by forearm brace (~8 wk)
- displaced: ORIF if >50% shaft displacement or >10° angulation

Galeazzi Fracture

Definition
- fracture of the distal radial shaft with disruption of the DRUJ
- most commonly in the distal 1/3 of radius near junction of metaphysis/diaphysis
- 3x more common than Monteggia fracture

Mechanism
- hand FOOSH with axial loading of pronated forearm

Investigations
- x-rays
  - shortening of distal radius >5 mm relative to the distal ulna
  - widening of the DRUJ space on AP
  - dislocation of radius with respect to ulna on true lateral

Treatment
- ORIF of radius; afterwards assess DRUJ stability by balloting distal ulna relative to distal radius
- if DRUJ is stable and reducible, splint for 10-14 d with early ROM encouraged
- if DRUJ is unstable, ORIF or percutaneous pinning with long arm cast in supination x 6 wk

Wrist

Colles’ Fracture

Definition
- extra-articular transverse distal radius fracture (about 2 cm proximal to the radiocarpal joint) with dorsal displacement ± ulnar styloid fracture

Epidemiology
- most common fracture in those >40 yr, especially in women and those with osteoporotic bone

Mechanism
- FOOSH

Clinical Features
- “dinner fork” deformity (Figures 23 and 24)
- swelling, ecchymoses, tenderness

Investigations
- x-ray: AP and lateral wrist

Treatment
- goal is to restore radial height, radial inclination (22°), volar tilt (11°) as well as DRUJ stability and useful forearm rotation
- closed reduction (think opposite of the deformity):
  - hematoma block (sterile prep and drape, local anesthetic injection directly into fracture site) or conscious sedation
  - closed reduction: 1) traction with extension (exaggerate injury), 2) traction with ulnar deviation, pronation, flexion (of distal fragment – not at wrist)
  - dorsal slab/below elbow cast for 5-6 wk
  - x-ray x 1 wk for 3 wk and at cessation of immobilization to ensure reduction is maintained
  - obtain post-reduction films immediately; repeat reduction if necessary, consider external fixation or ORIF if failure of adequate closed reduction
Smith’s Fracture

Definition
• volar displacement of the distal radius (i.e. reverse Colles’ fracture)

Mechanism
• fall onto the back of the flexed hand

Treatment
• usually unstable and needs ORIF
• if patient is poor operative candidate, may attempt non-operative treatment
• closed reduction with hematoma block (reduction opposite of Colles’)
• long-arm cast in supination x 6 wk

Complications of Wrist Fractures

• most common complications are poor grip strength, stiffness, and radial shortening
• distal radius fractures in individuals <40 yr of age are usually highly comminuted and are likely to require ORIF
• 80% have normal function in 6-12 mo

Table 11. Early and Late Complications of Wrist Fractures

<table>
<thead>
<tr>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficult reduction ± loss of reduction</td>
<td>Malunion, radial shortening (Figure 24)</td>
</tr>
<tr>
<td>Compartment syndrome</td>
<td>Painful wrist secondary to ulnar prominence</td>
</tr>
<tr>
<td>Extensor pollicis longus tendon rupture</td>
<td>Frozen shoulder (“shoulder-hand syndrome”)</td>
</tr>
<tr>
<td>Acute carpal tunnel syndrome</td>
<td>Post-traumatic arthritis</td>
</tr>
<tr>
<td>Finger swelling with venous block</td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td>Complications of a tight cast/splint</td>
<td>CRPS/RSD</td>
</tr>
</tbody>
</table>

Scaphoid Fracture

Epidemiology
• common in young men; not common in children or in patients beyond middle age
• most common carpal bone injured
• may be associated with other carpal or wrist injuries (e.g. Colle’s fracture)

Mechanism
• FOOSH: impaction of scaphoid on distal radius, most commonly resulting in a transverse fracture through the middle/waist (50%), distal (38%), or proximal (12%) scaphoid

Clinical Features
• pain with wrist movement
• tenderness in the anatomical "snuff box", over scaphoid tuber, and pain with long axis compression into scaphoid
• usually undisplaced

Investigations
• x-ray: PA, lateral, scaphoid views with wrist extension and ulnar deviation x 2 wk
• ± CT or MRI
• bone scan rarely used
• note: a fracture may not be radiologically evident up to 2 wk after acute injury, so if a patient complains of wrist pain and has anatomical snuff box tenderness but a negative x-ray, treat as if positive for a scaphoid fracture and repeat x-ray 2 wk later to rule out a fracture. If x-ray still negative order CT or MRI

Treatment
• early treatment critical for improving outcomes
• non-displaced (<1 mm displacement/<15° angulation): long-arm thumb spica cast x 4 wk then short arm cast until radiographic evidence of healing is seen (2-3 mo)
• displaced: ORIF with headless/countersink compression screw is the mainstay treatment, or percutaneous K-wire fixation (uncommon) (Figure 26)
Specific Complications (see General Fracture Complications, OR6)
- most common: non-union/mal-union (use bone graft from iliac crest or distal radius with fixation to heal)
- AVN of the proximal fragment
- delayed union (recommend surgical fixation)

Prognosis
- fractures of the proximal third of the scaphoid have 70% rate of non-union or AVN
- waist fractures have healing rates of 80-90%
- distal third fractures have healing rates close to 100%

Hand
- see Plastic Surgery, PL22

Spine

Table 12. Fracture Type and Column Involvement

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Column Failure</th>
<th>Stable/Unstable</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression</td>
<td>Anterior</td>
<td>Stable</td>
<td>Compression</td>
</tr>
<tr>
<td>Burst</td>
<td>Anterior, middle</td>
<td>± Unstable</td>
<td>High-energy axial loading + flexion</td>
</tr>
<tr>
<td>Fracture-dislocation</td>
<td>Anterior, middle, posterior</td>
<td>Unstable</td>
<td>Significant force applied to spine (flexion, extension, distraction, rotation, shear or axial load)</td>
</tr>
<tr>
<td>Flexion-distraction</td>
<td>Middle, posterior</td>
<td>± Unstable</td>
<td>MVC (lap belt only) causing flexion and distraction (Chance fracture)</td>
</tr>
</tbody>
</table>

Cervical Spine

General Principles
- C1 (atlas): no vertebral body, no spinous process
- C2 (axis): odontoid = dens
- 7 cervical vertebrae; 8 cervical nerve roots
- nerve root exits above vertebra (i.e. C4 nerve root exits above C4 vertebra), C8 nerve root exits below C7 vertebra
- radiculopathy = impingement of nerve root
- myelopathy = impingement of spinal cord

The proximal pole of the scaphoid receives as much as 100% of its arterial blood supply from the radial artery that enters at the distal pole. A fracture through the proximal third disrupts this blood supply and results in a high incidence of AVN/non-union.
Special Testing
- Compression test: pressure on head worsens radicular pain
- Distraction test: traction on head relieves radicular symptoms
- Valsalva test: Valsalva maneuver increases intrathecal pressure and causes radicular pain

Table 13. Cervical Radiculopathy/Neuropathy

<table>
<thead>
<tr>
<th>Root</th>
<th>C5</th>
<th>C6</th>
<th>C7</th>
<th>C8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td>Deltoid</td>
<td>Biceps</td>
<td>Triceps</td>
<td>Interossei</td>
</tr>
<tr>
<td></td>
<td>Biceps</td>
<td>Brachioradialis</td>
<td>Wrist flexion</td>
<td>Digital flexors</td>
</tr>
<tr>
<td>Sensory</td>
<td>Axillary nerve (patch over lateral deltid)</td>
<td>Thumb and index finger</td>
<td>Middle finger</td>
<td>Ring and little finger</td>
</tr>
<tr>
<td>Reflex</td>
<td>Biceps</td>
<td>Biceps</td>
<td>Triceps</td>
<td>Finger jerk</td>
</tr>
</tbody>
</table>

X-Rays for C-Spine
- AP spine: alignment
- AP odontoid: atlantoaxial articulation
- Lateral
  - Vertebral alignment: posterior vertebral bodies should be aligned (translation >3.5 mm is abnormal)
  - Angulation: between adjacent vertebral bodies (>11° is abnormal)
  - Disc or facet joint widening
  - Anterior soft tissue space (at C3 should be ≤3 mm; at C4 should be ≤8-10 mm)
- Oblique: evaluate pedicles and intervertebral foramen
- ± Swimmer’s view: lateral view with arm abducted 180° to evaluate C7-T1 junction if lateral view is inadequate
- ± Lateral flexion/extension view: evaluate subluxation of cervical vertebrae

Differential Diagnosis of C-Spine Pain
- Neck muscle strain, cervical spondylosis, cervical stenosis, rheumatoid arthritis (spondylitis), traumatic injury, whiplash, myofascial pain syndrome

C-Spine Injury
- See Neurosurgery, NS34

Thoracolumbar Spine

General Principles
- Spinal cord terminates at conus medullaris (L1)
- Individual nerve roots exit below pedicle of vertebra (i.e. L4 nerve root exits below L4 pedicle)

Special Tests
- Straight leg raise: passive lifting of leg (30-70°) reproduces radicular symptoms of pain radiating down posterior/lateral leg to knee ± into foot
- Lasegue maneuver: dorsiflexion of foot during straight leg raise makes symptoms worse or, if leg is less elevated, dorsiflexion will bring on symptoms
- Femoral stretch test: with patient prone, flexing the knee of the affected side and passively extending the hip results in radicular symptoms of unilateral pain in lumbar region, buttock, or posterior thigh

Table 14. Lumbar Radiculopathy/Neuropathy

<table>
<thead>
<tr>
<th>Root</th>
<th>L4</th>
<th>L5</th>
<th>S1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td>Quadriceps (knee extension + hip adduction)</td>
<td>Extensor hallucis longus</td>
<td>Peroneus longus + brevis (ankle eversion)</td>
</tr>
<tr>
<td></td>
<td>Tibialis anterior (ankle inversion + dorsiflexion)</td>
<td>Gastrocnemius + soleus (plantar flexion)</td>
<td></td>
</tr>
<tr>
<td>Sensory</td>
<td>Medial malleolus</td>
<td>1st dorsal webspace and lateral leg</td>
<td>Lateral foot</td>
</tr>
<tr>
<td>Reflex</td>
<td>Knee (Patellar)</td>
<td>Medial hamstring*</td>
<td>Ankle (Achilles)</td>
</tr>
<tr>
<td>Test</td>
<td>Femoral stretch</td>
<td>Straight leg raise</td>
<td>Straight leg raise</td>
</tr>
</tbody>
</table>

*Unreliable
Differential Diagnosis of Back Pain
1. mechanical or nerve compression (>90%)
   - degenerative (disc, facet, ligament)
   - peripheral nerve compression (disc herniation)
   - spinal stenosis (congenital, osteophyte, central disc)
   - cauda equina syndrome
2. others (<10%)
   - neoplastic (primary, metastatic, multiple myeloma)
   - infectious (osteomyelitis, TB)
   - metabolic (osteoporosis)
   - traumatic fracture (compression, distraction, translation, rotation)
   - spondyloarthropathies (ankylosing spondylitis)
   - referred (aorta, renal, ureter, pancreas)

DEGENERATIVE DISC DISEASE
- loss of vertebral disc height with age results in:
  - bulging and tears of annulus fibrosus
  - change in alignment of facet joints
  - osteophyte formation
- can cause back-dominant pain
- management
  - non-operative
    - staying active with modified activity
    - back strengthening
    - NSAIDs
    - do not treat with opioids; no proven efficacy of spinal traction or manipulation
  - operative – rarely indicated
    - decompression ± fusion
    - no difference in outcome between non-operative and surgical management at 2 yr

Table 15. Types of Low Back Pain
<table>
<thead>
<tr>
<th>Mechanical Back Pain</th>
<th>Direct Nerve Root Compression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disc Origin</td>
<td>Facet Origin</td>
</tr>
<tr>
<td>Pain Dominance</td>
<td>Back</td>
</tr>
<tr>
<td>Aggravation</td>
<td>Flexion</td>
</tr>
<tr>
<td>Onset</td>
<td>Gradual</td>
</tr>
<tr>
<td>Duration</td>
<td>Long (weeks, months)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Relief of strain, exercise</td>
</tr>
</tbody>
</table>

SPINAL STENOSIS
- definition: narrowing of spinal canal <10 mm
- etiology: congenital (idiopathic, osteoporosis, achondroplasia) or acquired (degenerative, iatrogenic – post spinal surgery, ankylosing spondylitis, Paget’s disease, trauma)
- clinical features
  - ± bilateral back and leg pain
  - neurogenic claudication (see Table 16)
  - ± motor weakness
  - normal back flexion; difficulty with back extension
- investigations: CT/MRI reveals narrowing of spinal canal, but gold standard = CT myelogram
- treatment
  - non-operative: vigorous physiotherapy (flexion exercises, stretch/strength exercises), NSAIDs, lumbar epidural steroids
  - operative: decompression surgery if conservative methods failed >6 mo

Table 16. Differentiating Claudication
<table>
<thead>
<tr>
<th>Neurogenic</th>
<th>Vascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggravation</td>
<td>With standing or exercise</td>
</tr>
<tr>
<td>Alleviation</td>
<td>Change in position (usually flexion, sitting, lying down)</td>
</tr>
<tr>
<td>Time</td>
<td>Relief in ~10 min</td>
</tr>
<tr>
<td>Character</td>
<td>Neurogenic ± neurological deficit</td>
</tr>
</tbody>
</table>
Figure 30. Approach to back pain

MECHANICAL BACK PAIN
- definition: back pain NOT due to prolapsed disc or any other clearly defined pathology
- clinical features
  - dull backache aggravated by activity
  - morning stiffness
  - no neurological signs
- treatment: symptomatic (analgesics, physiotherapy)
- prognosis: symptoms may resolve in 4-6 wk, others become chronic

LUMBAR DISC HERNIATION
- definition: tear in annulus fibrosus allows protrusion of nucleus pulposus causing either a central, posterolateral, or lateral disc herniation, most commonly at L5-S1 > L4-5 > L3-4
- etiology: usually a history of flexion-type injury
- clinical features
  - back dominant pain (central herniation) or leg dominant pain (lateral herniation)
  - tenderness between spines at affected level
  - muscle spasm ± loss of normal lumbar lordosis
  - neurological disturbance is segmental and varies with level of central herniation
    - motor weakness (L4, L5, S1)
    - diminished reflexes (L4, S1)
    - diminished sensation (L4, L5, S1)
  - +ve straight leg raise
  - +ve Lasegue test
  - bowel or bladder symptoms, decreased rectal tone suggests cauda equina syndrome due to central disc herniation – surgical emergency
- investigations: MRI, consider a post void residual volume to check for urinary retention
- treatment
  - symptomatic
    - extension protocol (physiotherapy)
    - NSAIDs
  - 90% resolve in 3 mo. Surgical discectomy reserved for progressive neurological deficit, failure of symptoms to resolve within 3 mo, or cauda equina syndrome due to central disc herniation

SPONDYLOLYSIS
- definition: defect in the pars interarticularis with no movement of the vertebral bodies
- etiology
  - trauma: gymnasts, weightlifters, backpackers, loggers, labourers
- clinical features: activity-related back pain, pain with unilateral extension (Michelis’ test)
- investigations
  - oblique x-ray: “collar” break in the “Scottie dog’s” neck
  - bone scan
  - CT scan
- treatment: activity restriction, brace, stretching exercise

SPONDYLOLISTHESIS
- definition: defect in pars interarticularis causing a forward slip of one vertebra on another usually at L5-S1, less commonly at L4-5
- etiology: congenital (children), degenerative (adults), traumatic, pathological, teratogenic
- clinical features: lower back pain radiating to buttocks

MRI abnormalities (e.g. spinal stenosis, disc herniation) are quite common in both asymptomatic and symptomatic individuals and are not necessarily an indication for intervention without clinical correlation.
Table 17. Classification and Treatment of Spondylolisthesis

<table>
<thead>
<tr>
<th>Class</th>
<th>Percentage of Slip</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0-25%</td>
<td>Symptomatic operative fusion only for intractable pain</td>
</tr>
<tr>
<td>2</td>
<td>25-50</td>
<td>Same as above</td>
</tr>
<tr>
<td>3</td>
<td>50-75</td>
<td>Decompression for spondylolisthesis and spinal fusion</td>
</tr>
<tr>
<td>4</td>
<td>75-100</td>
<td>Same as above</td>
</tr>
<tr>
<td>5</td>
<td>&gt;100</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

Specific Complications
- May present as cauda equina syndrome due to roots being stretched over the edge of L5 or sacrum

Pelvis

Pelvic Fracture

Mechanism
- Young: high energy trauma, either direct or by force transmitted longitudinally through the femur
- Elderly: fall from standing height, low energy trauma
- Lateral compression (most common), vertical shear, or anteroposterior compression fractures

Clinical Features
- Local swelling, tenderness
- Deformity of lower extremity
- Pelvic instability

Investigations
- X-ray: AP pelvis, inlet and outlet views, Judet views (obturatory and iliac oblique for acetabular fracture)
  - 6 cardinal radiographic lines of the acetabulum: ilioischial line, iliopectineal line, tear drop, roof, posterior rim, anterior rim
- CT scan useful for evaluating posterior pelvic injury and acetabular fracture

Classification

Table 18. Tile Classification of Pelvic Fractures (see Figure 34)

<table>
<thead>
<tr>
<th>Type</th>
<th>Stability</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Rotationally stable</td>
<td>A1: fracture not involving pelvic ring</td>
</tr>
<tr>
<td></td>
<td>Vertically stable</td>
<td>A2: minimally displaced fracture of pelvic ring (e.g. ramus fracture)</td>
</tr>
<tr>
<td>B</td>
<td>Rotationally unstable</td>
<td>B1: open book</td>
</tr>
<tr>
<td></td>
<td>Vertically stable</td>
<td>B2: lateral compression – ipsilateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B3: lateral compression – contralateral</td>
</tr>
<tr>
<td>C</td>
<td>Rotationally unstable</td>
<td>C1: unilateral</td>
</tr>
<tr>
<td></td>
<td>Vertically unstable</td>
<td>C2: bilateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C3: associated acetabular fracture</td>
</tr>
</tbody>
</table>

Treatment
- ABCDEs
- Assess genitourinary injury (rectal exam, vaginal exam, hematuria, blood at urethral meatus)
  - If involved, the fracture is considered an open fracture
- Stable fractures: non-operative treatment, protected weight bearing
- Emergency management
  - IV fluids/blood
  - Pelvic binder/sheeting
  - External fixation vs. emergent angiography/embolization
  - Laparotomy (if FAST/DPL positive)
- Indications for operative treatment
  - Unstable pelvic ring injury
  - Disruption of anterior and posterior SI ligament
  - Symphysis diastasis > 2.5 cm
  - Vertical instability of the posterior pelvis

Possible Radiological Findings:
- Pubic rami fractures: superior/inferior
- Pubic symphysis diastasis: common in AP compression (N=5 mm)
- Sacral fractures: common in lateral compression
- SI joint diastasis: common in AP compression (N=1-4 mm)
- Disrupted anterior column (ilipectineal line) or posterior column (ilioischial line)
- “Teardrop” displacement: acetabular fracture
- Iliac, ischial avulsion fractures
- Displacement of the major fragment: superior (VS), open book (APC), bucket handle (LC)
Specific Complications (see General Fracture Complications, OR6)
- hemorrhage (life-threatening)
- injury to rectum or urogenital structures
- obstetrical difficulties, sexual and voiding dysfunction
- persistent SI joint pain
- post-traumatic arthritis of the hip with acetabular fractures
- high risk of DVT/PE

Hip

Hip Dislocation
- full trauma survey (see Emergency Medicine, Initial Patient Assessment/Management, ER2)
- examine for neurovascular injury PRIOR to open or closed reduction
- reduce hip dislocations ASAP (ideally within 6 h) to decrease risk of AVN of the femoral head
- hip precautions (no extreme hip flexion, adduction, internal or external rotation) for 6 wk post-reduction
- also see Hip Dislocation after THA, OR28

ANTERIOR HIP DISLOCATION
- mechanism: posteriorly directed blow to knee with hip widely abducted
- clinical features: shortened, abducted, externally rotated limb
- treatment
  - closed reduction under conscious sedation/GA
  - post-reduction CT to assess joint congruity

POSTERIOR HIP DISLOCATION
- most frequent type of hip dislocation
- mechanism: severe force to knee with hip flexed and adducted
  - e.g. knee into dashboard in motor vehicle collision (MVC)
- clinical features: shortened, adducted and internally rotated limb
- treatment
  - closed reduction under conscious sedation/GA only if associated femoral neck fracture
  - ORIF if unstable, intra-articular fragments or posterior wall fracture
  - post-reduction CT to assess joint congruity and fractures
  - if reduction is unstable, put in traction x 4-6 wk

CENTRAL HIP DISLOCATION (rare)
- traumatic injury where femoral head is pushed medially through acetabulum

COMPLICATIONS FOR ALL HIP DISLOCATIONS
- post-traumatic osteoarthritis
- AVN of femoral head
- fracture of femoral head, neck, or shaft
- sciatic nerve palsy in 25% (10% permanent)
- HO
- thromboembolism – DVT/PE

Hip Fracture

General Features
- acute onset of hip pain
- unable to weight-bear
- shortened and externally rotated leg
- painful ROM

X-Ray Features of Subcapital Hip Fractures
- Disruption of Shenton’s line (a radiographic line drawn along the upper margin of the obturator foramen, extending along the inferomedial side of the femoral neck)
- Altered neck-shaft angle (normal is 120-130°)
**Table 19. Overview of Hip Fractures**

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Definition</th>
<th>Mechanism</th>
<th>Special Clinical Features</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral Neck</td>
<td>Intracapsular (See Garden Classification, Table 20)</td>
<td>Young: MVC, fall from height; Elderly: fall from standing, rotational force</td>
<td>Same as general</td>
<td>X-ray; AP hip, AP pelvis, cross table lateral hip</td>
<td>See Table 20</td>
<td>DVT, non-union, AVN</td>
</tr>
<tr>
<td>Intertrochanteric</td>
<td>Extracapsular fracture including the greater and lesser trochanters and transitional bone between the neck and shaft</td>
<td>Stable: intact posteromedial cortex; Unstable: non-intact posteromedial cortex</td>
<td>Ecchymosis at back of upper thigh</td>
<td>X-ray; AP pelvis, AP/lateral hip</td>
<td>Closed reduction under fluoroscopy, then dynamic hip screw or IM nail</td>
<td>DVT, varus displacement of proximal fragment, malrotation, non-union, failure of fixation device</td>
</tr>
<tr>
<td>Subtrochanteric</td>
<td>Fracture begins at or below the lesser trochanter and involves the proximal femoral shaft</td>
<td>Young: high energy trauma; Elderly: osteopenic bone + fall, pathological fracture</td>
<td>Ecchymosis at back of upper thigh</td>
<td>X-ray; AP pelvis, AP/lateral hip and femur</td>
<td>Closed/open under fluoroscopy, then plate fixation or IM nail</td>
<td>Malalignment, non-union, wound infection</td>
</tr>
</tbody>
</table>

**Table 20. Garden Classification of Femoral Neck Fractures**

<table>
<thead>
<tr>
<th>Type</th>
<th>Extent</th>
<th>Alignment</th>
<th>Trabeculae</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td>‘Incomplete’</td>
<td>Malaligned</td>
<td>Internal fixation to prevent displacement (valgus impacted fracture)</td>
</tr>
<tr>
<td>II</td>
<td>None</td>
<td>Complete</td>
<td>Neutral</td>
<td>Internal fixation to prevent displacement</td>
</tr>
<tr>
<td>III</td>
<td>Some</td>
<td>Complete</td>
<td>Varus</td>
<td>Young: ORIF; Elderly: hemi- or total hip arthroplasty</td>
</tr>
<tr>
<td>IV</td>
<td>Complete</td>
<td>Complete</td>
<td>Varus</td>
<td>Young: ORIF; Elderly: hemi- or total hip arthroplasty</td>
</tr>
</tbody>
</table>

**Arthritis of the Hip**

**Etiology**
- OA, inflammatory arthritis, post-traumatic arthritis, late effects of congenital hip disorders or septic arthritis

**Clinical Features**
- pain (groin, medial thigh) and stiffness aggravated by activity
- morning stiffness >1 h, multiple joint swelling, hand nodules (RA)
- decreased ROM (internal rotation is lost first)
- crepitus
- ± fixed flexion contracture leading to apparent limb shortening (Thomas test)
- ± Trendelenberg sign
Investigations
- x-ray
  - OA: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes
  - RA: osteopenia, erosion, joint space narrowing, subchondral cysts, symmetric joint space narrowing
- bloodwork: ANA, RF

Treatment
- non-operative: weight reduction, activity modification, physiotherapy, analgesics, walking aids
- operative: realign = osteotomy; replace = arthroplasty; fuse = arthrodesis
- complications with arthroplasty: component loosening, dislocation, HO, thromboembolism, infection, neurovascular injury, limb length discrepancy
- arthroplasty is standard of care in most patients with hip arthritis

Hip Dislocation after Total Hip Arthroplasty

Etiology
- THA that is unstable when hip is flexed, adducted and internally rotated or extended and externally rotated (avoid flexing hip >90° or crossing legs for approximately 6 wk after surgery)

Epidemiology
- occurs in 1-4% of primary THA and 10-16% of revision THAs
- risk factors: neurological impairment, post-traumatic arthritis, revision surgery, substance abuse

Treatment
- external abduction splint to prevent hip adduction
- constrained acetabular component for recurrent dislocation if no issue with position of acetabular/femoral implants + knee immobilizer

Complications
- sciatic nerve palsy in 25% (10% permanent)
- HO

Femoral Diaphysis Fracture

Mechanism
- high energy trauma (MVC, fall from height, gunshot wound)
- in children, can result from low energy trauma (spiral fracture)

Clinical Features
- shortened, externally rotated leg (if fracture displaced)
- inability to weight-bear
- often open injury, always a Gustilo III (see Table 4)

Investigations
- AP pelvis, AP/lateral hip, femur, knee

Complications
- hemorrhage requiring transfusion
- fat embolism leading to ARDS
- extensive soft tissue damage
- ipsilateral hip dislocation/fracture
- nerve injury

Treatment
- stabilize patient
- immobilize leg
- ORIF with anterograde or retrograde IM nail, external fixator for unstable patients, open fractures, or highly vascular areas, or plate and screws for open growth plates within 24 h
- early mobilization and strengthening
**Distal Femoral Fracture**

**Mechanism**
- direct high energy force or axial loading
- three types (Figure 38) in addition to classification as intra-articular or extra-articular

**Clinical Features**
- extreme pain
- knee effusion (hemarthrosis)
- shortened, externally rotated leg if displaced

**Treatment**
- ORIF if displaced or intra-articular; may choose to manage nonoperatively if nondisplaced or incomplete fracture
- early mobilization and strengthening

**Complications** (see General Fracture Complications, OR6)
- femoral artery tear
- nerve injury
- extensive soft tissue injury
- angulation deformities

---

**Knee**

**Evaluation of Knee**

**Common Complaints**
- general orthopedic history
- also inquire about common knee symptoms
  - locking: mechanical block to extension
    - torn meniscus/loose body in joint
  - pseudo-locking: limited ROM without mechanical block
    - effusion, muscle spasm after injury, arthritis
  - painful clicking (audible)
    - torn meniscus
  - giving way: instability
    - cruciate ligament or meniscal tear, patellar dislocation

**Special Tests of the Knee**
- **anterior and posterior drawer tests** (see Figure 41)
  - demonstrate ACL and PCL, respectively
    - knee flexed at 90°, foot immobilized, hamstrings released
      - if able to sublux tibia anteriorly (anterior drawer test), then ACL may be torn
      - if able to sublux tibia posteriorly (posterior drawer test), then PCL may be torn
    - anterior drawer test for ACL: 3.8 positive likelihood ratio, 0.30 negative likelihood ratio
  - **Lachmann test**
    - demonstrates torn ACL
    - hold knee in 10-20° flexion, stabilizing the femur
    - try to sublux tibia anteriorly on femur
    - similar to anterior drawer test, more reliable due to less muscular stabilization
    - for ACL: 25.0 positive likelihood ratio, 0.1 negative likelihood ratio
  - **Thessaly test**
    - demonstrates meniscal tear
    - patient stands flat footed on one leg while the examiner provides his or her hands for balance. The patient then flexes the knee to 20° and rotates the femur on the tibia medially and laterally three times while maintaining the 20° flexion
    - positive for a meniscal tear if the patient experiences medial or lateral joint line discomfort.
    - for medial meniscus: 29.67 positive likelihood ratio, 0.11 negative likelihood ratio
    - for lateral meniscus: 23.0 positive likelihood ratio, 0.083 negative likelihood ratio
  - **posterior sag sign**
    - demonstrates torn PCL
    - may give a false positive anterior draw sign
    - flex knees and hips to 90°, hold ankles and knees
    - view from the lateral aspect
      - if one tibia sags posteriorly compared to the other, its PCL is torn

6 Degrees of Freedom of the Knee: Flex. and ext., Ext. and int. rotation, Varus and valgus angulation, Ant. and post. glide, Med. and lat. shift, Compression and distraction

On physical exam of the knee, do not forget to evaluate the hip!
• **pivot shift sign**
  - demonstrates torn ACL
  - start with the knee in extension
  - internally rotate foot, slowly flex knee while palpating and applying a valgus force
  - normal knee will flex smoothly
  - if incompetent ACL, tibia will sublux anteriorly on femur at start of maneuver. During flexion, the tibia will reduce and externally rotate about the femur (the “pivot”)
  - reverse pivot shift (start in flexion, externally rotate, apply valgus and extend knee) suggests torn PCL
  - composite assessment for ACL: 25.0 positive likelihood ratio, 0.04 negative likelihood ratio
  - composite assessment for PCL: 21.0 positive likelihood ratio, 0.05 negative likelihood ratio

• **collateral ligament stress test**
  - palpate ligament for “opening” of joint space while testing
  - with knee in full extension, apply valgus force to test MCL, apply varus force to test LCL
  - repeat tests with knee in 20° flexion to relax joint capsule
  - opening only in 20° flexion due to MCL damage only
  - opening in 20° of flexion and full extension is due to MCL, cruciate, and joint capsule damage

• **tests for meniscal tear**
  - joint line tenderness
    - joint line pain when palpated
    - palpate one side at a time and watch patient’s eyes
    - for meniscal tear: 0.9 positive likelihood ratio, 1.1 negative likelihood ratio
  - crouch compression test
    - joint line pain when squatting (anterior pain suggests patellofemoral pathology)
  - McMurray’s test useful collaborative information (see Figure 42)
    - with knee in flexion, palpate joint line for painful “pop/click”
    - internally rotate foot, varus stress, and extend knee to test lateral meniscus
    - externally rotate foot, valgus stress, and extend knee to test medial meniscus
    - for meniscal tear: 1.3 positive likelihood ratio, 0.8 negative likelihood ratio
  - composite assessment for meniscal tears: 2.7 positive likelihood ratio, 0.4 negative likelihood ratio

**X-Rays**
- AP standing, lateral
- skyline: tangential view with knees flexed at 45° to see patellofemoral joint
- 3-foot standing view: useful in evaluating leg length and varus/valgus alignment
- Ottawa Knee Rules (see *Emergency Medicine*, ER17)

### Cruciate Ligament Tears

- ACL tear much more common than PCL tear

**Table 21. Comparison of ACL and PCL Injuries**

<table>
<thead>
<tr>
<th></th>
<th>Anterior Cruciate Ligament</th>
<th>Posterior Cruciate Ligament</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomy</strong></td>
<td>From medial wall of lateral femoral condyle to the anteromedial and posterolateral intercondylar eminence of the tibial plateau</td>
<td>Lateral wall of medial femoral condyle to posterior intercondylar eminence of the tibial plateau</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Sudden deceleration, Hyperextension and internal rotation of tibia on femur (i.e. “plant and turn”)</td>
<td>Sudden posterior displacement of tibia when knee is flexed or hyperextended (e.g. dashboard MVC injury)</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>Audible “pop”, Immediate swelling, Knee “giving way”, Inability to continue activity</td>
<td>Audible “pop”, Immediate swelling, Pain with push off, Cannot descend stairs</td>
</tr>
<tr>
<td><strong>Physical</strong></td>
<td>Effusion (hemarthrosis), Posterolateral joint line tenderness, Positive anterior drawer, Positive Lachmann, Pivot shift</td>
<td>Effusion (hemarthrosis), Anteromedial joint line tenderness, Positive posterior drawer, Reverse pivot shift, Other ligamentous, bony injuries</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Stable knee with minimal functional impairment: immobilization 2-4 wk with early ROM and strengthening</td>
<td>Unstable knee or young person/high-demand lifestyle: ligament reconstruction, Posterior sag</td>
</tr>
</tbody>
</table>

**Figure 41. Anterior and posterior drawer test**

**Figure 42. McMurray test**

**Figure 43. T1 MRI of torn ACL and PCL**
**Collateral Ligament Tears**

**Mechanism**
- valgus force to knee = MCL tear
- varus force to knee = LCL tear

**Clinical Features**
- swelling/effusion
- tenderness above and below joint line medially (MCL) or laterally (LCL)
- joint laxity with varus or valgus force to knee
  - laxity with endpoint suggests partial tear
  - laxity with no endpoint suggests a complete tear
- test for other injuries (e.g. O'Donoghue's unhappy triad), common peroneal nerve injury

**Treatment**
- partial tear: immobilization x 2-4 wk with early ROM and strengthening
- complete tear: immobilization at 30° flexion
- multiple ligamentous injuries: surgical repair of ligaments

**Meniscal Tears**

- medial tear much more common than lateral tear

**Mechanism**
- twisting force on knee when it is partially flexed (e.g. stepping down and turning)
- requires moderate trauma in young person but only mild trauma in elderly due to degeneration

**Clinical Features**
- immediate pain, difficulty weight-bearing, instability and clicking
- increased pain with squatting and/or twisting
- effusion (hemarthrosis) with insidious onset (24-48 h after injury)
- joint line tenderness medially or laterally
- locking of knee (if portion of meniscus mechanically obstructing extension)

**Investigations**
- MRI, arthroscopy

**Treatment**
- if not locked: ROM and strengthening (NSAIDs)
- if locked or failed above: arthroscopic repair/partial meniscectomy

**Quadriceps/Patellar Tendon Rupture**

**Mechanism**
- sudden forceful contraction of quadriceps during an attempt to stop
- more common in obese patients and those with pre-existing degenerative changes in tendon
  - DM, SLE, RA, steroid use, renal failure on dialysis

**Clinical Features**
- inability to extend knee or weight-bear
- possible audible "pop"
- patella in lower or higher position with palpable gap above or below patella respectively
- may have an effusion

**Investigations**
- ask patient to straight leg raise
- knee x-ray to rule out patellar fracture
- lateral view: patella alta with patellar tendon rupture, patella baja (infera) with quadriceps tendon rupture

**Treatment**
- nonoperative treatment for incomplete tears with preserved extension of knee
- surgical repair of tendon indicated for complete ruptures
- early surgical repair: better outcomes compared with delayed repair (>6 wk post injury)
- delayed repair complicated by quadriceps contracture, patella migration, and adhesions

**Tissue Sources for ACL Reconstruction**
- Hamstring
- Middle 1/3 patellar tendon (bone-patellar-bone)
- Allograft (e.g. cadaver)
Dislocated Knee

Mechanism
- high energy trauma
- by definition, caused by tears of multiple ligaments

Clinical Features
- classified by relation of tibia with respect to femur
  - anterior, posterior, lateral, medial, rotary
- knee instability
- effusion
- pain
- ischemic limb

Investigations
- x-rays: AP, lateral, skyline
  - associated radiographic findings include tibial plateau fracture dislocations, proximal fibular fractures, and avulsion of fibular head
- ankle brachial index (abnormal if <0.9)
- arteriogram if abnormal vascular exam (such as abnormal pedal pulses)

Treatment
- urgent closed reduction
  - complicated by interposed soft tissue
- assessment of peroneal nerve, tibial artery, and ligamentous injuries
- repair of associated injuries; also may need decompressive fasciotomy especially if vascular repair undertaken
- knee immobilization x 6-8 wk

Specific Complications
- high incidence of associated injuries
  - popliteal artery tear
  - peroneal nerve injury
  - capsular tear
- chronic: instability, stiffness, post-traumatic arthritis

Patella

Patellar Fracture

Mechanism
- direct blow to the patella: fall, MVC (dashboard)
- indirect trauma by sudden flexion of knee against contracted quadriceps

Clinical Features
- marked tenderness
- inability to extend knee or straight leg raise
- proximal displacement of patella
- patellar deformity
- ± effusion/hemarthrosis

Investigations
- x-rays: AP, lateral, skyline
  - consider bipartite patella: congenitally unfused ossification centres with smooth margins on x-ray

Treatment
- goal: restore extensor mechanism with maximal articular congruency
  - non-displaced (step-off <2-3 mm and fracture gap <1-4 mm)
    - straight leg immobilization 1-4 wk with hinged knee brace
    - physiotherapy: quadriceps strengthening when pain has subsided
- displaced: ORIF (>2 mm)
- comminuted: ORIF; may require partial/complete patellectomy
- disrupted extensor mechanism: ORIF

Complications
- Symptomatic wiring
- Hardware failure
- Knee stiffness
- Nonunion
- Infection
Patellar Dislocation

Mechanism
- lateral displacement of patella after contraction of quadriceps against a flexed knee

Risk Factors
- young, female
- obesity
- high-riding patella (patella alta)
- knock-knees (genu valgus)
- Q-angle (quadriceps angle) ≥20° (see Figure 45)
- shallow intercondylar groove
- weak vastus medialis
- tight lateral retinaculum

Clinical Features
- knee catches or gives way with walking
- severe pain, tenderness anteromedially from rupture of capsule
- weak knee extension or inability to extend leg unless patella reduced
- +ve patellar apprehension test
- patient apprehensive when examiner laterally displaces patella
- often recurrent, self-reducing
- concomitant MCL injury

Investigations
- x-rays: AP, lateral, skyline view of patella
- check for fracture of medial patella and lateral femoral condyle

Treatment
- non-operative first
  - knee immobilization x 4-6 wk
  - progressive weight bearing and isometric quadriceps strengthening
  - if recurrent
  - surgical tightening of medial capsule and release of lateral retinaculum, possible tibial tuberosity transfer, or proximal tibial osteotomy

Patellofemoral Syndrome (Chondromalacia Patellae)

Mechanism
- softening, erosion and fragmentation of articular cartilage, predominantly medial aspect of patella
- commonly seen in active young females

Predisposing Factors
- malalignment causing patellar maltracking (Q angle ≥20°, genu valgus)
- post-trauma
- deformity of patella or femoral groove
- recurrent patellar dislocation, ligamentous laxity
- excessive knee strain (athletes)

Clinical Features
- deep, aching anterior knee pain
  - exacerbated by prolonged sitting (theatre sign), strenuous athletic activities, stair climbing, squatting
  - sensation of instability, pseudolocking
  - pain with extension against resistance through terminal 30-40°
  - swelling rare, minimal if present

Investigations
- x-rays: AP, lateral, skyline

Treatment
- non-operative
  - continue non-impact activities
  - NSAIDs
  - physiotherapy: quadriceps strengthening
  - surgical with refractory patients
    - tibial tubercle elevation
    - arthroscopic shaving/debridement
    - lateral release of retinaculum

Patellar Open Reduction and Internal Fixation
- Longitudinal midline excision over patella
- Tension-band wiring fixation
- Preserve patellar bone
- Antibiotic, debridement, early fixation in open fracture
Tibia Plateau Fracture

Mechanism
- axial loading (e.g. fall from height)
- femoral condyles driven into proximal tibia
- can result from minor trauma in osteoporotics

Clinical Features
- lateral fractures more common than medial
- medial fractures require higher energy – often have concomitant vascular injuries
- knee effusion
- inability to bear weight
- swelling

Classification
- Schatzker classification (see sidebar)

Investigations
- x-rays: AP, lateral
- CT: pre-operative planning

Treatment

<table>
<thead>
<tr>
<th>Approach #1 (based on amount of depression seen on x-ray)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>If depression on x-ray is &lt;3 mm:</td>
<td>Straight leg immobilization x 4-6 wk with progressive ROM weight bearing</td>
</tr>
<tr>
<td>If depression is &gt;3 mm:</td>
<td>ORIF often requiring bone grafting to elevate depressed fragment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Approach #2 (based on varus/valgus instability)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>If minimal varus/valgus instability (&lt;15°)</td>
<td>Straight leg immobilization x 4-6 wk with progressive ROM weight bearing</td>
</tr>
<tr>
<td>If significant varus/valgus instability (&gt;15°)</td>
<td>ORIF often requiring bone grafting to elevate depressed fragment</td>
</tr>
</tbody>
</table>

Specific Complications (see General Fracture Complications, OR6)
- ligamentous injuries
- meniscal lesions
- AVN
- infection
- osteoarthritis

Schatzker Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of lateral plateau split fracture</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of lateral plateau: split depression fracture</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lateral plateau: pure depression fracture</td>
</tr>
<tr>
<td>IV</td>
<td>Medial plateau fracture</td>
</tr>
<tr>
<td>V</td>
<td>Bicondylar plateau fracture</td>
</tr>
<tr>
<td>VI</td>
<td>Bicondylar with metaphyseal/diaphyseal involvement</td>
</tr>
</tbody>
</table>

Tibial Shaft Fracture

Mechanism
- numerous, including MVC, falls, sporting injuries

Clinical Features
- open vs. closed
- amount of displacement
- neurovascular status
- most commonly fractured long bone
- most common open fracture

Investigations
- x-rays: AP, lateral, skyline

Treatment
- closed
  - minimally displaced: straight leg cast x 4-6 wk with early weight bearing
  - displaced: ORIF with reamed IM nail, plate and screws, or external fixator
- open
  - external fixation or IM nail
  - vascularized coverage of soft tissue defects (often heal poorly)

Specific Complications (see General Fracture Complications, OR6)
- high incidence of neurovascular injury and compartment syndrome
- poor soft tissue coverage

Figure 46. Tibial shaft fracture treated with intramedullary nail and screws
Ankle

Evaluation of Ankle and Foot Complaints

Special Tests
- anterior drawer: examiner attempts to displace the foot anteriorly against a fixed tibia
- talar tilt: foot is stressed in inversion and angle of talar rotation is evaluated by x-ray

X-Ray
- AP, lateral
- mortise view: ankle at 15° of internal rotation
  - gives true view of ankle joint
- joint space should be symmetric with no talar tilt
- Ottawa Ankle Rules should guide use of x-ray (see sidebar); nearly 100% sensitivity
- ± CT to better characterize fractures

Ankle Fracture

Mechanism
- pattern of fracture depends on the position of the ankle when trauma occurs
- generally involves
  - ipsilateral ligamentous tears or transverse bony avulsion
  - contralateral shear fractures (oblique or spiral)
- classification systems
  - Danis-Weber (see below)
  - Lauge-Hansen: based on foot's position and motion relative to leg

Danis-Weber Classification (Figure 47)
- based on level of fibular fracture relative to syndesmosis
- Type A (infra-syndesmotic)
  - pure inversion injury
  - avulsion of lateral malleolus below plafond or torn calcaneofibular ligament
  - ± shear fracture of medial malleolus
- Type B (trans-syndesmotic)
  - external rotation and eversion (most common)
  - ± avulsion of medial malleolus or rupture of deltoid ligament
  - spiral fracture of lateral malleolus starting at plafond
- Type C (supra-syndesmotic)
  - pure external rotation
  - avulsion of medial malleolus or torn deltoid ligament
  - ± posterior malleolus avulsion with posterior fibio-fibular ligament
  - fibular fracture is above plafond (called Maisonneuve fracture if at proximal fibula)
  - frequently tears syndesmosis

Treatment
- undisplaced: non-weight bearing below knee cast
- indications for ORIF
  - any fracture-dislocation: restore vascularity, minimize articular injury, reduce pain and skin pressure
  - most of type B, and all of type C
  - trimalleolar (medial, posterior, lateral) fractures
  - talar tilt >10°
  - medial clear space on x-ray greater than superior clear space
  - open fracture/open joint injury
- high incidence of post-traumatic arthritis
- wrinkle test: skin shows wrinkles, to determine if soft tissue swelling has resolved to an extent to reduce complications

Ligamentous Injuries
- see Figure 48 for ankle ligaments

Medial Ligament Complex (deltoid ligament)
- eversion injury
- usually avulses medial or posterior malleolus and strains syndesmosis
Lateral Ligament Complex (Anterior Talofibular, Calcaneofibular, Posterior Talofibular)

- inversion injury
- ATF most commonly and severely injured if ankle is plantar flexed
- swelling and tenderness anterior to lateral malleolus
- ++ ecchymoses
- ++ ankle anterior drawer
- may have significant medial talar tilt on inversion stress x-ray

Treatment
- microscopic tear (Grade I)
  - rest, ice, compression, elevation (RICE)
- macroscopic tear (Grade II)
  - strap ankle in dorsiflexion and eversion x 4-6 wk
  - physiotherapy: strengthening and proprioceptive retraining
- complete tear (Grade III)
  - below knee walking cast x 4-6 wk
  - physiotherapy: strengthening and proprioceptive retraining
  - surgical intervention may be required if chronic symptomatic instability develops

Foot

Talar Fracture

Mechanism
- axial loading or hyperdorsiflexion (MVC, fall from height)
- 60% of talus covered by articular cartilage
- tenuous blood supply runs distal to proximal along talar neck
  - high risk of AVN with displaced fractures

Investigations
- x-rays: AP, lateral
- CT to better characterize fracture
- MRI can clearly define extent of AVN

Treatment
- undisplaced: non-weight bearing below knee cast x 20-24 wk
- displaced: ORIF (high rate of nonunion, AVN)

Calcaneal Fracture

Mechanism
- axial loading: fall from height onto heels
- 10% of fractures associated with compression fractures of thoracic or lumbar spine
- 5% are bilateral

Physical Examination
- swelling, bruising on heel/sole
- wider, shortened, flatter heel when viewed from behind
- varus heel

Investigations
- x-rays: AP, lateral, oblique (Broden’s view)
- loss of Bohler’s angle
- CT: assess intra-articular extension

Treatment
- closed vs. open reduction is controversial
- non-weight bearing cast x 3 mo with early ROM and strengthening

Achilles Tendonitis

Mechanism
- chronic inflammation from activity or poor-fitting footwear
- may also develop heel bumps (retrocalcaneobursitis)
Physical Examination
• pain, stiffness and crepitus with ROM
• thickened tendon, palpable bump

Treatment
• rest, NSAIDs
• gentle stretching, deep tissue calf massage
• orthotics, open back shoes
• shockwave therapy in chronic tendonitis
• DO NOT inject steroids (risk of tendon rupture)

Achilles Tendon Rupture

Mechanism
• loading activity, stop-and-go sports (e.g. squash, tennis, basketball)
• secondary to chronic tendonitis, steroid injection

Clinical Features
• audible pop, sudden pain with push off movement
• sensation of being kicked in heel when trying to plantar flex
• palpable gap
• apprehensive toe off when walking
• weak plantar flexion strength
• Thompson test: with patient prone, squeezing the calf muscles should passively plantar flex the foot to demonstrate intact Achilles tendon
  • +ve test = no passive plantar flexion = ruptured tendon

Treatment
• low demand or elderly: cast foot in plantar flexion (to relax tendon) x 8-12 wk
• high demand: surgical repair, then cast as above x 6-8 wk

Plantar Fasciitis (Heel Spur Syndrome)

Mechanism
• repetitive strain injury causing microtears and inflammation of plantar fascia
• female: male = 2:1
• common in athletes (especially runners)
• also associated with obesity, DM, seronegative and seropositive arthritis

Clinical Features
• morning pain and stiffness
• intense pain when walking from rest that subsides as patient continues to walk
• swelling, tenderness over sole
• greatest at medial calcaneal tubercle and 1-2 cm distal along plantar fascia
• pain with toe dorsiflexion (stretches fascia)

Investigations
• plain radiographs to rule out fractures
• often see bony exostoses (heel spurs) at insertion of fascia into medial calcaneal tubercle
  (see Figure 49)
• spur is secondary to inflammation, not the cause of pain

Treatment
• rest, ice, NSAIDs, steroid injection
• physiotherapy: stretching, ultrasound, extracorporeal shockwave therapy
• orthotics with heel cup
  • to counteract pronation and disperse heel strike forces
• endoscopic surgical release of fascia in refractory cases
• spur removal is not required

Bunions (Hallux Valgus)

Mechanism
• valgus alignment on 1st MTP (hallux valgus) causes eccentric pull of extensor and intrinsic muscles
• reactive exostosis forms with thickening of the skin creating a bunion
• most often associated with poor-fitting footwear but can be hereditary
• 10x more frequent in women
Clinical Features
- painful bursa over medial eminence of 1st metatarsal head
- pronation (rotation inward) of great toe
- numbness over medial aspect of great toe

Investigations
- x-ray: standing AP/lateral/sesamoid view, non-weight bearing oblique

Treatment
- indications: painful corn or bunion, overriding 2nd toe
- non-operative first
  - properly fitted shoes (low heel) and toe spacer
- surgical: goal is to restore normal anatomy
  - osteotomy with realignment of 1st MTP joint (Chevron Procedure)
  - arthrodesis

Metatarsal Fracture
- as with the hand, 1st, 4th, 5th MT are relatively mobile, while the 2nd and 3rd are fixed (Table 22)
- use Ottawa Foot Rules to determine need for x-ray (see sidebar)

Table 22. Types of Metatarsal Fractures

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Mechanism</th>
<th>Clinical</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avulsion of base of 5th MT</td>
<td>Sudden inversion followed by contraction of peroneus brevis</td>
<td>Tender base of 5th MT</td>
<td>Requires ORIF if displaced</td>
</tr>
<tr>
<td>Midshaft 5th MT (Jones fracture)</td>
<td>Stress injury</td>
<td>Painful shaft of 5th MT</td>
<td>*NWB BK cast x 6 wk ORIF if athlete</td>
</tr>
<tr>
<td>Shaft 2nd, 3rd MT (March fracture)</td>
<td>Stress injury</td>
<td>Painful shaft of 2nd or 3rd MT</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>1st MT</td>
<td>Trauma</td>
<td>Painful 1st MT</td>
<td>ORIF if displaced otherwise NWB BK cast x 3 wk then walking cast x 2 wk</td>
</tr>
<tr>
<td>Tarso-MT fracture – dislocation</td>
<td>Fall onto plantar flexed foot or direct crush injury</td>
<td>Shortened forefoot prominent base</td>
<td>ORIF</td>
</tr>
</tbody>
</table>

*NWB BK = Non weight bearing, below knee

Pediatric Orthopedics

Fractures in Children
- type of fracture
  - thicker, more active periosteum results in pediatric specific fractures: greenstick, torus (buckle) and plastic (bowing)
  - adults fracture through both cortices
  - epiphyseal growth plate
    - weaker part of bone, susceptible to fractures
    - plate often mistaken for fracture on x-ray and vice versa (x-ray opposite limb for comparison), especially in elbow (see sidebar)
    - tensile strength of bone < ligaments in children, therefore clinician must be confident that fracture and/or growth plate injury have been ruled out before diagnosing a sprain
    - intra-articular fractures have worse consequences in children because they usually involve the growth plate
  - anatomic reduction
    - gold standard with adults
    - may cause limb length discrepancy in children (overgrowth)
    - accept greater angular deformity in children (remodeling minimizes deformity)
  - time to heal
    - shorter in children
- always be aware of the possibility of child abuse
  - make sure stated mechanism compatible with injury
  - high index of suspicion with fractures in non-ambulating children (<1 yr); look for other signs, including x-ray evidence of healing fractures at different sites and different stages of healing
**Stress Fractures**

**Mechanism**
- insufficiency fracture
  - stress applied to a weak or structurally deficient bone
- fatigue fracture
  - repetitive, excessive force applied to normal bone
- most common in adolescent athletes
- tibia is most common site

**Diagnosis and Treatment**
- localized pain and tenderness over the involved bone
- plain films may not show fracture for 2 wk
- bone scan +ve in 12-15 d
- treatment is rest from strenuous activities to allow remodeling (can take several months)

**Evaluation of the Limping Child**
- see Pediatrics, P96

**Epiphyseal Injury**

*Table 23. Salter-Harris Classification of Epiphyseal Injury*

<table>
<thead>
<tr>
<th>SALT(E)R–Harris Type</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Straight through; Stable)</td>
<td>Transverse through growth plate</td>
<td>Closed reduction and cast immobilization (except SCFE – ORIF); heals well, 95% do not affect growth</td>
</tr>
<tr>
<td>II (Above)</td>
<td>Through metaphysis and along growth plate</td>
<td>Closed reduction and cast if anatomic; otherwise ORIF</td>
</tr>
<tr>
<td>III (Low)*</td>
<td>Through epiphysis to plate and along growth plate</td>
<td>Anatomic reduction by ORIF to prevent growth arrest, avoid fixation across growth plate</td>
</tr>
<tr>
<td>IV (Through and through)*</td>
<td>Through epiphysis and metaphysis</td>
<td>Closed reduction and cast if anatomic; otherwise ORIF</td>
</tr>
<tr>
<td>V (Ram)*</td>
<td>Crush injury of growth plate</td>
<td>High incidence of growth arrest; no specific treatment</td>
</tr>
</tbody>
</table>

* Types III – IV are more likely to cause growth arrest and progressive deformity

**Slipped Capital Femoral Epiphysis (SCFE)**

- type I Salter-Harris epiphyseal injury at proximal hip
- most common adolescent hip disorder, peak incidence at pubertal growth spurt
- risk factors: male, obese, hypothyroid

**Etiology**
- multifactorial
  - genetic: autosomal dominant, blacks > caucasians
  - cartilaginous physis thickens rapidly under growth hormone effects
  - sex hormone secretion, which stabilizes physis, has not yet begun
  - overweight: mechanical stress
  - trauma: causes acute slip

**Clinical Features**
- acute: sudden, severe pain with limp
- chronic: limp with medial knee or anterior thigh pain
- +ve Trendelenburg sign on affected side, due to weakened gluteal muscles
- tender over joint capsule
- restricted internal rotation, abduction, flexion
- Whitman’s sign: with flexion there is an obligate external rotation of the hip
- pain at extremes of ROM

**Investigations**
- x-rays: AP, frog-leg, lateral radiographs
  - posterior and medial slip
  - disruption of Klein’s line (see sidebar)
  - AP view may be normal or show slightly widened growth plate compared with opposite side

**Ossification Centres of the Elbow**

<table>
<thead>
<tr>
<th>Centres</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capitellum</td>
<td>1 yr</td>
</tr>
<tr>
<td>Radial head</td>
<td>4 yr</td>
</tr>
<tr>
<td>Internal (medial) epicondyle</td>
<td>6 yr</td>
</tr>
<tr>
<td>Trochlea</td>
<td>8 yr</td>
</tr>
<tr>
<td>Olecranon</td>
<td>10 yr</td>
</tr>
<tr>
<td>External (lateral) epicondyle</td>
<td>12 yr (± 1 yr)</td>
</tr>
</tbody>
</table>

**Figure 52. Salter-Harris classification**

- SCFE – Klein’s Line
  - On AP view, line drawn along suprolateral border of femoral neck should cross at least a portion of the femoral epiphysis. If it doesn’t, suspect SCFE.
Treatment and Complications
• mild/moderate slip: stabilize physis with pins in current position
• severe slip: ORIF or pin physis without reduction and osteotomy after epiphyseal fusion
• complications: AVN (most common), chondrolysis (loss of articular cartilage, resulting in narrowing of joint space), pin penetration, premature OA, loss of ROM

Developmental Dysplasia of the Hip
• formerly called congenital dysplasia of the hip
• due to ligamentous laxity, muscular underdevelopment, and abnormal shallow slope of acetabular roof
• spectrum of conditions that lead to hip subluxation and dislocation
  • dislocated femoral head completely out of acetabulum
  • dislocatable head in socket
  • head subluxates out of joint when provoked
  • dysplastic acetabulum, more shallow and more vertical than normal
• painless (if painful suspect septic dislocation)

Physical Examination
• diagnosis is clinical
  • limited abduction of the flexed hip (<50-60°)
  • affected leg shortening results in asymmetry in skin folds and gluteal muscles, wide perineum
  • Barlow's test (for dislocatable hip)
    • flex hips and knees to 90° and grasp thigh
    • fully adduct hips, push posteriorly to try to dislocate hips
  • Ortolani's test (for dislocated hip)
    • initial position as above but try to reduce hip with fingertips during abduction
    • positive test: palpable clunk is felt (not heard) if hip is reduced
  • Galeazzi's sign
    • knees at unequal heights when hips and knees flexed
    • dislocated hip on side of lower knee
    • difficult test if child <1 yr
  • Trendelenburg test and gait useful if older (>2 yr)

Investigations
• U/S in first few months to view cartilage (bone is not calcified in newborns)
• follow up radiograph after 3 mo
• x-ray signs: false acetabulum, acetabular index >30°, broken Shenton's line, femoral neck above Hilgenreiner's line, ossification centre outside of inner lower quadrant (quadrants formed by intersection of Hilgenreiner's and Perkin's line)

Treatment and Complications
• 0-6 mo: reduce hip using Pavlik harness to maintain abduction and flexion
• 6-18 mo: reduction under GA, hip spica cast x 2-3 mo (if Pavlik harness fails)
• >18 mo: open reduction; pelvic and/or femoral osteotomy
• complications
  • redislocation, inadequate reduction, stiffness
• AVN of femoral head

Legg-Calvé-Perthes Disease (Coxa Plana)
• self-limited AVN of femoral head, presents at 4-10 yr of age
• etiology unknown, 20% bilateral, males > females, 1/10,000
• associations
  • family history
  • low birth weight
  • abnormal pregnancy/delivery
  • history of trauma to affected hip
• key features
  • AVN of proximal femoral epiphysis, abnormal growth of the physis, and eventual remodelling of regenerated bone

Clinical Features
• child with hip pain and limp
• tender over anterior thigh
• flexion contracture: decreased internal rotation and abduction of hip
Investigations
- x-rays
  - may be negative early (if high index of suspicion, move to bone scan or MRI)
  - eventually, characteristic collapse of femoral head (diagnostic)

Treatment
- goal is to preserve ROM and preserve femoral head in acetabulum
- physiotherapy: ROM exercises
- brace in flexion and abduction x 2-3 yr
- femoral or pelvic osteotomy
  - prognosis better in males, <5 yr old, <50% of femoral head involved, abduction >30°
  - 50% of involved hips do well with non-operative treatment
  - complicated by early onset osteoarthritis and decreased ROM

**Osgood-Schlatter Disease**

Mechanism
- repetitive tensile stress on insertion of patellar tendon over the tibial tuberosity causes minor avulsion at the site and subsequent inflammatory reaction (tibial tubercle apophysitis)

Clinical Features
- tender lump over tibial tuberosity
- pain on resisted leg extension
- anterior knee pain exacerbated by jumping or kneeling, relieved by rest

Investigations
- x-rays: fragmentation of the tibial tubercle, ± ossicles in patellar tendon

Treatment
- benign, self-limited condition
- may restrict activities such as basketball or cycling
- flexibility, isometric strengthening exercises

**Congenital Talipes Equinovarus (Club Foot)**

- etiology: intrinsic causes (neurologic, muscular, or connective tissue diseases) vs. extrinsic (intrauterine growth restriction), may be idiopathic, neurogenic, or syndrome-associated
- fixed deformity
- 3 parts to deformity
  - talipes: talus is inverted and internally rotated
  - equinus: ankle is plantar flexed
  - varus: heel and forefoot are in varus (supinated)
- 1-2/1,000 newborns, 50% bilateral, occurrence M>F, severity F>M

Physical Examination
- examine hips for associated DDH
- examine knees for deformity
- examine back for dysraphism (unfused vertebral bodies)

Treatment
- correct deformities in the following order (Ponseti Technique):
  - forefoot adduction, ankle inversion, equinus
    - change strapping/cast q1-2wk
  - surgical release in refractory case (rare)
    - delayed until 3-4 mo of age
- 3 yr recurrence rate = 5-10%
- mild recurrence common; affected foot is permanently smaller/stiffer than normal foot with calf muscle atrophy

**Scoliosis**

Definition
- lateral curvature of spine with vertebral rotation

Epidemiology
- age: 10-14 yr
- more frequent and more severe in females
Etiology
• idiopathic: most common (90%)
• congenital: vertebrae fail to form or segment
• neuromuscular: UMN or LMN lesion, myopathy
• postural: leg length discrepancy, muscle spasm
• other: osteochondrodystrophies, neoplastic, traumatic

Clinical Features
• ± back pain
• 1º curve where several vertebrae affected
• 2º curves above and below fixed 1º curve to try and maintain normal position of head and pelvis
• asymmetric shoulder height when bent forward
• Adam's test: rib hump when bent forward
• prominent scapulae, creased flank, asymmetric pelvis
• associated posterior midline skin lesions in neuromuscular scolioses
  • café-au-lait spots, dimples, neurofibromas
  • axillary freckling, hemangiomas, hair patches
• associated pes cavus or leg atrophy
• apparent leg length discrepancy

X-Rays
• 3-foot standing, AP, lateral
  • measure curvature: Cobb angle (Figure 55)
  • may have associated kyphosis

Treatment
• based on Cobb angle
  • <20°: observe for changes
  • >20° or progressive: bracing (many types) that halt/slow curve progression but do NOT reverse deformity
  • >40°, cosmetically unacceptable or respiratory problems: surgical correction (spinal fusion)

Bone Tumours
• primary bone tumours are rare after 3rd decade
• metastases to bone are relatively common after 3rd decade

Table 24. Distinguishing Benign from Malignant Bone Lesions on X-ray

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>No periosteal reaction</td>
<td>Acute periosteal reaction</td>
</tr>
<tr>
<td>Thick endosteal reaction</td>
<td>Codman’s triangle</td>
</tr>
<tr>
<td>Well developed bone formation</td>
<td>“Onion skin”</td>
</tr>
<tr>
<td>Intraosseous and even calcification</td>
<td>“Sunburst”</td>
</tr>
<tr>
<td></td>
<td>Broad border between lesion and normal bone</td>
</tr>
<tr>
<td></td>
<td>Varied bone formation</td>
</tr>
<tr>
<td></td>
<td>Extraosseous and irregular calcification</td>
</tr>
</tbody>
</table>

Adapted from: Bucholtz RW and Heckman JD. Rockwood and Green’s Fractures in Adults. Volume 1. Philadelphia: Lippincott Williams & Wilkins, 2001, 558

Diagnosis
• pain, swelling, tenderness, rarely regional adenopathy
• routine x-ray findings
  • location (which bone, diaphysis, metaphysis, epiphysis)
  • size
  • lytic/lucent vs. sclerotic
  • involvement (cortex, medulla, soft tissue)
  • matrix (radiolucent, radiodense or calcified)
  • periosteal reaction
  • margin (geographic vs. permeative)
  • any pathological fracture
  • soft tissue swelling
• malignancy is suggested by rapid growth, warmth, tenderness, lack of sharp definition
• staging should include
  • bloodwork including liver enzymes
  • CT chest
  • bone scan
  • bone biopsy
    • should be referred to specialized centre prior to biopsy
    • classified into benign, benign aggressive, and malignant
  • MRI of affected bone

Red Flags
• Persistent skeletal pain
• Localized tenderness
• Spontaneous fracture
• Enlarging mass/soft tissue swelling

Figure 55. Cobb angle — used to monitor the progression of the scoliotic curve

In structural or fixed scoliosis, bending forwards makes the curve more obvious.

Postural scoliosis can be corrected by correcting the underlying problem.

Figure 56. Codman’s triangle — a radiographic finding in malignancy, where the partially ossified periosteum is lifted off the cortex by neoplastic tissue
### Benign Active Bone Tumours

#### BONE-FORMING TUMOURS

**Osteoid Osteoma**
- peak incidence in 2nd and 3rd decades, M:F = 3:1 (young males)
- tibia and femur most common locations
- not known to metastasize
- radiographic findings: small, round radiolucent nidus (<1 cm) surrounded by dense sclerotic bone (“bull’s-eye”)
- symptoms: produces severe intermittent pain, mostly at night (diurnal prostaglandin production), characteristically relieved by NSAIDs
- treatment: NSAIDs for night pain; surgical resection of nidus

**FIBROUS LESIONS**

**Fibrous Cortical Defect**
- occur in as many as 35% of children, peak incidence between 2-20 yr old, higher prevalence in males
- femur and proximal tibia most common locations, 50% of patients have multiple defects usually bilateral, symmetrical
- radiographic findings: circular/oval, eccentric radiolucency near physis; thin smooth/lobulated well-defined sclerotic margin
- treatment: resolves spontaneously

**Osteochondroma**
- 2nd and 3rd decades, M:F = 1.8:1
- most common of all benign bone tumours ~ 45%
- metaphysis of long bone (usually distal femur, proximal tibia or proximal humerus)
  - radiographic findings: cartilage-capped bony spur on surface of bone (“mushroom” on x-ray)
  - may be multiple (hereditary, autosomal dominant form) – higher risk of malignant change
- generally very slow growing and asymptomatic unless impinging on neurovascular structure
  - growth usually ceases when skeletal maturity is reached
- malignant degeneration occurs in 1-2% (becomes painful or rapidly grows)

**Enchondroma** (Figure 57)
- 2nd and 3rd decades
- 50% occur in the small tubular bones of the hand and foot; others in femur, humerus, ribs
- benign cartilagenous growth, develops in medullary cavity
  - single/multiple enlarged rarefied areas in tubular bones
  - lytic lesion with sharp margination and central calcification
- malignant degeneration to chondrosarcoma occurs in 1-2% (pain in absence of pathologic fracture is an important clue)
- not known to metastasize

**CYSTIC LESIONS**

**Unicameral/Solitary Bone Cyst**
- most common cystic lesion
- children and young adults, peak incidence during first 2 decades, M:F = 2:1
- proximal humerus and femur most common
- symptoms: asymptomatic, or local pain; complete pathological fracture (50% presentations) or incidental detection
- radiographic findings: lytic translucent area on metaphyseal side of growth plate, cortex thinned/expanded; well defined lesion
- treatment: aspiration followed by steroid injection; curettage ± bone graft indicated if re-fracture likely

#### Benign Aggressive Bone Tumours

**Giant Cell Tumours/Aneurysmal Bone Cyst/Osteoblastoma** (Figure 58)
- affects patients of skeletal maturity, peak 3rd decade
- osteoblastoma: found in the distal femur, proximal tibia, distal radius, sacrum, tarsal bones, spinae
- giant cell tumour: pulmonary metastases in 3%
- aneurysmal bone cysts: either solid with fibrous/granular tissue, or blood-filled
• **radiographic findings:**
  - giant cell tumour: eccentric lytic lesions, in epiphyses adjacent to subchondral bone; may break through cortex; T2 MRI enhances fluid within lesion (hyper-intense signal)
  - aneurysmal bone cyst: expanded with honeycomb shape
  - osteoblastoma: often nonspecific; calcified central nidus with radiolucent halo and sclerosis
• **symptoms:** local tenderness and swelling, pain may be progressive (giant cell tumours), ± symptoms of nerve root compression (osteoblastoma)
• 15% recur within 2 yr of surgery

**Treatment**
• intralesional curettage + bone graft or cement
• wide local excision of expendable bones

### Malignant Bone Tumours

<table>
<thead>
<tr>
<th>Age</th>
<th>Tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>1-10</td>
<td>Ewing’s of tubular bones</td>
</tr>
<tr>
<td>10-30</td>
<td>Osteosarcoma, Ewing’s of flat bones</td>
</tr>
<tr>
<td>30-40</td>
<td>Reticulum cell sarcoma, fibrosarcoma, periosteal osteosarcoma, malignant giant cell tumour, lymphoma</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Metastatic carcinoma, multiple myeloma, chondrosarcoma</td>
</tr>
</tbody>
</table>

**Osteosarcoma (Figure 59)**
- most frequently diagnosed in 2nd decade of life (60%), 2nd most common primary malignancy in adults
- history of Paget’s disease, previous radiation treatment
- predilection for sites of rapid growth: distal femur (45%), proximal tibia (20%), and proximal humerus (15%)
  - invasive, variable histology; frequent metastases without treatment (lung most common)
- painful symptoms: progressive pain, night pain, poorly defined swelling, decreased ROM
- radiographic findings:
  - characteristic periosteal reaction: Codman’s triangle (Figure 56) or “sunburst” spicule formation (tumour extension into periosteum)
  - destructive lesion in metaphysis may cross epiphyseal plate
- management: complete resection (limb salvage, rarely amputation), neo-adjuvant chemo; bone scan – rule out skeletal metastases, CT chest – rule out pulmonary metastases
- prognosis: 70% (high-grade); 90% (low-grade)

**Chondrosarcoma (Figure 60)**
- primary (2/3 cases)
  - previous normal bone, patient over 40; expands into cortex to give pain, pathological fracture, flecks of calcification
- secondary (1/3 cases)
  - malignant degeneration of pre-existing cartilage tumour such as enchondroma or osteochondroma
  - younger age group and better prognosis than primary chondrosarcoma
- symptoms: progressive pain, uncommonly palpable mass
- radiographic findings: in medullary cavity, irregular “popcorn” calcification
- treatment: unresponsive to chemotherapy, treat with aggressive surgical resection + reconstruction; regular follow-up x-rays of resection site and chest
- prognosis: 10-yr survival 90% low-grade, 20-40% high-grade

**Ewing’s Sarcoma**
- most occur between 5-20 yr old
- florid periosteal reaction in metaphyses of long bone with diaphyseal extension
- metastases frequent without treatment
- signs/symptoms: presents with pain, mild fever, erythema and swelling, anemia, increased WBC, ESR, LDH
- radiographic findings: moth-eaten appearance with periosteal lamellated pattern (“onion-skinning”)
- treatment: resection, chemotherapy, radiation
- prognosis – 70%, worst prognostic factor is distant metastases

**Multiple Myeloma**
- most common primary malignant tumour of bone in adults (~43%)
- 90% occur in people >40 yr old, M:F = 2:1
- signs/symptoms: bone pain (cardinal early symptom), compression/pathological fractures, renal failure, nephritis, high incidence of infections (e.g. pyelonephritis/pneumonia), systemic (weakness, weight loss, anorexia)
- labs: anemia, thrombocytopenia, increased ESR, hypercalcemia
• radiographic findings: multiple, “punched-out” well-demarcated lesions, no surrounding sclerosis, marked bone expansion
• diagnosis:
  ▪ serum/urine immunoelectrophoresis (monoclonal gammopathy)
  ▪ CT-guided biopsy of lytic lesions at multiple bony sites
• treatment: chemotherapy, radiation, surgery for symptomatic lesions or impending fractures – debulking, internal fixation
• prognosis: most 3 yr after diagnosis
  see Hematology, H47

Bone Metastases
• 2/3 from breast or prostate; also consider thyroid, lung, kidney
• usually osteolytic; prostate occasionally osteoblastic
• bone scan for MSK involvement, MRI for spinal involvement may be helpful
• stabilization of impending fractures
  ▪ internal fixation, IM rods
  ▪ bone cement

Table 26. Mirel’s Criteria for Impending Fracture Risk and Prophylactic Internal Fixation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number Assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Mild</td>
</tr>
<tr>
<td>Lesion</td>
<td>Blastic</td>
</tr>
<tr>
<td>Size</td>
<td>&lt;1/3 bone diameter</td>
</tr>
</tbody>
</table>

Table 27. Common Medications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>cefazolin (Ancef®)</td>
<td>1-2 g IV q8h</td>
<td>Prophylactically before orthopedic surgery</td>
<td>First generation cephalosporin; do not use with penicillin allergy</td>
</tr>
<tr>
<td>heparin</td>
<td>5000 IU SC q12h</td>
<td>To prevent venous thrombosis and pulmonary emboli</td>
<td>Monitor platelets, follow PTT which should rise 1.5-2x</td>
</tr>
<tr>
<td>LMWH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dalteparin (Fragmin®)</td>
<td>5000 IU SC OD</td>
<td>DVT prophylaxis esp. in hip and knee surgery</td>
<td>Fixed dose, no monitoring, improved bioavailability, increased bleeding rates</td>
</tr>
<tr>
<td>enoxaparin (Lovenox®)</td>
<td>30-40 mg SC bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fondaparinux (Arixtra®)</td>
<td>2.5 mg SC OD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>midazolam (Versed®)</td>
<td>0.02 mg/kg IV</td>
<td>Conscious sedation for short procedures</td>
<td>Medication used during fracture reduction – monitor for respiratory depression</td>
</tr>
<tr>
<td>fentanyl (Sublimaze®)</td>
<td>0.5-3 µg/kg IV</td>
<td>Conscious sedation for short procedures</td>
<td>Short acting anesthetic used in conjunction with midazolam (Versed®)</td>
</tr>
<tr>
<td>tramcinolone (Aristocort®) – an injectable steroid</td>
<td>0.5-1 mL of 25 mg/mL Suspension (injected into inflamed joint or bursa)</td>
<td>Potent anti-inflammatory effect; increased pain for 24 h, rarely causes fat necrosis and skin deigmentation</td>
<td></td>
</tr>
<tr>
<td>naproxen (Aleve®, Naprosyn®)</td>
<td>250-500 mg bid</td>
<td>Pain due to inflammation, arthritis, soft tissue injury</td>
<td>NSAID, may cause gastric erosion and bleeding</td>
</tr>
<tr>
<td>misoprostol (Cytotec®)</td>
<td>200 µg qid</td>
<td>Prophylaxis of heterotopic ossification after THA</td>
<td>Use with indomethacin</td>
</tr>
<tr>
<td>indomethacin (Indocid®)</td>
<td>25 mg PO tid</td>
<td>Prophylaxis of heterotopic ossification after THA</td>
<td>Use with misoprostol</td>
</tr>
<tr>
<td>ibuprofen (Advil®, Motrin®)</td>
<td>200-400 mg tid</td>
<td>Pain (including post-op), inflammation (including arthritis)</td>
<td>NSAID, may cause gastric erosion and bleeding</td>
</tr>
<tr>
<td>propofol (Diprivan®)</td>
<td>1-2 mg/kg IV Maint. 0.5 mg/kg</td>
<td>Conscious sedation for short procedures</td>
<td>Short acting anesthetic often used in conjunction with fentanyl (Sublimaze®)</td>
</tr>
</tbody>
</table>

**Signs of Hypercalcemia**
“Bones, Stones, Moans, Groans, Psychiatric overtones”
CNS: headache, confusion, irritability, blurred vision
GI: NBV, abdominal pain, constipation, weight loss
MSK: fatigue, weakness, unsteady gait, bone and joint pain
GU: nocturia, polydipsia, polyuria, UTIs
References

Textbooks

Journal Articles
Acronyms ........................................... 2

Basic Anatomy Review .......................... 2
Ear
Nose
Throat
Head and Neck
Anatomical Triangles of the Neck

Differential Diagnoses of Common Presenting Problems ......................... 5
Dizziness
Otalgia
Hearing Loss
Tinnitus
Nasal Obstruction
Hoarseness
Neck Mass

Hearing ............................................. 9
Normal Hearing Physiology
Types of Hearing Loss
Pure Tone Audiometry
Speech Audiometry
Impedance Audiometry
Auditory Brainstem Response
Otoacoustic Emissions
Aural Rehabilitation

Vertigo ............................................. 12
Evaluation of the Dizzy Patient
Benign Paroxysmal Positional Vertigo
Menière’s Disease (Endolymphatic Hydrops)
Vestibular Neuronitis
Labyrinthitis
Acoustic Neuroma (Vestibular Schwannoma)

Tinnitus .......................................... 15
Diseases of the External Ear ................. 15
Cerumen Impaction
Exostoses
Otitis Externa (OE)
Malignant (Necrotizing) Otitis Externa (Skull Base Osteomyelitis)

Diseases of the Middle Ear ................. 17
Acute Otitis Media and Otitis Media with Effusion
Cholesteatoma
Mastoiditis
Otosclerosis

Diseases of the Inner Ear ...................... 18
Congenital Sensorineural Hearing Loss
Presbycusis
Sudden Sensorineural Hearing Loss
Autoimmune Inner Ear Disease
Drug Ototoxicity
Noise-Induced Sensorineural Hearing Loss
Temporal Bone Fractures

Facial Nerve (CN VII) Paralysis .............. 21
Rhinitis .......................................... 22
Allergic Rhinitis (Hay Fever)
Vasomotor Rhinitis

Rhinosinusitis .................................. 24
Acute Bacterial Rhinosinusitis
Chronic Rhinosinusitis

Epistaxis ......................................... 26

Hoarseness ...................................... 27
Acute Laryngitis
Chronic Laryngitis
Vocal Cord Polyps
Vocal Cord Nodules
Benign Laryngeal Papillomas
Laryngeal Carcinoma

Salivary Glands ................................. 29
Sialadenitis
Sialolithiasis
Salivary Gland Neoplasms
Parotid Gland Neoplasms

Neck Masses .................................... 31
Approach to a Neck Mass
Evaluation

Congenital Neck Masses ....................... 32
Branchial Cleft Cysts/Fistula
Thyroglossal Duct Cysts
Lymphatic Malformation

Neoplasms of the Head and Neck .......... 34
Thyroid Carcinoma

Pediatric Otolaryngology ..................... 38
Acute Otitis Media (AOM)
Otitis Media with Effusion (OME)
Adenoid Hypertrophy
Adenoidectomy
Sleep-Disordered Breathing in Children
Acute Tonsillitis
Peritonsillar Abscess (Quinsy)
Tonsillectomy
Airway Problems in Children
Signs of Airway Obstruction
Acute Laryngotracheobronchitis (Croup)
Acute Epiglottitis
Subglottic Stenosis
Laryngomalacia
Foreign Body
Deep Neck Space Infection

Common Medications ......................... 47

References ..................................... 48
Basic Anatomy Review

Ear

**Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABR</td>
<td>auditory brainstem response</td>
</tr>
<tr>
<td>AC</td>
<td>air conduction</td>
</tr>
<tr>
<td>ACM</td>
<td>acute otitis media</td>
</tr>
<tr>
<td>BAHA</td>
<td>bone anchored hearing aid</td>
</tr>
<tr>
<td>BC</td>
<td>bone conduction</td>
</tr>
<tr>
<td>CHL</td>
<td>conductive hearing loss</td>
</tr>
<tr>
<td>CPA</td>
<td>cymbelomiptaneous angle</td>
</tr>
<tr>
<td>EAC</td>
<td>external auditory canal</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>ABR</td>
<td>auditory brainstem response</td>
</tr>
<tr>
<td>AC</td>
<td>air conduction</td>
</tr>
<tr>
<td>ACM</td>
<td>acute otitis media</td>
</tr>
<tr>
<td>BAHA</td>
<td>bone anchored hearing aid</td>
</tr>
<tr>
<td>BC</td>
<td>bone conduction</td>
</tr>
<tr>
<td>CHL</td>
<td>conductive hearing loss</td>
</tr>
<tr>
<td>CPA</td>
<td>cymbelomiptaneous angle</td>
</tr>
<tr>
<td>EAC</td>
<td>external auditory canal</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein-Barr virus</td>
</tr>
</tbody>
</table>

**Figure 1.** Surface anatomy of the external ear; anatomy of ear

**Figure 2.** Normal appearance of right tympanic membrane on otoscopy
**Nose**

Figure 3. Nasal anatomy

Figure 4. Nasal septum and its arterial supply (see *Epistaxis* section for detailed blood supply)

Figure 5. Anatomy of the four paranasal sinuses: maxillary, ethmoid, sphenoid, and frontal

Reprinted from Dhillon R.S, and East CA. Ear, Nose and Throat and Head and Neck Surgery, 2nd ed. Copyright 1999, with permission from Elsevier.

**Throat**

Figure 6. Anatomy of a normal larynx; superior view of larynx on indirect laryngoscopy
Head and Neck

**Anatomical Triangles of the Neck**

**Anterior triangle:**
- bounded by anterior border of SCM, midline of neck, and lower border of mandible
- divided into:
  - **submental triangle:** bounded by both anterior bellies of digastric and hyoid bone
  - **digastric triangle:** bounded by anterior and posterior bellies of digastric, and inferior border of mandible
  - **carotid triangle:** bounded by sternocleidomastoid, anterior belly of omohyoid, and posterior belly of digastric
    - contains: tail of parotid, submandibular gland, hypoglossal nerve, carotid bifurcation, and lymph nodes

**Posterior triangle:**
- bounded by posterior border of sternocleidomastoid, anterior border of trapezius, and middle third of clavicle
- divided into:
  - **occipital triangle:** superior to posterior belly of the omohyoid
  - **subclavian triangle:** inferior to posterior belly of omohyoid
  - contains: spinal accessory nerve and lymph nodes
Table 1. Lymphatic Drainage of Nodal Groups and Anatomical Triangles of Neck

<table>
<thead>
<tr>
<th>Nodal Group/Level</th>
<th>Location</th>
<th>Drainage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Suboccipital (S)</td>
<td>Base of skull, posterior</td>
<td>Posterior scalp</td>
</tr>
<tr>
<td>2. Retroauricular (R)</td>
<td>Superficial to mastoid process</td>
<td>Scalp, temporal region, external auricular meatus, posterior pinna</td>
</tr>
<tr>
<td>3. Parotid-preauricular (P)</td>
<td>In front of ear</td>
<td>External auditory meatus, anterior pinna, soft tissue of front and temporal regions, root of nose, eyelids, palpebral conjunctiva</td>
</tr>
<tr>
<td>4. Submental (Level IA)</td>
<td>(Midline) Anterior bellies of digastic muscles, tip of mandible, and hyoid bone</td>
<td>Floor of mouth, anterior oral tongue, anterior mandibular alveolar ridge, lower lip</td>
</tr>
<tr>
<td>5. Submandibular (Level IB)</td>
<td>Anterior belly of digastic muscle, stylohyoid muscle, body of mandible</td>
<td>Oral cavity, anterior nasal cavity, soft tissues of the mid-face, submandibular gland</td>
</tr>
<tr>
<td>6. Upper jugular (Levels IIA and IIB)</td>
<td>Skull base to inferior border of hyoid bone along SCM muscle</td>
<td>Oral cavity, nasal cavity, naso/oro/hypopharynx, larynx, parotid glands</td>
</tr>
<tr>
<td>7. Middle jugular (Level III)</td>
<td>Inferior border of hyoid bone to inferior border of clavicular cartilage along SCM muscle</td>
<td>Oral cavity, naso/oro/hypopharynx, larynx</td>
</tr>
<tr>
<td>8. Lower jugular* (Level IV)</td>
<td>Inferior border of clavicular cartilage to clavicle along SCM muscle</td>
<td>Hypopharynx, thyroid, cervical esophagus, larynx</td>
</tr>
<tr>
<td>9. Posterior triangle** (Levels VA and VB)</td>
<td>Posterior border of SCM, anterior border of trapezoid, from skull base to clavicle</td>
<td>Nasopharynx and oropharynx, cutaneous structures of the posterior scalp and neck</td>
</tr>
<tr>
<td>10. Anterior compartment*** (Level VI)</td>
<td>(Midline) Hyoid bone to suprasternal notch between the common carotid arteries</td>
<td>Thyroid gland, glistening and subglistening larynx, apex of corniculate, cervical esophagus</td>
</tr>
</tbody>
</table>

*Virchow node: left lower level IV suprascapular node
**Includes some suprascapular nodes
***Includes pretracheal, precricoid, paratracheal, and perithyroidal nodes

** Differential Diagnoses of Common Presenting Problems **

**Dizziness**

- **True Vertigo**
  - Benign paroxysmal positional vertigo (BPPV)
  - Labyrinthitis
  - Menière's disease
  - Recurrent vestibulopathy
  - Temporal bone fracture
  - Superior semicircular canal dehiscence
  - Ototoxic drug exposure
  - Autoimmune inner ear disease
  - Perilymph fistula
  - Cholesteatoma

- **Central**
  - Cerebrovascular disorders
    - Vertebrobasilar insufficiency
    - Transient ischemic attacks
    - Wallenberg's syndrome
    - Cerebellar infarction
    - Migrainous vertigo
    - Multiple sclerosis
      - Tumours
      - CPA tumours
      - Posterior fossa tumours
      - Glomas tumours
      - Inflammation
      - Meningitis
      - Cerebellar abscess
      - Trauma: cerebellar contusion
      - Toxic: alcohol, hypnotics, drugs

- **Non-Vertiginous**
  - Organic Diseases
    - Cardiac
      - Arrhythmias
      - Aortic stenosis
      - Vasovagal
      - Orthostatic hypotension
      - Anemia
      - Peripheral neuropathy
      - Visual impairment
  - Functional
    - Depression
      - Anxiety
      - Panic disorder
      - Hyperventilation
      - Personality disorder
      - Phobic dizziness

**Common causes in bold**

**Figure 10. Anatomy of the thyroid gland**

**5 Ds of Vertebrobasilar Insufficiency**

- Drop attacks
- Diplopia
- Dysarthria
- Dizziness
- Dysphagia

**Left-sided** enlargement of a suprascapular node (Virchow's node) may indicate an abdominal malignancy

**Right-sided** enlargement may indicate malignancy of the mediastinum, lungs, or esophagus

**Occipital and/or posterior auricular node** enlargement may indicate rubella

**4 Strap Muscles of the Neck**

- Thyrohyoid
- Omohyoid
- Sternothyroid
- Sternohyoid

**Figure 11. Differential diagnosis of dizziness**

True nystagmus and vertigo caused by a peripheral lesion will never last longer than a couple of weeks because of compensation. Central lesions do not compensate, hence nystagmus and vertigo will persist.
### Otalgia

**External Ear**
- Infection
  - Otitis externa
  - Herpes simplex/zoster
  - Auricular cellulitis
- Trauma
  - Frostbite
- Other
  - Neoplasm of external canal
  - Foreign body
  - Cerumen impaction

**Middle/Inner Ear**
- Infection
  - AOM
  - Otitis media with effusion
  - Mastoiditis
  - Myringitis
  - Skull base infections
- Trauma
  - Traumatic perforation
  - Barotrauma
- Other
  - Neoplasm
  - Wegener’s
  - Cholesteatoma

**Referred Pain**
- Infection
  - Tonsillitis
  - Tracheitis
  - Ramsay Hunt syndrome
- Trauma
  - Thyroiditis
  - Cervical arthritis
- Other
  - TMJ syndrome
  - Teeth
  - Trismus
  - Glossopharyngeal neuralgia
  - Neoplasm of oral cavity, larynx, pharynx

*Figure 12. Differential diagnosis of otalgia*

### Hearing Loss

#### Conductive
- External Ear
  - Impacted cerumen
  - Otitis externa
  - Foreign body
  - Keratitis obturans
  - Exostoses, osteomas
  - Tumour of canal
  - Congenital stenosis/microtia
- Middle Ear
  - AOM
  - Otitis media with effusion
  - TM perforation
  - Otosclerosis
  - Tymanosclerosis
  - Eustachian tube dysfunction
  - Cholesteatoma
  - OSScular malformations
  - OSScular discontinuity
  - Hemotympanum
  - Middle ear tumour

#### Sensorineural
- Congenital
- Acquired
  - Genetic
  - Non-syndrome associated
  - Syndrome associated
  - Intrauterine infections (i.e., TORCH)
  - Teratogens
  - Perinatal hypoxia
  - Prematurity/low birth weight
  - Hyperbilirubinemia
  - Presbycusis
  - Noise-induced
  - Menière’s disease
  - Labyrinthitis
  - Sudden SNHL
  - Autoimmune inner ear disease
  - Ototoxic drug exposure
  - Temporal bone trauma
  - Infectious
  - Postmeningitis
  - Syphilis
  - Viral: mumps, CMV, HSV
  - Neoplastic
  - Acoustic neuroma
  - CPA tumours
  - Vascular occlusion/emboli
  - Auditory neuropathy

*Figure 13. Differential diagnosis of hearing loss*
## Tinnitus

### Subjective
- Only heard by patient
  - (common)

### Objective
- Can be heard by others
  - (rare)

<table>
<thead>
<tr>
<th>Otologic</th>
<th>Vascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presbycusis</td>
<td>Benign intracranial hypertension</td>
</tr>
<tr>
<td>Noise-induced hearing loss</td>
<td>Arteriovenous malformation</td>
</tr>
<tr>
<td>Otitis media with effusion</td>
<td>Glomus tympanicum</td>
</tr>
<tr>
<td>Meniere's disease</td>
<td>Glomus jugulare</td>
</tr>
<tr>
<td>Otosclerosis</td>
<td>Arterial bruits:</td>
</tr>
<tr>
<td>Cerumen</td>
<td>High-riding carotid artery</td>
</tr>
<tr>
<td>Foreign body against TM</td>
<td>Vascular loop</td>
</tr>
<tr>
<td>Drugs</td>
<td>Persistent stapedial artery</td>
</tr>
<tr>
<td>ASA</td>
<td>Carotid stenosis</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Venous hum:</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>High jugular bulb</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>Hyper/hypothyroidism</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Mechanicl</td>
</tr>
<tr>
<td>Hyper/hypothyroidism</td>
<td>Patulous eustachian tube</td>
</tr>
<tr>
<td>Hyperlipademia</td>
<td>Palatal myoclonus</td>
</tr>
<tr>
<td>Vitamin A, B, Zinc deficiency</td>
<td>Stapedius muscle spasm</td>
</tr>
<tr>
<td>Neurologic</td>
<td></td>
</tr>
<tr>
<td>Head trauma</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td>CPA tumours</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Differential Diagnosis of Nasal Obstruction

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Congenital</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nasal Cavity</strong></td>
<td><strong>Nasal Cavity</strong></td>
</tr>
<tr>
<td>• Rhinitis</td>
<td>• Nasal dermoid cyst</td>
</tr>
<tr>
<td>• Acute/chronic</td>
<td>• Encephalocele</td>
</tr>
<tr>
<td>• Vasomotor</td>
<td>• Gloma</td>
</tr>
<tr>
<td>• Allergic</td>
<td>• Choanal atresia</td>
</tr>
<tr>
<td>• Rhinosinusitis</td>
<td></td>
</tr>
<tr>
<td>• Foreign bodies</td>
<td></td>
</tr>
<tr>
<td>• Enlarged turbinates</td>
<td></td>
</tr>
<tr>
<td>• Tumour</td>
<td></td>
</tr>
<tr>
<td>• Benign: polyps, inverting papilloma</td>
<td></td>
</tr>
<tr>
<td>• Malignant</td>
<td></td>
</tr>
<tr>
<td>• SCC</td>
<td></td>
</tr>
<tr>
<td>• Esthesioneuroblastoma (olfactory neuroblastoma)</td>
<td></td>
</tr>
<tr>
<td>• Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td><strong>Nasal Septum</strong></td>
<td><strong>Nasal Septum</strong></td>
</tr>
<tr>
<td>• Septal deviation</td>
<td>• Septal deviation</td>
</tr>
<tr>
<td>• Septal hematoma/abscess</td>
<td>• Septal hematoma/abscess</td>
</tr>
<tr>
<td>• Dislocated septum</td>
<td>• Dislocated septum</td>
</tr>
<tr>
<td><strong>Nasopharynx</strong></td>
<td><strong>Nasopharynx</strong></td>
</tr>
<tr>
<td>• Adenoid hypertrophy</td>
<td></td>
</tr>
<tr>
<td>• Tumour</td>
<td></td>
</tr>
<tr>
<td>• Benign: juvenile nasopharyngeal angiofibroma (JNA), polyps</td>
<td></td>
</tr>
<tr>
<td>• Malignant: nasopharyngeal carcinoma</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td><strong>Systemic</strong></td>
</tr>
<tr>
<td>• Granulomatous diseases, diabetes, vasculitis</td>
<td></td>
</tr>
</tbody>
</table>
### Hoarseness

#### Table 3. Differential Diagnosis of Hoarseness

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious</strong></td>
<td>• Acute/chronic laryngitis</td>
</tr>
<tr>
<td></td>
<td>• Laryngotracheobronchitis (croup)</td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
<td>• GERD</td>
</tr>
<tr>
<td></td>
<td>• Vocal cord polyps/nodules</td>
</tr>
<tr>
<td></td>
<td>• Lifestyle: smoking, chronic EtOH use</td>
</tr>
<tr>
<td><strong>Trauma</strong></td>
<td>• External laryngeal trauma</td>
</tr>
<tr>
<td></td>
<td>• Endoscopy and endotracheal tube (e.g. intubation granuloma)</td>
</tr>
<tr>
<td><strong>Neoplasia</strong></td>
<td>• Benign tumour</td>
</tr>
<tr>
<td></td>
<td>• Papillomas (HPV infection)</td>
</tr>
<tr>
<td></td>
<td>• Minor salivary gland tumours</td>
</tr>
<tr>
<td></td>
<td>• Other</td>
</tr>
<tr>
<td><strong>Cysts</strong></td>
<td>• Retention cysts</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td>• Endocrine</td>
</tr>
<tr>
<td></td>
<td>• Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>• Virilization</td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
<td>• Central lesions</td>
</tr>
<tr>
<td></td>
<td>• Cerebrovascular accident (CVA)</td>
</tr>
<tr>
<td></td>
<td>• Head injury</td>
</tr>
<tr>
<td></td>
<td>• Multiple sclerosis (MS)</td>
</tr>
<tr>
<td></td>
<td>• Skull base tumours</td>
</tr>
<tr>
<td></td>
<td>• Arnold-Chiari malformation</td>
</tr>
<tr>
<td></td>
<td>• Peripheral lesions</td>
</tr>
<tr>
<td></td>
<td>• Unilateral</td>
</tr>
<tr>
<td></td>
<td>• Lung malignancy</td>
</tr>
<tr>
<td><strong>Functional</strong></td>
<td>• Psychogenic aphony</td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
<td>• Laryngomalacia</td>
</tr>
<tr>
<td></td>
<td>• Laryngeal web</td>
</tr>
<tr>
<td></td>
<td>• Laryngeal atresia</td>
</tr>
<tr>
<td><strong>Lung malignancy</strong></td>
<td>is the most common cause of extralaryngeal vocal cord paralysis.</td>
</tr>
</tbody>
</table>

#### Neck Mass

![Figure 15. Differential diagnosis of a neck mass](Image)

- **Inflammatory/Infections**
  - Reactive lymphadenopathy
  - TB or atypical mycobacteria
  - Infectious mononucleosis
  - Abscesses
  - Cat scratch fever
  - Sarcoïdosis
  - Kawasaki’s
  - HIV

- **Congenital**
  - Thyroglossal duct cyst
  - Thymus tumour/pleura
  - Pyramidal lobe of thyroid gland
  - Ranula

- **Neoplastic**
  - Branchial cleft cyst
  - Cystic hygroma

- **Malignant**
  - Salivary gland neoplasm
  - Lipoma
  - Fibroma
  - Vascular

- **Benign**
  - Lymphoma
  - Thyroid
  - Sarcoma
  - Salivary gland neoplasm
  - Rhabdomyosarcoma
  - Neuroblastoma

- **Head and neck primary**
  - Infraclavicular primary
  - Leukemia
Hearing

Normal Hearing Physiology

- **Conductive pathway (external auditory canal to cochlea):** air conduction of sound energy down the EAC → vibration of the tympanic membrane (area effect) → sequential vibration of the middle ear ossicles: malleus, incus, stapes (leverage effect) → transmission of amplified vibrations from the stapes footplate in the middle ear to the oval window of the cochlea in the inner ear → pressure differential on cochlear fluid creates movement along the basilar membrane within the cochlea from base to apex

- **Neural pathway (nerve to brain):** basilar membrane vibration stimulates overlying hair cells in the organ of Corti → stimulation of bipolar neurons in the spiral ganglion of the cochlear division of CN VIII → cochlear nucleus → superior olivary nucleus → lateral lemniscus → inferior colliculus → Sylvian fissure of temporal lobe

Types of Hearing Loss

1. **Conductive Hearing Loss (CHL)**
   - the conduction of sound to the cochlea is impaired
   - can be caused by external and middle ear disease

2. **Sensorineural Hearing Loss (SNHL)**
   - due to a defect in the conversion of sound into neural signals or in the transmission of those signals to the cortex
   - can be caused by disease of the cochlea, acoustic nerve (CN VIII), brainstem, or cortex

3. **Mixed Hearing Loss**
   - both a conductive hearing loss and a sensorineural hearing loss are present

Auditory Acuity

- whispered-voice test: mask one ear and whisper into the other
- tuning fork tests (see Table 4) (audiogram is of greater utility)
- sensitivity depends on which tuning fork used (256 Hz, 512 Hz, 1024 Hz)
  - Rinne test:
    - 512 Hz tuning fork is struck and held firmly on mastoid process to test BC. The tuning fork is then placed beside the pinna to test AC
    - If AC > BC → positive Rinne, which is normal
  - Weber test:
    - 512 Hz tuning fork is held on vertex of head and patient states whether it is heard centrally (Weber negative) or is lateralized to one side (Weber right, Weber left)
    - can place vibrating fork on patient’s chin while they clench their teeth, or directly on teeth to elicit more reliable response
    - will only lateralize if difference in hearing loss between ears is >6 dB

Table 4. The Interpretation of Tuning Fork Tests

<table>
<thead>
<tr>
<th>Examples</th>
<th>Weber</th>
<th>Rinne</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or bilateral sensorineural hearing loss</td>
<td>Central</td>
<td>AC &gt; BC (+) bilaterally</td>
</tr>
<tr>
<td>Right-sided conductive hearing loss, normal left ear</td>
<td>Lateralizes to right</td>
<td>BC &gt; AC (--) right</td>
</tr>
<tr>
<td>Right-sided sensorineural hearing loss, normal left ear</td>
<td>Lateralizes to left</td>
<td>AC &gt; BC (+) bilaterally</td>
</tr>
<tr>
<td>Right-sided severe sensorineural hearing loss or deaf right ear, normal left ear</td>
<td>Lateralizes to left</td>
<td>BC &gt; AC (--) right*</td>
</tr>
</tbody>
</table>

* a vibrating tuning fork on the mastoid stimulates the cochllea bilaterally, therefore in this case, the left cochllea is stimulated by the Rinne test on the right, i.e. a false negative test. These tests are not valid if the ear canals are obstructed with cerumen (i.e. will create conductive loss)

Pure Tone Audiometry

- a threshold is the lowest intensity level at which a patient can hear the tone 50% of the time
- thresholds are obtained for each ear for frequencies 250 to 8000 Hz
- air conduction thresholds are obtained with headphones and measure outer, middle, inner ear, and auditory nerve function
- bone conduction thresholds are obtained with bone conduction oscillators which bypass the outer and middle ear

Degree of Hearing Loss

- determined on basis of the pure tone average (PTA) at 500, 1000, and 2000 Hz
**PURE TONE PATTERNS**

1. **Conductive Hearing Loss (CHL)** (Figure 16B and 16C)
   - BC in normal range
   - AC outside of normal range
   - gap between AC and BC thresholds >10 dB (an air-bone gap)

2. **Sensorineural Hearing Loss (SNHL)** (Figure 16D and 16E)
   - both air and bone conduction thresholds below normal
   - gap between AC and BC <10 dB (no air-bone gap)

3. **Mixed Hearing Loss**
   - both air and bone conduction thresholds below normal
   - gap between AC and BC thresholds >10 dB (an air-bone gap)

**Speech Audiology**

**Speech Reception Threshold (SRT)**
- lowest hearing level at which patient is able to repeat 50% of two syllable words which have equal emphasis on each syllable (spondee words)
- SRT and best pure tone threshold in the 500 to 2000 Hz range (frequency range of human speech) usually agree within 5 dB. If not, suspect a retrocochlear lesion or functional hearing loss
- used to assess the reliability of the pure tone audiometry

**Speech Discrimination Test**
- percentage of words the patient correctly repeats from a list of 50 monosyllabic words
- tested at a level 35 to 50 dB > SRT, therefore degree of hearing loss is taken into account
- patients with normal hearing or conductive hearing loss score >90%
- score depends on extent of SNHL
- rollover effect: a decrease in discrimination as sound intensity increases. Typical of a retrocochlear lesion (e.g. acoustic neuroma)
- investigate further if scores differ more than 20% between ears as asymmetry may indicate a retrocochlear lesion
- used as best predictor of hearing aid response; if patient has HL and problems with word discrimination, hearing aids may not be helpful
Impedance Audiometry

Tymanogram
- the Eustachian tube equalizes the pressure between the external and middle ear
- tympanograms graph the compliance of the middle ear system against a pressure gradient ranging from −400 to +200 mmH₂O
- tympanogram peak occurs at the point of maximum compliance: where the pressure in the external canal is equivalent to the pressure in the middle ear
- normal range: −100 to +50 mmH₂O

Figure 17. Tympanograms

Static Compliance
- volume measurement reflecting overall stiffness of the middle ear system
- normal range: 0.3 to 1.6 cc
- negative middle ear pressure and abnormal compliance indicate middle ear pathology
- in a type B curve, ear canal volumes of greater than 2 cc in children and 2.5 cc in adults indicate TM perforation or presence of a patent ventilation tube

Acoustic Stapedial Reflexes
- stapedius muscle contracts due to loud sound
- acoustic reflex thresholds = 70 to 100 dB greater than hearing threshold; if hearing threshold >85 dB, reflex likely absent
- stimulating either ear causes bilateral and symmetrical reflexes
- for reflex to be present, CN VII must be intact and no conductive hearing loss in monitored ear
- if reflex is absent without conductive or severe sensorineural loss, suspect CN VII lesion
- acoustic reflex decay test = ability of stapedius muscle to sustain contraction for 10 s at 10 dB
  - normally, little reflex decay occurs at 500 and 1000 Hz
  - with cochlear hearing loss, acoustic reflex thresholds are 25 to 60 dB
  - with retrocochlear hearing loss (acoustic neuroma), absent acoustic reflexes or marked reflex decay (>50%) within 5 s

Auditory Brainstem Response (ABR)
- measures neuroelectric potentials (waves) in response to a stimulus in five different anatomic sites (refer to Order of Neural Pathway sidebar on OT9). This test can be used to map the lesion according to the site of the defect
- delay in brainstem response suggests cochlear or retrocochlear abnormalities
- does not require volition or co-operation of patient (therefore of value in children and in malingerers)

Otoacoustic Emissions
- objective test of hearing where a series of clicks is presented to the ear and the cochlea generates an echo which can be measured
- often used in newborn screening
- can be used to uncover normal hearing in malingering patients
- absence of emissions can be due to hearing loss or fluid in the middle ear
Aural Rehabilitation

- dependent on degree of hearing loss, communicative requirements, motivation, expectations, age, and physical and mental abilities
- negative prognostic factors:
  - poor speech discrimination
  - narrow dynamic range (recruitment)
  - unrealistic expectations
- types of hearing aids:
  - BTE: behind the ear (with occlusive mould or open fit which allows natural sound to pass – for milder hearing losses)
  - ITE: in-the-ear, placed in concha
  - ITC: in-the-canal, placed entirely in ear canal
  - CIC: contained-in-canal, placed deeply in ear canal
  - bone conduction – bone-anchored hearing aid (BAHA): attached to the skull
- contralateral routing of signals (CROS)
- assistive listening devices:
  - direct/indirect audio output
  - infrared, FM radio, or induction loop systems
  - telephone, television, or alerting devices
- cochlear implants:
  - electrode is inserted into the cochlea to allow direct stimulation of the auditory nerve
  - for profound bilateral sensorineural hearing loss not rehabilitated with conventional hearing aids
- established indication: post-lingually deafened adults, pre- and post-lingually deaf children

Vertigo

Evaluation of the Dizzy Patient

- vertigo: illusion of rotational, linear, or tilting movement of self or environment
  - vertigo is produced by peripheral (inner ear) or central (brainstem-cerebellum) stimulation
  - it is important to distinguish vertigo from other disease entities that may present with similar complaints of “dizziness” (e.g. cardiovascular, psychiatric, neurological, aging)

Table 5. Peripheral vs. Central Vertigo

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Peripheral</th>
<th>Central</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imbalance</td>
<td>Moderate-severe</td>
<td>Mild-moderate</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Severe</td>
<td>Variable</td>
</tr>
<tr>
<td>Auditory symptoms</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Compensation</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Unidirectional</td>
<td>Bidirectional</td>
</tr>
<tr>
<td></td>
<td>Horizontal or rotatory</td>
<td>Horizontal or vertical</td>
</tr>
</tbody>
</table>

Table 6. Differential Diagnosis of Vertigo Based on History

<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration</th>
<th>Hearing Loss</th>
<th>Tinnitus</th>
<th>Aural Fullness</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign paroxysmal positional vertigo (BPPV)</td>
<td>Seconds</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Menière’s disease</td>
<td>Minutes to hours</td>
<td>Uni/bilateral, fluctuating</td>
<td>+</td>
<td>Pressure/warmth</td>
<td></td>
</tr>
<tr>
<td>Vestibular neuronitis</td>
<td>Hours to days</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Recent AOM</td>
</tr>
<tr>
<td>Labyrinthitis</td>
<td>Days</td>
<td>Unilateral</td>
<td>Whistling</td>
<td>–</td>
<td>Ataxia</td>
</tr>
<tr>
<td>Acoustic neuroma</td>
<td>Chronic</td>
<td>Progressive</td>
<td>–</td>
<td>–</td>
<td>CN VII palsy</td>
</tr>
</tbody>
</table>

Benign Paroxysmal Positional Vertigo (BPPV)

Definition

- acute attacks of transient vertigo lasting seconds to minutes initiated by certain head positions, accompanied by torsional (i.e. rotatory) nystagmus (geotropic = fast phase towards the floor)

Etiology

- due to canalithiasis (migration of free floating otoliths within the endolymph of the semicircular canal) or cupulolithiasis (otolith attached to the cupula of the semicircular canal)
  - can affect each of the 3 semicircular canals, although the posterior canal is affected in >90% of cases
Vertigo

• causes: head injury, viral infection (URTI), degenerative disease, idiopathic
• results in slightly different signals being received by the brain from the two balance organs resulting in sensation of movement

Diagnosis
• history
• positive Dix-Hallpike maneuver (sensitivity 82%, specificity 71%)

Dix-Hallpike Positional Testing (see website for video and illustrations)
• the patient is rapidly moved from a sitting position to a supine position with the head hanging over the end of the table, turned to one side at 45° and neck extended 20° holding the position for 20 s
• onset of vertigo and rotary nystagmus indicate a positive test for the dependent side

Treatment
• reassure patient that process resolves spontaneously
• particle repositioning maneuvers
  • Epley maneuver (performed by MD)
  • Brandt-Daroff exercises (performed by patient)
• surgery for refractory cases
• anti-emetics for nausea/vomiting
• drugs to suppress the vestibular system delay eventual recovery and are therefore not used

Menière’s Disease (Endolymphatic Hydrops)

Definition
• episodic attacks of tinnitus, hearing loss, aural fullness, and vertigo lasting minutes to hours

Proposed Etiology
• inadequate absorption of endolymph leads to endolymphatic hydrops (over accumulation) that distorts the membranous labyrinth

Epidemiology
• peak incidence 40 to 60 yr
• bilateral in 35% of cases

Clinical Features
• vertigo, fluctuating low frequency SNHL, tinnitus, and aural fullness
• ± drop attacks (Tumarkin crisis), ± nausea and vomiting
• vertigo disappears with time (minutes to hours), but hearing loss remains
• early in the disease: fluctuating SNHL
• later stages: persistent tinnitus and progressive hearing loss
• attacks come in clusters and can be debilitating to the patient
• triggers: high salt intake, caffeine, stress, nicotine, and alcohol

Treatment
• acute management may consist of bed rest, antiemetics, antivertiginous drugs [e.g. betahistine (Serc®)], and low molecular weight dextrans (not commonly used)
• long term management may include:
  • medical:
    • low salt diet, diuretics (e.g. hydrochlorothiazide, triamterene, amiloride)
    • Serc® prophylactically to decrease intensity of attacks
  • local application of gentamicin to destroy vestibular end-organ, results in complete SNHL
  • surgical:
    • selective vestibular neurectomy or transtympanic labyrinthectomy
    • vestibular implants have recently been introduced, experimentally
• must monitor opposite ear as bilaterality occurs in 35% of cases

Vestibular Neuronitis

Definition
• acute onset of disabling vertigo often accompanied by nausea, vomiting, and imbalance without hearing loss that resolves over days leaving a residual imbalance that lasts days to weeks

Etiology
• thought to be due to a viral infection (e.g. measles, mumps, herpes zoster)
• ~30% of cases have associated URTI symptoms
• other: microvascular events, diabetes, autoimmune process
• considered to be the vestibular equivalent of Bell’s palsy, sudden hearing loss, and acute vocal cord palsy
Clinical Features
• acute phase:
  ▪ severe vertigo with nausea, vomiting, and imbalance lasting 1 to 5 d
  ▪ irritative nystagmus (fast phase towards the offending ear)
  ▪ patient tends to veer towards affected side
• convalescent phase:
  ▪ imbalance and motion sickness lasting days to weeks
  ▪ spontaneous nystagmus away from affected side
  ▪ gradual vestibular adaptation requires weeks to months
• incomplete recovery likely with the following risk factors: elderly, visual impairment, poor ambulation
• repeated attacks can occur

Treatment
• acute phase:
  ▪ bed rest, vestibular sedatives (Gravol\textsuperscript{®}), diazepam
• convalescent phase:
  ▪ progressive ambulation especially in the elderly
  ▪ vestibular exercises: involve eye and head movements, sitting, standing, and walking

Labyrinthitis
Definition
• acute infection of the inner ear resulting in vertigo and hearing loss

Etiology
• may be serous (viral) or purulent (bacterial)
• occurs as a complication of acute and chronic otitis media, bacterial meningitis, cholesteatoma, and temporal bone fractures
• bacterial: S. pneumoniae, H. influenzae, M. catarrhalis, P. aeruginosa, P. mirabilis
• viral: rubella, CMV, measles, mumps, varicella zoster

Clinical Features
• sudden onset of vertigo, nausea, vomiting, tinnitus, and unilateral hearing loss, with no associated fever or pain
• meningitis is a serious complication

Investigations
• CT head
• if meningitis is suspected: lumbar puncture, blood cultures

Treatment
• treat with IV antibiotics, drainage of middle ear ± mastoidectomy

Acoustic Neuroma (Vestibular Schwannoma)
Definition
• schwannoma of the vestibular portion of CN VIII

Pathogenesis
• starts in the internal auditory canal and expands into cerebellopontine angle (CPA), compressing cerebellum and brainstem
• when associated with type 2 neurofibromatosis (NF2): bilateral acoustic neuromas, café-au-lait skin lesions, and multiple intracranial lesions

Clinical Features
• usually presents with unilateral SNHL or tinnitus
• dizziness and unsteadiness may be present, but true vertigo is rare as tumour growth occurs slowly and thus compensation occurs
• facial nerve palsy and trigeminal (V\textsubscript{1}) sensory deficit (corneal reflex) are late complications

Diagnosis
• MRI with gadolinium contrast is the gold standard
• audiogram (to assess SNHL)
• poor speech discrimination relative to the hearing loss
• stapedial reflex absent or significant reflex decay
• ABR – increase in latency of the 5th wave
• vestibular tests: normal or asymmetric caloric weakness (an early sign)

Treatment
• expectant management if tumour is very small, or in elderly
• definitive management is surgical excision
• other options: gamma knife, radiation
Tinnitus

Definition
• an auditory perception in the absence of an acoustic stimuli, likely related to loss of input to neurons in central auditory pathways and resulting in abnormal firing

History
• subjective vs. objective (see Figure 14, OT7)
• continuous vs. pulsatile (vascular in origin)
• unilateral vs. bilateral
• associated symptoms: hearing loss, vertigo, aural fullness, otalgia, otorrhea

Investigations
• audiology
• if unilateral:
  ▪ ABR, gadolinium enhanced MRI to exclude a retrocochlear lesion
  ▪ CT to diagnose glomus tympanicum (rare)
  ▪ MRI or angiogram to diagnose AVM
• if suspect metabolic abnormality: lipid profile, TSH

Treatment
• if a cause is found, treat the cause (e.g. drainage of middle ear effusion, embolization or excision of AVM)
• with no treatable cause: 50% will improve, 25% worsen, 25% remain the same
• avoid loud noise, ototoxic meds, caffeine, smoking
• tinnitus clinics
• identify situations where tinnitus is most bothersome (e.g. quiet times), mask tinnitus with soft music or “white noise”
• hearing aid if coexistent hearing loss
• tinnitus instrument: combines hearing aid with white noise masker
• trial of tocainamide

Cerumen Impaction

Etiology
• ear wax is a mixture of secretions from ceruminous and pilosebaceous glands, squames of epithelium, dust, and debris

Risk Factors
• hairy or narrow ear canals, in-the-ear hearing aids, cotton swab usage, osteomata

Clinical Features
• hearing loss (conductive)
• ± tinnitus, vertigo, otalgia, aural fullness

Treatment
• cerumenolytic drops (bicarbonate solution, olive oil, glycerine, Cerumenol®, Cerumenex®)
• syringing
• manual debridement (by MD)

Exostoses

Definition
• bony protuberances in the external auditory canal composed of lamellar bone

Etiology
• possible association with swimming in cold water

Clinical Features
• usually an incidental finding
• if large, they can cause cerumen impaction or otitis externa

Treatment
• no treatment required unless symptomatic
Otitis Externa (OE)

Etiology
- bacteria (~90% of OE): Pseudomonas aeruginosa, Pseudomonas vulgaris, E. coli, S. aureus
- fungus: Candida albicans, Aspergillus niger

Risk Factors
- associated with swimming (“swimmer’s ear”)
- mechanical cleaning (Q-tips®), skin dermatitis, aggressive scratching
- devices that occlude the ear canal: hearing aids, headphones, etc.

Clinical Features
- acute:
  - pain aggravated by movement of auricle (traction of pinna or pressure over tragus)
  - otorrhea (sticky yellow purulent discharge)
  - conductive hearing loss ± aural fullness 2º to obstruction of external canal by swelling and purulent debris
  - post-auricular lymphadenopathy
  - complicated OE exists if the pinna and/or the periauricular soft tissues are erythematosus and swollen
- chronic:
  - pruritus of external ear ± excoriation of ear canal
  - atrophic and scaly epidermal lining, ± otorrhea, ± hearing loss
  - wide meatus but no pain with movement of auricle
  - tympanic membrane appears normal

Treatment
- clean ear under magnification with irrigation, suction, dry swabbing, and C&S
- bacterial etiology
  - antipseudomonal otic drops (e.g. ciprofloxacin) or a combination of antibiotic and steroid (e.g. Cipro HC®)
  - do not use aminoglycoside if the tympanic membrane (TM) is perforated because of the risk of ototoxicity
  - introduction of fine gauze wick (pope wick) if external canal edematous
  - ± 3% acetic acid solution to acidify ear canal (low pH is bacteriostatic)
  - systemic antibiotics if either cervical lymphadenopathy or cellulitis is present
- fungal etiology
  - repeated debridement and topical antifungals (gentian violet, Mycostatin® powder, boric acid, Locacorten®, Vioform® drops)
  - ± analgesics
  - chronic otitis externa (pruritus without obvious infection) → corticosteroid alone (e.g. diprosalic acid)

Malignant (Necrotizing) Otitis Externa (Skull Base Osteomyelitis)

Definition
- osteomyelitis of the temporal bone

Epidemiology
- occurs in elderly diabetics and immunocompromised patients

Etiology
- rare complication of otitis externa
- Pseudomonas infection in 99% of cases

Clinical Features
- otalgia and purulent otorrhea that is refractory to medical therapy
- granulation tissue on the floor of the auditory canal

Complications
- cranial nerve palsies (most commonly VII>X>XI)
- systemic infection, death

Management
- imaging: high resolution temporal bone CT scan, gadolinium enhanced MRI, technetium scan
- requires hospital admission, debridement, IV antibiotics, hyperbaric O₂
- may require OR for debridement of necrotic tissue/bone

Gallium and Technetium Scans
Gallium scans are used to show sites of active infection. Gallium is taken up by PMNs and therefore only lights up when active infection is present. It will not show the extent of osteomyelitis. Technetium scans provide information about osteoblastic activity and as such are used to demonstrate sites of osteomyelitis. Technetium scans help with diagnosis whereas gallium scans are useful in follow-up.
Diseases of the Middle Ear

Acute Otitis Media (AOM) and Otitis Media with Effusion (OME)

• see Pediatric Otolaryngology, OT38

Cholesteatoma

Definition
• a cyst composed of keratinizing squamous epithelium occurring in the middle ear, mastoid, and temporal bone
• two types: congenital and acquired

Congenital
• presents as a “small white pearl” behind an intact tympanic membrane (anterior and medial to the malleus) or as a conductive hearing loss
• believed to be due to aberrant migration of external canal ectoderm during development
• not associated with otitis media/Eustachian tube dysfunction

Acquired (more common)
• generally occurs as a consequence of otitis media and chronic Eustachian tube dysfunction
• frequently associated with retraction pockets in the pars flaccida (1° acquired) and marginal perforations (2° acquired) of the tympanic membrane
• the associated chronic inflammatory process causes progressive destruction of surrounding bony structures

Clinical Features
• symptoms:
  ▪ history of otitis media (especially if unilateral), ventilation tubes, ear surgery
  ▪ progressive hearing loss (predominantly conductive although may get sensorineural hearing loss in late stage)
  ▪ otalgia, aural fullness, fever
• signs:
  ▪ retraction pocket in TM, may contain keratin debris
  ▪ TM perforation
  ▪ granulation tissue, polyp visible on otoscopy
  ▪ malodorous, unilateral otorrhea

Complications

<table>
<thead>
<tr>
<th>Local</th>
<th>Intracranial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ossicular erosion: conductive hearing loss</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Inner ear erosion: SNHL, dizziness, and/or labyrinthitis</td>
<td>Sigmoid sinus thrombosis</td>
</tr>
<tr>
<td>Temporal bone infection: mastoiditis, petrositis</td>
<td>Intracranial abscess (subdural, epidural, cerebellar)</td>
</tr>
<tr>
<td>Facial paralysis</td>
<td></td>
</tr>
</tbody>
</table>

Investigations
• audiogram and CT scan

Treatment
• there is no conservative therapy for cholesteatoma
• surgical: mastoidectomy ± tympanoplasty ± ossicular reconstruction

Mastoiditis

Definition
• infection (usually subperiosteal) of mastoid air cells, most commonly seen approximately two weeks after onset of untreated or inadequately treated acute suppurative otitis media

Etiology
• acute mastoiditis caused by the same organisms as AOM: S. pneumoniae, H. influenzae, M. catarrhalis, S. pyogenes, S. aureus, P. aeruginosa

Complications of AOM are rare due to rapid and effective treatment of AOM with antibiotics.
Clinical Features
- otorrhea
- tenderness to pressure over the mastoid
- retroauricular swelling with protruding ear
- fever, hearing loss, ± TM perforation (late)
- CT radiologic findings: opacification of mastoid air cells by fluid and interruption of normal trabeculations of cells (coalescence)

Treatment
- IV antibiotics with myringotomy and ventilation tubes – usually all that is required acutely
- cortical mastoidectomy:
  - debridement of infected tissue allowing aeration and drainage
- indications for surgery:
  - failure of medical treatment after 48 h
  - symptoms of intracranial complications
  - aural discharge persisting for 4 wk and resistant to antibiotics

Otosclerosis

Definition
- fusion of stapes footplate to oval window so that it cannot vibrate

Etiology
- autosomal dominant, variable penetrance approximately 40%
- female > male, progresses during pregnancy (hormone responsive)

Clinical Features
- progressive conductive hearing loss first noticed in teens and 20s (may progress to sensorineural hearing loss if cochlea involved)
- ± pulsatile tinnitus
- tympanic membrane normal ± pink blush (Schwartz's sign) associated with the neovascularization of otosclerotic bone
- characteristic dip at 2000 Hz (Carhart's notch) on audiogram (see Figure 16C, OT10)

Treatment
- monitor with serial audiograms if coping with loss
- hearing aid (air conduction, bone conduction, BAHA)
- stapedectomy or stapedotomy (with laser or drill) with prosthesis is definitive treatment

Diseases of the Inner Ear

Congenital Sensorineural Hearing Loss

Hereditary Defects
- non-syndrome associated (70%):
  - often idiopathic, autosomal recessive
  - connexin 26 (GJB2) most common
- syndrome associated (30%):
  - Waardenburg: white forelock, heterochromia iridis (each eye different color), wide nasal bridge and increased distance between medial canthi
  - Pendred: deafness associated with thyroid gland disorders, SLC26A4 gene, enlarged vestibular aqueducts
  - Treacher-Collins: first and second branchial cleft anomalies
  - Alport: hereditary nephritis

Prenatal TORCH Infections
- toxoplasmosis, rubella, CMV, herpes simplex, others (e.g. HIV, syphilis)

Perinatal
- Rh incompatibility
- anoxia
- hyperbilirubinemia
- birth trauma (hemorrhage into inner ear)

Postnatal
- meningitis, mumps, measles
High Risk Factors (for Hearing Loss in Newborns)
- low birth weight/prematurity
- perinatal anoxia (low APGARs)
- kernicterus: bilirubin >25 mg/dL
- craniofacial abnormality
- family history of deafness in childhood
- 1st trimester illness: TORCH infections
- neonatal sepsis
- ototoxic drugs
- perinatal infection, including post-natal meningitis
- consanguinity
- 50-75% of newborns with sensorineural hearing loss have at least one of the above risk factors, and 90% of these have spent time in the NICU
- presence of any risk factor: ABR study performed before leaving NICU and at 3 mo adjusted age
- early rehabilitation improves speech and school performance

Presbycusis

Definition
- sensorineural hearing loss associated with aging (starting in 5th and 6th decades)

Etiology
- hair cell degeneration
- age related degeneration of basilar membrane, possibly genetic etiology
- cochlear neuron damage
- ischemia of inner ear

Clinical Features
- progressive, bilateral hearing loss initially at high frequencies, then middle frequencies
- loss of discrimination of speech especially with background noise present - patients describe people as mumbling
- recruitment phenomenon: inability to tolerate loud sounds
- tinnitus

Treatment
- hearing aid if patient has difficulty functioning, hearing loss >30-35 dB, and good speech discrimination
- ± lip reading, auditory training, auditory aids (doorbell and phone lights)

Sudden Sensorineural Hearing Loss

Clinical Features
- presents as a sudden onset of significant SNHL (usually unilateral) ± tinnitus, aural fullness
- usually idiopathic, rule out other causes:
  - autoimmune causes (e.g. ESR, rheumatoid factor, ANA)
  - MRI to rule out tumour and/or CT to rule out ischemic/hemorrhagic stroke if associated with any other focal neurological signs (e.g. vertigo, ataxia, abnormality of CN V or VII, weakness)

Treatment
- oral corticosteroids within 3 d of onset: prednisone 1 mg/kg/d for 10-14 d

Prognosis
- depends on degree of hearing loss
- 70% resolve within 10 to 14 d
- 20% experience partial resolution
- 10% experience permanent hearing loss

Autoimmune Inner Ear Disease

Etiology
- idiopathic
- may be associated with systemic autoimmune diseases (i.e. rheumatoid arthritis, SLE), vasculitides (i.e. granulomatosis with polyangiitis, polyarteritis nodosa) and allergies

Epidemiology
- most common between ages 20-50
Clinical Features
• rapidly progressive or fluctuating bilateral SNHL
• ± tinnitus, aural fullness, vestibular symptoms (i.e. ataxia, disequilibrium, vertigo)

Investigations
• autoimmune work-up: CBC, ESR, ANA, rheumatoid factor

Treatment
• high-dose corticosteroids: treat early for at least 30 d
• consider cytotoxic medication for steroid non-responders

Drug Ototoxicity

Aminoglycosides
• streptomycin and gentamicin (vestibulotoxic), kanamycin and tobramycin (cochleotoxic)
• toxic to hair cells by any route: oral, IV, and topical (if the TM is perforated)
• destroys sensory hair cells: outer first, inner second (therefore otoacoustic emissions are lost first)
• high frequency hearing loss develops earliest
• ototoxicity occurs days to weeks post-treatment
• must monitor with peak and trough levels when prescribed, especially if patient has neutropenia and/or history of ear or renal problems
• q24h dosing recommended (with amount determined by creatinine clearance)
• aminoglycoside toxicity displays saturable kinetics therefore once daily dosing presents less risk than divided daily doses
• duration of treatment is the most important predictor of ototoxicity
• treatment: immediately stop aminoglycosides

Salicylates
• hearing loss with tinnitus, reversible if discontinued

Antimalarials (Quinines)
• hearing loss with tinnitus
• reversible if discontinued but can lead to permanent loss

Others
• many antineoplastic agents are ototoxic (weigh risks vs. benefits)
• loop diuretics

Noise-Induced Sensorineural Hearing Loss

Pathogenesis
• 85 to 90 dB over months or years or single sound impulses >135 dB can cause cochlear damage
• bilateral SNHL initially and most prominently at 4000 Hz (resonant frequency of the temporal bone), known as “boilermaker's notch” on audiogram, extends to higher and lower frequencies with time (see Figure 16D, OT10)
• speech reception not altered until hearing loss >30 dB at speech frequency, therefore considerable damage may occur before patient complains of hearing loss
• difficulty with speech discrimination, especially in situations with competing noise

Phases of Hearing Loss
• dependent on: intensity of sound and duration of exposure
• temporary threshold shift:
  ▪ when exposed to loud sound, decreased sensitivity or increased threshold for sound
  ▪ may have associated aural fullness and tinnitus
  ▪ with removal of noise, hearing returns to normal
• permanent threshold shift:
  ▪ hearing does not return to previous state

Treatment
• hearing aid
• prevention:
  ▪ ear protectors: muffs, plugs
  ▪ limit exposure to noise with frequent rest periods
  ▪ regular audiologic follow-up
Temporal Bone Fractures

Table 8. Features of Temporal Bone Fractures (see Figure 18)

<table>
<thead>
<tr>
<th>Extension</th>
<th>Transverse (1)</th>
<th>Longitudinal (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>10 to 20%</td>
<td>70 to 90%</td>
</tr>
<tr>
<td>Etiology</td>
<td>Frontal/occipital trauma</td>
<td>Lateral skull trauma</td>
</tr>
<tr>
<td>CN pathology</td>
<td>CN VII palsy (50%)</td>
<td>CN VII palsy (10 to 20%)</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>Sensorineural loss due to direct cochlear injury</td>
<td>Conductive hearing loss secondary to ossicular injury</td>
</tr>
<tr>
<td>Vestibular symptoms</td>
<td>Sudden onset vestibular symptoms due to direct semicircular canal injury (vertigo, spontaneous nystagmus)</td>
<td>Rare</td>
</tr>
<tr>
<td>Other features</td>
<td>Intact external auditory meatus, tympanic membrane ± hematotympanum</td>
<td>Torn tympanic membrane or hematotympanum</td>
</tr>
<tr>
<td></td>
<td>Spontaneous nystagmus</td>
<td>Bleeding from external auditory canal</td>
</tr>
<tr>
<td></td>
<td>CSF leak in Eustachian tube to nasopharynx ± rhinorrhea (risk of meningitis)</td>
<td>Step formation in external auditory canal</td>
</tr>
</tbody>
</table>

• characterized as longitudinal or transverse relative to the long axis of the petrous temporal bone
• rarely are temporal bone fractures purely transverse or longitudinal, often it is a mixed picture

Diagnosis
• otoscopy
• do not syringe or manipulate external auditory meatus due to risk of inducing meningitis via TM perforation
• CT head
• audiology, facial nerve tests (for transverse fractures), Schirmer’s test (of lacrimation), stapedial reflexes if CN VII palsy
• if suspecting CSF leak: look for halo sign, send fluid for β-2 transferrin

Treatment
• ABCs
• medical – expectant, prevent otogenic meningitis
• surgical – explore temporal bone, indications:
  • CN VII palsy (immediate and complete)
  • gunshot wound
  • depressed fracture of external auditory meatus
  • early meningitis (mastoidectomy)
  • bleeding intracranially from sinus
  • CSF otorrhea (may resolve spontaneously)

Complications
• acute otitis media ± labyrinthitis ± mastoiditis
• meningitis/epidural abscess/brain abscess
• post-traumatic cholesteatoma

Facial Nerve (CN VII) Paralysis

Etiology
• supranuclear and nuclear (MS, poliomyelitis, cerebral tumours)
• infranuclear (see Table 9)

Treatment
• treat according to etiology plus provide corneal protection with artificial tears, nocturnal lid taping, tarsorrhaphy, gold weighting of upper lid
• facial paralysis that does not resolve with time or with medical treatment will often be referred for possible reanimation techniques to restore function
  • common reanimation techniques include:
    • direct facial nerve anastomosis
    • interpositional grafts
    • anastomosis to other motor nerves
    • muscle transpositions

House-Brackmann Facial Nerve Grading System

Grade I: Normal facial motor function
Grade II: Mild dysfunction
  • Slight weakness
  • Normal symmetry and tone at rest
  • Complete eye closure
Grade III: Moderate dysfunction
  • Obvious weakness
  • Incomplete eye closure
  • No forehead motion
  • Mouth asymmetric motion
Grade IV: Moderately severe dysfunction
  • Obvious weakness
  • Disfiguring asymmetry
  • No forehead motion
Grade V: Severe dysfunction
  • Barely perceptible motion of mouth
  • Asymmetric at rest
Grade VI: Total paralysis
  • No movement
<table>
<thead>
<tr>
<th>Etiology</th>
<th>Incidence</th>
<th>Findings</th>
<th>Investigations</th>
<th>Treatment, Follow-up, and Prognosis (Px)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell’s Palsy</td>
<td>80 to 90%</td>
<td>Hx: Acute onset, Numbness of ear, Schirmer’s test, Recurrence (12%), + Hfx (14%), Hyperacusis (30%)</td>
<td>Stapedial reflex absent, Audiology normal (or baseline)</td>
<td>Rx: Protect the eye to prevent exposure keratitis with patching or tarsorrhaphy Systemic steroids may lessen degeneration and hasten recovery Consider antiviral (acyclovir)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P/E: Paralysis or paresis of all muscle groups on one side of the face, Absence of signs of CNS disease, Absence of signs of ear or CPA diseases</td>
<td>EMG – best measure for prognosis Topognostic testing MRI with gadolinium – enhancement of CN VII and VIII High resolution CT</td>
<td>F/U: Spontaneous remission should begin within 3 wk of onset Delayed (3 to 6 mo) recovery portends at least some functional loss PxF: 90% recover spontaneously and completely overall; &gt;90% recovery if paralysis was incomplete Poorer if hyperacusis, &gt;60 yr, diabetes, HTN, severe pain</td>
</tr>
<tr>
<td>Ramsay-Hunt Syndrome (Herpes Zoster Oticus) Varicella zoster infection of CN VII/VIII</td>
<td>4.5 to 9%</td>
<td>Hx: Hyperacusis, SNHL, Severe pain of pinna, mouth, or face P/E: Vesicles on pinna, ext. canal (erupt 3-7 d after onset of pain) Associated herpes zoster ophthalmicus (uvitis, keratoconjunctivitis, optic neuritis, or glaucoma)</td>
<td>Stapedial reflex absent, Audiology – SNHL Viral ELISA studies to confirm MRI with gadolinium (86% of facial nerves enhance)</td>
<td>Rx: Pt. should avoid touching lesions to prevent spread of infection Systemic steroids can relieve pain, vertigo, avoid postherpetic neuralgia Acyclovir may lessen pain, aid healing of vesicles F/U: 2 to 4 wk PxF: Poorer prognosis than Bell’s palsy; 22% recover completely, 66% incomplete paralysis, 10% complete paralysis</td>
</tr>
<tr>
<td>TEMPORAL BONE FRACTURE</td>
<td></td>
<td>Hx: Blow to side of head P/E: Trauma to side of head Neuro findings consistent with epidural/subdural bleed</td>
<td>Skull X-rays CT head</td>
<td>Px: Injury usually due to stretch or impingement; may recover with time</td>
</tr>
<tr>
<td>Longitudinal (90%)</td>
<td>20% have PFP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transverse (10%)</td>
<td>40% have PFP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Introgenic</td>
<td>Variable (depending on level of injury)</td>
<td></td>
<td>Wait for lidocaine to wear off EMG</td>
<td>Rx: Exploration if complete nerve paralysis No exploration if any movement present</td>
</tr>
<tr>
<td>Source: Paul Warrick, MD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Rhinitis**

**Definition**
- Inflammation of the lining (mucosa) of the nasal cavity

**Table 10. Classification of Rhinitis**

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Non-Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perennial non-allergic</td>
<td>Rhinitis medicamentosa</td>
</tr>
<tr>
<td>Asthma, ASA sensitivity</td>
<td>Topical decongestants</td>
</tr>
<tr>
<td>Allergic</td>
<td>Hormonal</td>
</tr>
<tr>
<td>Seasonal</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Perennial</td>
<td>Estrogens</td>
</tr>
<tr>
<td>Atrophic</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Primary: Klebsiella ozena (especially in elderly)</td>
<td>Idiopathic vasoconstrictor</td>
</tr>
<tr>
<td>Acquired: post-surgery if too much mucosa or turbinate has been resected</td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td>Viral: e.g. rhinovirus, influenza, para influenza, etc.</td>
<td></td>
</tr>
<tr>
<td>Bacterial: e.g. S. aureus</td>
<td></td>
</tr>
<tr>
<td>Fungal</td>
<td></td>
</tr>
<tr>
<td>Granulomatous: TB, syphilis, leprosy</td>
<td></td>
</tr>
<tr>
<td>Non-infectious</td>
<td></td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td></td>
</tr>
<tr>
<td>Granulomatosis with polyangiitis</td>
<td></td>
</tr>
<tr>
<td>Irritant</td>
<td></td>
</tr>
<tr>
<td>Dust</td>
<td></td>
</tr>
<tr>
<td>Chemicals</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
</tr>
</tbody>
</table>

**Rhinitis medicamentosa:** Rebound congestion due to the overuse of intranasal vasoconstrictors. For prevention, use of these medications for only 5-7 d is recommended.
Table 11. Nasal Discharge: Character and Associated Conditions

<table>
<thead>
<tr>
<th>Character</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watery/mucoid</td>
<td>Allergic, viral, vasomotor, CSF leak (halo sign)</td>
</tr>
<tr>
<td>Mucopurulent</td>
<td>Bacterial, foreign body</td>
</tr>
<tr>
<td>Serosanguinous</td>
<td>Neoplasia</td>
</tr>
<tr>
<td>Bloody</td>
<td>Trauma, neoplasia, bleeding disorder, hypertension/vascular disease</td>
</tr>
</tbody>
</table>

**Allergic Rhinitis (Hay Fever)**

**Definition**
- rhinitis characterized by an IgE-mediated hypersensitivity to foreign allergens
- acute-and-seasonal or chronic-and-perennial
- perennial allergic rhinitis often confused with recurrent colds

**Etiology**
- when allergens contact the respiratory mucosa, specific IgE antibody is produced in susceptible hosts
- concentration of allergen in the ambient air correlates directly with the rhinitis symptoms

**Epidemiology**
- age at onset usually <20 yr
- more common in those with a personal or family history of allergies/atopy

**Clinical Features**
- nasal: obstruction with pruritus, sneezing
- clear rhinorrhea (containing increased eosinophils)
- itching of eyes with tearing
- frontal headache and pressure
- mucosa: swollen, pale, “boggy”
- seasonal (summer, spring, early autumn)
  - pollens from trees
  - lasts several weeks, disappears and recurs following year at same time
- perennial
  - inhaled: house dust, wool, feathers, foods, tobacco, hair, mould
  - ingested: wheat, eggs, milk, nuts
  - occurs intermittently for years with no pattern or may be constantly present

**Complications**
- chronic sinusitis/polyps
- serous otitis media

**Diagnosis**
- history
- direct exam
- allergy testing

**Treatment**
- education: identification and avoidance of allergen
- nasal irrigation with saline
- antihistamines (e.g. diphenhydramine, fexofenadine)
- oral decongestants (e.g. pseudoephedrine, phenylpropanolamine)
- topical decongestant (may lead to rhinitis medicamentosa)
- other topicals: steroids (fluticasone), disodium cromoglycate, antihistamines, ipratropium bromide
- oral steroids if severe
- desensitization by allergen immunotherapy
Vasomotor Rhinitis

- neurovascular disorder of nasal parasympathetic system (vidian nerve) affecting mucosal blood vessels
- nonspecific reflex hypersensitivity of nasal mucosa
- caused by:
  - temperature change
  - alcohol, dust, smoke
  - stress, anxiety, neurosis
  - endocrine: hypothyroidism, pregnancy, menopause
  - parasympathomimetic drugs
- beware of rhinitis medicamentosa: reactive vasodilation due to prolonged use (>5 d) of nasal drops and sprays (Dristan®, Otrivin®)

Clinical Features
- chronic intermittent nasal obstruction, varies from side to side
- rhinorrhea: thin, watery
- mucosa and turbinates: swollen
- nasal allergy must be ruled out

Treatment
- elimination of irritant factors
- parasympathetic blocker (Atrovent® nasal spray)
- steroids (e.g. beclomethasone, fluticasone)
- surgery (often of limited lasting benefit): electrocautery, cryosurgery, laser treatment or removal of inferior or middle turbinates
- vidian neurectomy (rarely done)
- symptomatic relief with exercise (increased sympathetic tone)

Rhinosinusitis

Pathogenesis of Rhinosinusitis
- ostial obstruction or dysfunctional cilia permit stagnant mucous and consequently infection
- all sinuses drain to a common prechamber under the middle meatus called the osteomeatal complex

Definition
- inflammation of the mucosal lining of the sinuses and nasal passages

Classification
- acute: <4 wk
- subacute: 4-8 wk
- chronic: >8-12 wk

Table 12. Etiologies of Rhinosinusitis

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Inflammation</th>
<th>Mechanical</th>
<th>Immune</th>
<th>Systemic</th>
<th>Direct extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ostial obstruction</td>
<td>URTI</td>
<td>Septal deviation</td>
<td>Granulomatosis with polyangitis</td>
<td>Cystic fibrosis</td>
<td>Dental</td>
</tr>
<tr>
<td></td>
<td>Allergy</td>
<td>Turbinate hypertrophy</td>
<td>Lymphoma, leukemia</td>
<td>Immotile cilia (e.g. Kartagener’s)</td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polyps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adenoid hypertrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Foreign body</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital abnormalities (e.g. cleft palate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Acute Bacterial Rhinosinusitis**

**Definition**
- bacterial infection of the paranasal sinuses and nasal passages lasting >7 d
- clinical diagnosis requiring ≥2 major symptoms, at least one of the symptoms is either nasal obstruction or purulent/dischcoloured nasal discharge

- **major symptoms**
  - facial pain/pressure/fullness
  - nasal obstruction
  - purulent/discoloured nasal discharge
  - hyposmia/anosmia

- **minor symptoms**
  - headache
  - halitosis
  - fatigue
  - dental pain
  - cough
  - ear pain/fullness

**Etiology**
- bacteria: *S. pneumoniae* (35%), *H. influenzae* (35%), *M. catarrhalis*, *S. aureus*, anaerobes (dental)
- children are more prone to a bacterial etiology, but viral is still more common
- maxillary sinus most commonly affected
- must rule out fungal causes (mucormycosis) in immunocompromised hosts (especially if painless, black or pale mucosa on examination)

**Clinical Features**
- sudden onset of
  - nasal blockage/congestion and/or purulent nasal discharge/posterior nasal drip
  - ± facial pain or pressure, hyposmia, sore throat
- persistent/worsening symptoms >5 to 7 d or presence of purulence for 3 to 4 d with high fever
- speculum exam: erythematous mucosa, mucopurulent discharge, pus originating from the middle meatus
- predisposing factors: viral URTI, allergy, dental disease, anatomical defects
- differentiate from acute viral rhinosinusitis (course: <10 d, peaks by 3 d)

**Management**
- depends on symptom severity (i.e. intensity/duration of symptoms, impact on quality of life)
- mild-moderate: INCS
  - if no response within 72 h, add antibiotics
- severe: INCS + antibiotics
- antibiotics:
  - 1st line: amoxicillin x 10 d (TMP-SMX or macrolide if penicillin allergy)
  - if no response to 1st line antibiotics within 72 h, switch to 2nd line
  - 2nd line: fluoroquinolones or amoxicillin-clavulanic acid inhibitors
- adjuvant therapy (saline irrigation, analgesics, oral/topical decongestant) may provide symptomatic relief
- CT indicated only if complications are suspected

**Chronic Rhinosinusitis**

**Definition**
- inflammation of the mucosa of paranasal sinuses and nasal passages >8 to 12 wk
- diagnosis requiring ≥2 major symptoms for >8 to 12 wk and ≥1 objective finding of inflammation of the paranasal sinuses (CT/endoscopy)

**Etiology**
- unclear etiology but the following may contribute or predispose:
  - inadequate treatment of acute rhinosinusitis
  - bacterial colonization/biofilms
    - *S. aureus*, *enterobacteriaeae*, *pseudomonas*, *S. pneumoniae*, *H. influenzae*, β-hemolytic streptococci
  - fungal infection (e.g. *Aspergillus*, *Zygomycetes*, *Candida*)
  - anatomic abnormality (e.g. lost ostia patency, deviated septum – predisposing factors)
  - allergy/allergic rhinitis
  - ciliary disorder (e.g. cystic fibrosis, Kartenger’s)
  - chronic inflammatory disorder (e.g. granulomatosis with polyangiitis)
  - untreated dental disease

**Acute Rhinosinusitis Complications**
Consider hospitalization if any of the following are suspected
- Orbital (Chandler’s classification)
  - Periorbital cellulitis
  - Orbital cellulitis
  - Subperiosteal abscess
  - Orbital abscess
  - cavernous sinus thrombosis
- Intracranial
  - Meningitis
  - Abscess
- Bony
  - Subperiosteal frontal bone abscess (“Pott’s Puffy tumour”)
  - Osteomyelitis
- Neurologic
  - Superior orbital fissure syndrome (CN III/IV/VI palsy, immobile globe, dilated pupils, ptosis, V1 hypesthesia)
  - Orbital apex syndrome (as above, plus neuritis, papilledema, decreased visual acuity)

**FESS = Functional Endoscopic Sinus Surgery**
Opening of the entire osteomeatal complex in order to facilitate drainage while sparing the sinus mucosa.

**Allergic fungal rhinosinusitis** is a chronic sinusitis affecting mostly young, immunocompetent, atopic individuals. Treatment options include FESS ± intranasal topical steroids, antifungals, and immunotherapy.
Clinical Features (similar to acute, but less severe)
- chronic nasal obstruction
- purulent anterior/posterior nasal discharge
- facial congestion/fullness
- facial pain/pressure
- hyposmia/anosmia
- halitosis
- chronic cough
- maxillary dental pain

Management
- identify and address contributing or predisposing factors
- obtain CT or perform endoscopy
- if polyps present: INCS, oral steroids ± antibiotics (if signs of infection), refer to Otolaryngologist/Head and Neck Surgeon
- if polyps absent: INCS, antibiotics, saline irrigation, oral steroids (severe cases)
- antibiotics for 3 to 6 wk
  - amoxillin-clavulanic acid inhibitors, fluoroquinolone (moxifloxacin), macrolide (clarithromycin), clindamycin, Flagyl® (metronidazole)
- surgery if medical therapy fails or fungal sinusitis: FESS, balloon sinoplasty

Complications
- same as acute sinusitis, mucocele

Epistaxis

Blood Supply to the Nasal Septum (see Figure 4, OT3)
1. Superior posterior septum:
   - internal carotid → ophthalmic → anterior/posterior ethmoidal
2. Posterior septum:
   - external carotid → internal maxillary → sphenopalatine artery → nasopalatine
3. Lower anterior septum:
   - external carotid → facial artery → superior labial artery → nasal branch
   - external carotid → internal maxillary → descending palatine → greater palatine
- these arteries all Anastomose to form Kiesselbach's plexus, located at Little's area (anterior-inferior portion of the cartilaginous septum)
- bleeding from above middle turbinate is internal carotid, and from below is external carotid

Table 13. Etiology of Epistaxis

<table>
<thead>
<tr>
<th>Type</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>Tumours: polyps, inverting papilloma, angiofibroma</td>
</tr>
<tr>
<td></td>
<td>Malignant: squamous cell carcinoma, esthesioneuroblastoma</td>
</tr>
<tr>
<td></td>
<td>Inflammation: Rhinitis: allergic, non-allergic</td>
</tr>
<tr>
<td></td>
<td>Infecions: bacterial, viral, fungal</td>
</tr>
<tr>
<td>Barometric changes</td>
<td></td>
</tr>
<tr>
<td>Nasal dryness: dry air ± septal deformities</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Septal perforation</td>
<td></td>
</tr>
<tr>
<td>Chemical: cocaine, nasal sprays, ammonia, etc.</td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>Coagulopathies:</td>
</tr>
<tr>
<td></td>
<td>• Meds: anticoagulants, NSAIDs</td>
</tr>
<tr>
<td></td>
<td>• Hemophilia, von Willebrand's</td>
</tr>
<tr>
<td></td>
<td>• Hematological malignancies</td>
</tr>
<tr>
<td></td>
<td>• Liver failure, uremia</td>
</tr>
<tr>
<td>Vascular: hypertension, atherosclerosis, Osler-Weber-Rendu (hereditary hemorrhagic telangectasia)</td>
<td></td>
</tr>
<tr>
<td>Others: GPA, SLE</td>
<td></td>
</tr>
</tbody>
</table>

Special Cases
- Adolescent male with unilateral recurrent epistaxis – consider juvenile nasopharyngeal angiofibroma (JNA). This is the most common benign tumour of the nasopharynx
- Thrombocytopenic patients – use resorbable packs to avoid risk of re-bleeding caused by pulling out the removable pack

Investigations
- CBC, PT/PTT (if indicated)
- x-ray, CT as needed

Treatment
- locate bleeding and achieve hemostasis

1. ABCs
- patient leans forward to minimize swallowing blood and avoid airway obstruction
- apply constant firm pressure for 20 min on cartilaginous part of nose (not bony pyramid)
- if significant bleeding, assess vitals for signs of hemorrhagic shock ± IV NS, cross match blood
2. Determine Site of Bleeding
- anterior/posterior hemorrhage defined by location in relationship to bony septum
- visualize nasal cavity with speculum
- use cotton pledget with topical lidocaine ± topical decongestant (i.e. Otrivin®) to help identify area of bleeding (often anterior septum)
- if suspicion of bleeding disorder, coagulation workup (platelet number and platelet function assay)

3. Control the Bleeding
- first line topical vasoconstrictors (Otrivin®)
- if first line fails and bleeding adequately visualized, cauterize with silver nitrate
- **do not cauterize both sides of the septum** at one time due to risk of septal perforation from loss of septal blood supply

   A. Anterior hemorrhage treatment
   - if fail to achieve hemostasis with cauterization:
     - place anterior pack* with half inch Vaseline®-soaked ribbon gauze strips layered from nasal floor toward nasal roof extending to posterior choanae or lubricated absorbable packing (i.e. Gelfoam wrapped in Surgicel®) for 2 to 3 d
     - can also attempt packing with Merocel® or nasal tampons of different shapes
     - can also apply Floseal® (hemostatic matrix consisting of topical human thrombin and cross-linked gelatin) if other methods fail

   B. Posterior hemorrhage treatment
   - if unable to visualize bleeding source, then usually posterior source:
     - place posterior pack* using a Foley catheter, gauze pack, or Epistat® balloon
     - subsequently, layer anterior packing bilaterally
     - admit to hospital with packs in for 3 to 5 d
     - watch for complications: hypoxemia (naso-pulmonic reflex), toxic shock syndrome (Rx: remove packs immediately), pharyngeal fibrosis/stenosis, alar/septal necrosis, aspiration

   C. If anterior/posterior packs fail to control epistaxis
   - ligation or embolization of culprit arterial supply by interventional radiology
   - ± septoplasty

* antibiotics for any posterior pack or any pack left for >48 h because of risk of toxic shock syndrome

4. Prevention
- prevent drying of nasal mucosa with humidifiers, saline spray, or topical ointments
- avoidance of irritants
- medical management of hypertension and coagulopathies

---

**Hoarseness**

**Definitions**
- hoarseness: change in voice quality, ranging from voice harshness to voice weakness. Reflects abnormalities anywhere along the vocal tract from oral cavity to lungs
- dysphonia: a general alteration in voice quality
- aphonia: no sound emanates from vocal folds

**Acute Laryngitis**

**Definition**
- <2 wk inflammatory changes in laryngeal mucosa

**Etiology**
- viral: influenza, adenovirus
- bacterial: Group A Streptococcus
- mechanical acute voice strain ✄ submucosal hemorrhage ✄ vocal cord edema ✄ hoarseness
- environmental: toxic fume inhalation

**Clinical Features**
- URTI symptoms, hoarseness, aphony, cough attacks, ± dyspnea
- true vocal cords erythematous/edematous with vascular injection and normal mobility

**Treatment**
- usually self-limited, resolves within ~1 wk
- voice rest
- humidification
- hydration
- avoid irritants (e.g. smoking)
- treat with antibiotics if there is evidence of coexistent bacterial pharyngitis

If hoarseness present for > 2 wk in a smoker, laryngoscopy must be done to rule out malignancy.

**Vocal Cord Paralysis**

Unilateral: affected cord lies in the parmedian position, inadequate glottic closure during phonation → weak, breathy voice. Usually medializes with time whereby phonation and aspiration improve. Treatment options include voice therapy, injection laryngoplasty (Radiesse), medialization using silastic block.

Bilateral: cords rest in midline therefore voice remains good but respiratory function is compromised and may present as stridor. If no respiratory issues, may monitor closely and wait for improvement. If respiratory issues, intubate and will likely require a tracheotomy.
Chronic Laryngitis

Definition
• >2 wk inflammatory changes in laryngeal mucosa

Etiology
• repeated attacks of acute laryngitis
• chronic irritants (dust, smoke, chemical fumes)
• chronic voice strain
• chronic rhinosinusitis with postnasal drip
• chronic alcohol use
• esophageal disorders: GERD, Zenker's diverticulum, hiatus hernia
• systemic: allergy, hypothyroidism, Addison's disease

Clinical Features
• chronic dysphonia: rule out malignancy
• cough, globus sensation, frequent throat clearing 2º to GERD
• laryngoscopy: cords erythematous, thickened with ulceration/granuloma formation, and normal mobility

Treatment
• remove offending irritants
• treat related disorders (e.g. antisecretory therapy for GERD)
• speech therapy with voice rest
• ± antibiotics ± steroids to decrease inflammation
• laryngoscopy to rule out malignancy

Vocal Cord Polyps

Definition
• structural manifestation of vocal cord irritation
• acutely, polyp forms 2º to capillary damage in the subepithelial space during extreme voice exertion

Etiology
• most common benign tumour of vocal cords
• voice strain (muscle tension dysphonia)
• laryngeal irritants (GERD, allergies, tobacco)

Epidemiology
• 30 to 50 yr of age
• M>F

Clinical Features
• hoarseness, aphony, cough attacks ± dyspnea
• pedicled or sessile polyp on free edge of vocal cord
• typically polyp asymmetrical, soft, and smooth
• more common on the anterior 1/3 of the vocal cord
• intermittent respiratory distress with large polyps

Treatment
• avoid irritants
• endoscopic laryngeal microsurgical removal if persistent or if high risk of malignancy

Vocal Cord Nodules

Definition
• vocal cord callus
• aka “screamer's or singer's nodules”

Etiology
• early nodules occur 2º to submucosal hemorrhage
• mature nodules result from hyalinization which occurs with long term voice abuse
• chronic voice strain
• frequent URTI, smoke, alcohol
Epidemiology
- frequently in singers, children, bartenders, and school teachers
- F>M

Clinical Features
- hoarseness worst at end of day
- on laryngoscopy:
  - often bilateral
  - at the junction of the anterior 1/3 and posterior 2/3 of the vocal cords – point of maximal cord vibration
- chronic nodules may become fibrotic, hard, and white

Treatment
- voice rest
- hydration
- speech therapy
- avoid irritants
- surgery rarely indicated for refractory nodules

Benign Laryngeal Papillomas

Etiology
- HPV types 6, 11
- possible hormonal influence, possibly acquired during delivery

Epidemiology
- biphasic distribution: 1) birth to puberty (most common laryngeal tumour) and 2) adulthood

Clinical Features
- hoarseness and airway obstruction
- can seed into tracheobronchial tree
- highly resistant to complete removal
- some juvenile papillomas resolve spontaneously at puberty
- may undergo malignant transformation
- laryngoscopy shows wart-like lesions in supraglottic larynx and trachea

Treatment
- microdebridement or CO₂ laser
- adjuvants under investigation: interferon, cidofovir, acyclovir
- HPV vaccine may prevent/decrease the incidence but more research is needed

Laryngeal Carcinoma

- see Neoplasms of the Head and Neck, OT34

Salivary Glands

Sialadenitis

Definition
- inflammation of salivary glands

Etiology
- viral most common (mumps)
- bacterial causes: S. aureus, S. pneumoniae, H. influenzae
- obstructive vs. non-obstructive
- obstructive infection involves salivary stasis and bacterial retrograde flow

Predisposing Factors
- HIV
- anorexia/bulimia
- Sjögren's syndrome
- Cushing’s, hypothyroidism, DM
- hepatic/renal failure
- meds that increase stasis: diuretics, TCAs, β-blockers, anticholinergics, antibiotics
- sialolithiasis (can cause chronic sialadenitis)
Clinical Features
- acute onset of pain and edema of parotid or submandibular gland that may lead to marked swelling
- ± fever
- ± leukocytosis
- ± suppurative drainage from punctum of the gland

Investigations
- U/S imaging to differentiate obstructive vs. non-obstructive sialadenitis

Treatment
- bacterial: treat with cloxacillin ± abscess drainage, sialogogues
- viral: no treatment

Sialolithiasis

Definition
- ductal stone (mainly hydroxyapatite) in adults, sand/sludge in children, leading to chronic sialadenitis
- 80% in submandibular gland, <20% in parotid gland, ~1% in sublingual gland

Risk Factors
- any condition causing duct stenosis or a change in salivary secretions (e.g. dehydration, diabetes, EtOH, hypercalcemia, psychiatric medication)

Clinical Features
- pain and tenderness over involved gland
- intermittent swelling related to meals
- digital palpation reveals presence of calculus

Investigations
- ultrasound ± sialogram

Treatment
- may resolve spontaneously
- encourage salivation to clear calculus
- massage, analgesia, antibiotics, sialogogues (e.g. lemon wedges, sour lemon candies), warm compresses
- remove calculi endoscopically, by dilating duct or orifice, or by excision through floor of the mouth
- if calculus is within the gland parenchyma, the whole gland must be excised

Salivary Gland Neoplasms

Etiology
- anatomic distribution
  - parotid gland: 70-85%
  - submandibular gland: 8-15%
  - sublingual gland: 1%
  - minor salivary glands, most concentrated in hard palate: 5-8%
- malignant (see Table 15, OT35 and Table 16, OT36)
- benign
  - benign mixed (pleomorphic adenoma): 80%
  - Warthin's tumour (5 to 10% bilateral, M>F): 10%
  - cysts, lymph nodes and adenomas: 10%
  - oncocytoma: <1%

Epidemiology
- 3 to 6% of all head and neck neoplasms in adults
- mean age at presentation: 55 to 65
- M=F
Parotid Gland Neoplasms

Clinical Features
- 80% benign (pleomorphic adenoma – most common), 20% malignant (mucoepidermoid – most common)
- painless slow-growing mass
- if bilateral, suggests benign process (Warthin’s tumour, Sjögren’s, bulimia, mumps) or possible lymphoma

Investigations
- FNA biopsy
- CT or MRI to determine extent of tumour

Treatment
- treatment of choice is surgery for all salivary gland neoplasms – benign and malignant
- pleomorphic adenomas are excised due to risk of malignant transformation (5% risk over prolonged period of time)
  - superficial tumour
    - superficial parotidectomy above plane of CN VII ± radiation
    - incisional biopsy contraindicated
  - deep lesion
    - near-total parotidectomy sparing as much of CN VII as possible
    - if CN VII involved then it is removed and cable grafted
- complications of parotid surgery
  - hematoma, infection, salivary fistula, temporary facial paresis, Frey’s syndrome (gustatory sweating)

Prognosis
- benign: excellent, <5% of pleomorphic adenomas may recur
- malignant: dependent on stage and type of malignancy (see OT36)

Neck Masses

Approach to a Neck Mass

- ensure that the neck mass is not a normal neck structure (hyoid, transverse process of C1 vertebra, prominent carotid bulb)
- any neck mass persisting for more than 2 wk should be investigated for possible neoplastic causes

Table 14. Acquired Causes of Neck Lumps According to Age

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Possible Causes of Neck Lump</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-40</td>
<td>1. Inflammatory 2. Congenital 3. Neoplastic</td>
</tr>
<tr>
<td>&gt;40</td>
<td>1. Neoplastic 2. Inflammatory 3. Congenital</td>
</tr>
</tbody>
</table>

Differential Diagnosis
- congenital
  - lateral (branchial cleft cyst, lymphatic/venous/venolymphatic malformation)
  - midline (thyroglossal duct cyst, dermoid cyst, laryngocele)
- infectious/inflammatory
  - reactive lymphadenopathy (2nd to tonsillitis, pharyngitis)
  - infectious mononucleosis
  - Kawasaki, Kikuchi, Kimura
  - HIV
  - salivary gland calculi, sialadenitis
  - thyroiditis
- granulomatous disease
  - mycobacterial infections
  - sarcoidosis
- neoplastic
  - lymphoma
  - salivary gland tumours
  - thyroid tumours
  - metastatic malignancy (“unknown primary”)
## Evaluation

### Investigations
- history and physical (including nasopharynx and larynx)
- all other investigations and imaging are dependent upon clinical suspicion following history and physical
- laboratory investigations
  - WBC: infection vs. lymphoma
  - Mantoux TB test
  - thyroid function tests and scan
- imaging
  - neck U/S
  - CT scan
  - angiography: vascularity and blood supply to mass
  - radiologic exam of stomach, bowel and sinuses
- biopsy: for histologic examination
  - FNA: least invasive
  - needle biopsy
  - open biopsy: for lymphoma
- identification of possible primary tumour (rule out a metastatic lymph node from an “unknown primary”)
  - panendoscopy: nasopharyngoscopy, laryngoscopy, esophagoscopy, bronchoscopy with washings, and biopsy of suspicious lesions
  - biopsy of normal tissue of nasopharynx, tonsils, base of tongue, and hypopharynx
  - primary identified 95% of time → stage and treat
  - primary occult 5% of time: excisional biopsy of node for histologic diagnosis → manage with radiotherapy and/or neck dissection (squamous cell carcinoma)

## Congenital Neck Masses

### Branchial Cleft Cysts/Fistula

#### Embryology
- at the 6th week of development, the 2nd branchial arch grows over the 3rd and 4th arches and fuses with the neighbouring caudal pre-cardial swelling forming the cervical sinus
- 3 types of malformations:
  1. branchial fistula: persistent communication between skin and GI tract
  2. branchial sinus: blind-ended tract opening to skin
  3. branchial cyst: persistent cervical sinus with no external opening

#### Clinical Features
- 2nd branchial cleft malformations most common
  - sinuses and fistulae present in infancy as a small opening anterior to the sternocleidomastoid muscle
  - cysts present as a smooth, painless, slowly enlarging lateral neck mass, often following an URTI
- 1st branchial cleft malformations present as sinus/fistula or cyst in preauricular area or over angle of mandible
- 3rd branchial cleft malformations present as recurrent thyroiditis or thyroid abscess and have a tract leading usually to the left pyriform sinus
- there is controversy whether or not 4th branchial cleft anomalies exist, as they may be remnants of the thyrothymic axis

#### Treatment
- surgical removal of cyst or fistula tract
- if infected: allow infection to settle before removal
Thyroglossal Duct Cysts

Embryology
- thyroid originates as ventral midline diverticulum at base of tongue caudal to junction of 3rd and 4th branchial arches (foramen cecum) and migrates down to inferior aspect of neck
- thyroglossal duct cysts are vestigial remnants of tract

Clinical Features
- usually presents in childhood or 2nd to 4th decades as a midline cyst that enlarges with URTI and elevates with swallowing and tongue protrusion

Treatment
- pre-operative antibiotics to reduce inflammation
- small potential for neoplastic transformation so complete excision of cyst and tissue around tract up to foramen cecum at base of tongue with removal of central portion of hyoid bone (Sistrunk procedure) recommended
**Lymphatic Malformation**

**Definition**
- lymphatic malformation arising from vestigial lymph channels of neck

**Clinical Features**
- usually present by age 2
- can be macrocystic (composed of large thin-walled cysts, usually below level of mylohyoid muscle) or microcystic (composed of minute cysts, usually above level of mylohyoid muscle)
- usually painless, soft, compressible
- infection causes a sudden increase in size

**Treatment**
- can regress spontaneously after bacterial infection, therefore do not plan surgical intervention until several months after infection
- macrocystic lesions can be treated by sclerotherapy or surgical excision
- microcystic lesions are difficult to treat, but can be debulked

---

**Neoplasms of the Head and Neck**

**Pre-Malignant Disease**
- leukoplakia
  - hyperkeratosis
  - risk of malignant transformation 5 to 20%
- erythroplakia
  - red superficial patches adjacent to normal mucosa
  - commonly associated with epithelial dysplasia
  - associated with carcinoma in situ or invasive tumour in 40% of cases
- dysplasia
  - histopathologic presence of mitoses and prominent nucleoli
  - involvement of entire mucosal thickness = carcinoma in situ
  - associated progression to invasive cancer in 15 to 30% of cases

**Investigations**
- initial metastatic screen includes chest x-ray
- scans of liver, brain, and bone only if clinically indicated
- CT scan is superior to MRI for the detection of pathologic nodal disease and bone cortex invasion
- MRI is superior to discriminate tumour from mucus and to detect bone marrow invasion
- ± PET scans

**Treatment**
- treatment depends on:
  - histologic grade of tumour
  - stage
  - physical and psychological health of patient
  - facilities available
  - expertise and experience of the medical and surgical oncology team
- in general:
  - 1st surgery for malignant oral cavity tumours with radiotherapy reserved for salvage or poor prognostic indicators
  - 1st radiotherapy for nasopharynx, oropharynx, hypopharynx, larynx malignancies with surgery reserved for salvage
  - palliative chemotherapy for metastatic or incurable disease
  - concomitant chemotherapy increases survival in advanced disease
  - chemotherapy has a role as induction therapy prior to surgery and radiation
  - panendoscopy to detect primary disease when lymph node metastasis is identified
  - anti-EGFR treatment (ceftumab, panitumumab) has a role as concurrent therapy with radiation (for advanced local and regional disease)

**Prognosis**
- synchronous tumours occur in 9 to 15% of patients
- late development of 2nd primary most common cause of post-treatment failure after 36 mo
### Table 15. Quick Look-Up Summary of Head and Neck Malignancies – Etiology and Epidemiology

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Epidemiology</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Cavity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% SCC</td>
<td>Mean age: 50 to 60</td>
<td>Smoking/EtOH</td>
</tr>
<tr>
<td>others: sarcoma, melanoma, minor salivary gland tumour</td>
<td>M:F</td>
<td>Poor oral hygiene</td>
</tr>
<tr>
<td></td>
<td>Most common site of H&amp;N cancers</td>
<td>Leukoplakia, erythroplakia</td>
</tr>
<tr>
<td></td>
<td>50% on anterior 2/3 of tongue</td>
<td>Lichen planus, chronic inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sun exposure – lip</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HPV infection</td>
</tr>
</tbody>
</table>

| **Nose and Paranasal Sinus** | | |
| 75 to 80% SCC | Mean age: 50 to 70 | Wood/shoe/textile industry |
| Adenocarcinoma (2nd most common) and mucoepidermoid | Rare tumours | Hardwood dust (nasal/ethmoid sinus) |
| 99% in maxillary/ethmoid sinus | ↓ incidence in last 5 to 10 yr | Nickel, chromium (maxillary sinus) |
| 10% arise from minor salivary glands | | Air pollution |
| | | Chronic rhinosinusitis |

| **Carcinoma of the Pharynx – Subtypes (Nasopharynx, Oropharynx, Hypopharynx and Larynx)** | | |
| Nasopharynx | | |
| 90% SCC | Mean age: 50 to 59 | Epstein-Barr virus (EBV) |
| ~10% lymphoma | M:F = 2:4:1 | Salted fish |
| | Incidence 0.8 per 100,000 | Nickel exposure |
| | 100x increased incidence in Southern Chinese | Poor oral hygiene |
| | | Genetic – Southern Chinese |

| Oropharynx | Mean age: 50 to 70 | Smoking/EtOH |
| 95% SCC – poorly differentiated | M:F = 4:1 | HPV Infection |
| | | |

| Hypopharynx | | |
| 95% SCC | Mean age: 50 to 70 | Smoking/EtOH |
| 3 sites: | M:F | HPV infection strongly associated with the risk of laryngeal squamous cell cancers (Li et al., 2013) |
| 1. pyriform sinus (60%) | | |
| 2. post-cricoid (30%) | | |
| 3. post pharyngeal wall (10%) | | |

| Larynx | Mean age: 45 to 75 | Smoking/EtOH |
| SCC most common | M:F = 10:1 | HPV 16 infection strongly associated with the risk of laryngeal squamous cell cancers (Li et al., 2013) |
| 3 sites: | | |
| 1. supraglottic (30 to 35%) | | |
| 2. glottic (60 to 65%) | | |
| 3. subglottic (1%) | | |

| Salivary Gland | Mean age: 55 to 65 | |
| 40% mucoepidermoid | M:F | |
| 30% adenoid cystic | 3 to 6% of all H&N cancer | |
| 5% acinic cell | Rate of malignancy: | |
| 5% malignant mixed | Perotid 15 to 25% | |
| 5% lymphoma | Submandibular 37 to 43% | |
| | Minor salivary >80% | |

| Thyroid (90% benign – 10% malignant) | | |
| >80% papillary | Children | Radiation exposure |
| 5-15% follicular | Adults <30 or >60 | Family history – papillary CA or multiple endocrine neoplasia – MEN II |
| 5% medullary | Nodules more common in females | Older age |
| <5% anaplastic | Malignancy more common in males | Male |
| 1 to 5% Hurthle cell | | Papillary – Gardner’s, Cowden’s, familial adenomatous polyposis (FAP) |
| 1 to 2% metastatic | | |

| Parathyroid | Mean age: 44 to 55 yr | |
| Rare tumour | | |

**Risk Factors for Head and Neck Cancer include:**
- Smoking
- EtOH (this is synergistic with smoking)
- Radiation
- Occupational/Environmental exposures
- Oral HPV infection (independent of smoking and EtOH exposure)
<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Cavity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic neck mass (30%)</td>
<td>Biopsy</td>
<td>1st surgery ± neck resection</td>
<td>5 yr survival: - T1/T2: 75%</td>
</tr>
<tr>
<td>Non-healing ulcer ± bleeding</td>
<td>CT</td>
<td>local resection</td>
<td>- T3/T4: 30 to 35%</td>
</tr>
<tr>
<td>Dysphagia, sialorhea, dysphonia</td>
<td></td>
<td>± neck dissection</td>
<td>Poor prognostic indicators:</td>
</tr>
<tr>
<td>Oral, orolalia, leukoplakia or erythroplakia (pre-malignant changes or CIS)</td>
<td></td>
<td>± reconstruction</td>
<td>Depth of invasion, close surgical margins location (tongue worse than floor of mouth)</td>
</tr>
<tr>
<td><strong>Nose and Paranasal Sinus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early symptoms:</td>
<td></td>
<td>Surgery and radiation</td>
<td>5 yr survival: 30 to 60%</td>
</tr>
<tr>
<td>Unilateral nasal obstruction</td>
<td>CT/MRI</td>
<td>Chemoradiotherapy</td>
<td>Poor prognosis 2nd to late presentation</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>Biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nasopharynx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical nodes (60 to 90%)</td>
<td>Nasopharyngoscopy</td>
<td>1st radiation, chemoradiation</td>
<td>5 yr survival: - I: 79%</td>
</tr>
<tr>
<td>Nasal obstruction, epistaxis</td>
<td>Biopsy</td>
<td>Surgery for limited or recurrent disease</td>
<td>- II: 72%</td>
</tr>
<tr>
<td>Unilateral otitis media ± hearing loss</td>
<td>CT/MRI</td>
<td></td>
<td>- III: 50 to 60%</td>
</tr>
<tr>
<td>CN III to VI, IX to XII (25%)</td>
<td></td>
<td></td>
<td>- IV: 36 to 42%</td>
</tr>
<tr>
<td>Proptosis, voice change, dysphagia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oropharynx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odynophagia, otolalia</td>
<td>Biopsy</td>
<td>1st radiation</td>
<td></td>
</tr>
<tr>
<td>Ulcerated/enlarged tonsil</td>
<td>CT</td>
<td>2nd surgery</td>
<td></td>
</tr>
<tr>
<td>Fixed tongue/trismus/dysarthria</td>
<td></td>
<td>± neck dissection</td>
<td></td>
</tr>
<tr>
<td>Oral, orolalia, bloody sputum</td>
<td></td>
<td>± reconstruction</td>
<td></td>
</tr>
<tr>
<td>Cervical lymphadenopathy (60%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant mets: lung/bone/liver (7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypopharynx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia, odynophagia</td>
<td>Pharyngoscopy</td>
<td>1st radiation</td>
<td>5 yr survival: T1: 53%</td>
</tr>
<tr>
<td>Otalgia, hoarseness</td>
<td>Biopsy</td>
<td>2nd surgery</td>
<td>T2/T3: 36-39%</td>
</tr>
<tr>
<td>Cervical lymphadenopathy</td>
<td>CT</td>
<td></td>
<td>T4: 24%</td>
</tr>
<tr>
<td><strong>Larynx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia, odynophagia, globus</td>
<td>Laryngoscopy</td>
<td>1st radiation</td>
<td>5 yr survival: T4 &gt;40% (surgery with radiation)</td>
</tr>
<tr>
<td>Otalgia, hoarseness, Dyspnea/stridor</td>
<td>CT/MRI</td>
<td>2nd surgery</td>
<td>Control rate early lesions &gt;90% (radiation)</td>
</tr>
<tr>
<td>Cough/hemoptysis</td>
<td></td>
<td>1st surgery for bulky T4 disease</td>
<td>10 to 12% of small lesions fail radiotherapy</td>
</tr>
<tr>
<td>Cervical nodes (rare w/ glotic CA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Salivary Gland</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painless mass</td>
<td>FNA</td>
<td>1st surgery ± neck dissection:</td>
<td>Parotid:</td>
</tr>
<tr>
<td>CN VII palsy</td>
<td>MRI/CT</td>
<td>Post-op radiotherapy</td>
<td>10 yr survival: 85, 69, 43, and 14% for stages I to IV</td>
</tr>
<tr>
<td>Cervical lymphadenopathy</td>
<td></td>
<td>Chemotherapy if unresectable</td>
<td>Submandibular:</td>
</tr>
<tr>
<td>Rapid growth</td>
<td></td>
<td></td>
<td>2 yr survival: 82%, 5 year: 69%</td>
</tr>
<tr>
<td>Invasion of skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constitutional signs/symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thyroid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid mass, cervical nodes</td>
<td>FNA</td>
<td>1st surgery</td>
<td>Recurrences occur within 5 yr</td>
</tr>
<tr>
<td>Vocal cord paralysis</td>
<td>U/S</td>
<td>I131 for intermediate and high risk well differentiated thyroid cancer</td>
<td>Need long-term f/u: clinical exam, thyroglobulin</td>
</tr>
<tr>
<td>Hyper/hypothyroidism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Parathyroid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased serum Ca²⁺</td>
<td>Sestamibi</td>
<td>Wide surgical excision</td>
<td>Recurrence rates</td>
</tr>
<tr>
<td>Neck mass</td>
<td></td>
<td>Post-op monitoring of serum Ca²⁺</td>
<td>1 yr: 27%</td>
</tr>
<tr>
<td>Bone disease, renal disease</td>
<td></td>
<td></td>
<td>5 yr: 82%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
<td></td>
<td>10 yr: 91%</td>
</tr>
<tr>
<td>Mean survival</td>
<td></td>
<td></td>
<td>6 to 7 yr</td>
</tr>
</tbody>
</table>
Table 17. Bethesda Classification of Thyroid Cytology

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk of Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diagnostic or unsatisfactory</td>
<td>Unknown</td>
</tr>
<tr>
<td>Benign</td>
<td>0-3%</td>
</tr>
<tr>
<td>Follicular lesion of undetermined significance/Atypia of undetermined significance</td>
<td>5-15%</td>
</tr>
<tr>
<td>Follicular/Hurthle cell neoplasms</td>
<td>15-30%</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>60-75%</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99%</td>
</tr>
</tbody>
</table>

Table 18. Thyroid Carcinoma

<table>
<thead>
<tr>
<th>Incidence (% of all thyroid cancers)</th>
<th>Papillary</th>
<th>Follicular</th>
<th>Medullary</th>
<th>Anaplastic</th>
<th>Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 to 75%</td>
<td>10%</td>
<td>3 to 5%</td>
<td>&lt;5%</td>
<td>&lt;1%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Route of Spread</th>
<th>Lymphatic</th>
<th>Hematogenous</th>
<th>Lymphatic and hematogenous</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>Capsular/vascular invasion</th>
<th>Amyloid</th>
<th>Giant cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orphan Annie nuclei</td>
<td>Invasion influences prognosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psammoma bodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary architecture</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
<th>Ps – Papillary cancer</th>
<th>Fs – Follicular cancer</th>
<th>Ms – Medullary cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ps – Papillary cancer</td>
<td>For away mets</td>
<td>Far away mets</td>
<td>Multiple endocrine neoplasia</td>
</tr>
<tr>
<td>Palpable lymph nodes</td>
<td>Female (3:1)</td>
<td>NOT FNA (can’t be diagnosed by FNA)</td>
<td>(MEN IIa or IIb)</td>
</tr>
<tr>
<td>Positive 131 uptake</td>
<td>Favourable prognosis</td>
<td>nMyloid</td>
<td></td>
</tr>
<tr>
<td>Positive prognosis</td>
<td></td>
<td>Median node dissection</td>
<td></td>
</tr>
<tr>
<td>Post-op 131 scan to guide treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Prognosis                            | 98% at 10 yr                | 92% at 10 yr            | 50% at 10 yr           | 20 to 35% at 1 yr | 13% at 10 yr |
|                                      | 20% at 10 yr                | 20% at 10 yr            | 20% at 10 yr           | 5 yr survival    | Stage IE 55%-80% |

| Treatment                            | Small tumours:              | Small tumours:          | Total thyroidectomy    | Radiation and chemotherapy |
|                                      | Near total thyroidectomy or lobectomy | Modified neck dissection | Median lymph node dissection | Total thyroidectomy |
|                                      | Diffuse/bilateral:          | Post-op 131 bx          | Total thyroidectomy    |                         |
|                                      | Total thyroidectomy         |                        |                         |                         |
|                                      | = Post-op 131 bx             |                        |                         |                         |

* B symptoms = fever, night sweats, weight loss >10% in 6 mo  ** CHOP = cyclophosphamide, adriamycin, vincristine, prednisone

### Approach to Thyroid Nodule

- all patients with thyroid nodules require evaluation of serum TSH and ultrasound
- any nodule >5 mm with suspicious sonographic features (particularly microcalcifications) should undergo FNA
- any nodule >1 cm should undergo FNA
- when performing repeat FNA on initially non-diagnostic nodules, U/S-guided FNA should be employed
- nuclear scanning has minimal value in the investigation of the thyroid nodule

Table 19. Management of the Thyroid Nodule

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radioiodine therapy</td>
<td>For the treatment of hyperthyroidism or as adjuvant treatment after surgery in the treatment of papillary or follicular carcinoma</td>
</tr>
<tr>
<td>Chemotherapy and/or radiotherapy</td>
<td>Anaplastic CA or thyroid lymphoma</td>
</tr>
<tr>
<td>Surgical excision</td>
<td>Mass that is “suspicious” on FNA</td>
</tr>
<tr>
<td></td>
<td>Malignancy other than anaplastic CA or thyroid lymphoma</td>
</tr>
<tr>
<td></td>
<td>Mass that on FNA is benign but increasing in size on serial imaging and/or &gt;3-4 cm in size</td>
</tr>
<tr>
<td></td>
<td>Hyperthyroidism not amenable to medical therapy</td>
</tr>
</tbody>
</table>

* U/S findings: cystic: risk of malignancy <1%, solid: risk of malignancy approx. 10%, solid with cystic components: risk of malignancy same as if solid
Acute Otitis Media (AOM)

Definition
- acute inflammation of middle ear

Epidemiology
- 60 to 70% of children have at least 1 episode of AOM before 3 yr of age
- 18 mo to 6 yr most common age group
- peak incidence January to April
- one third of children have had ≥3 episodes by age 3

Etiology
- *S. pneumoniae*: 35% of cases (incidence decreasing due to pneumococcus vaccine)
- *H. influenzae*: 25% of cases
- *M. catarrhalis*: 10% of cases
- *S. aureus* and *S. pyogenes* (all β-lactamase producing)
- anaerobes (newborns)
- Gram-negative enterics (infants)
- viral

Predisposing Factors
- Eustachian tube dysfunction/obstruction:
  - swelling of tubal mucosa:
    - upper respiratory tract infection (URTI)
    - allergic rhinitis
    - chronic rhinosinusitis
  - obstruction/infiltration of Eustachian tube ostium:
    - tumour: nasopharyngeal carcinoma (adults)
    - adenoid hypertrophy (not due to obstruction but by maintaining a source of infection)
    - barotrauma (sudden changes in air pressure)
  - inadequate tensor palatini function: cleft palate (even after repair)
  - abnormal Eustachian tube:
    - Down syndrome (horizontal position of Eustachian tube), Crouzon syndrome, and Apert syndrome
- disruption of action of:
  - cilia of Eustachian tube: Kartagener’s syndrome
  - mucus secreting cells
  - capillary network that provides humoral factors, PMNs, phagocytic cells
- immunosuppression/deficiency due to chemotherapy, steroids, diabetes mellitus, hypogammaglobulinemia, cystic fibrosis

Risk Factors
- bottle feeding, pacifier use
- second-hand smoke
- crowded living conditions (day care/group child care facilities) or sick contacts
- male
- family history

Pathogenesis
- obstruction of Eustachian tube → air absorbed in middle ear → negative pressure (an irritant to middle ear mucosa) → edema of mucosa with exudate/effusion → infection of exudate from nasopharyngeal secretions

Clinical Features
- triad of otalgia, fever (especially in younger children), and conductive hearing loss
- rarely tinnitus, vertigo, and/or facial nerve paralysis
- otorrhea if tympanic membrane perforated
- infants/toddlers
  - ear-tugging (this alone is not a good indicator of pathology)
  - hearing loss, balance disturbances (rare)
  - irritable, poor sleeping
  - vomiting and diarrhea
  - anorexia
- otoscopy of TM
  - hyperemia
  - bulging, pus may be seen behind TM
  - loss of landmarks: handle and long process of malleus not visible

Clinical Assessment of AOM in Pediatrics
*JAMA* 2010;304:2161-2169
In assessment of AOM in pediatrics, ear pain is the most useful symptom with a likelihood ratio (LR) between 3.0 and 7.3. Useful otoscopic signs include erythematous (LR 8.4, 95% CI 7-11), cloudy (LR 34, 95% CI 28-42), bulging (LR 51, 95% CI 36-73), and immobile tympanic membrane on pneumatic otoscopy (LR 31, 95% CI 26-37).
Diagnosis and Management

- American Academy of Pediatrics (AAP) Guidelines 2013 suggest the following action statements (adapted):
  - Diagnose AOM if:
    1. Moderate to severe bulging of TM or new onset of otorrhea not due to otitis externa
    2. Mild bulging of tympanic membrane and recent (<48 h) ear pain or intense erythema of TM
    3. Do not diagnose AOM if no middle ear effusion (based on pneumatic otoscopy or tympanometry)

Management of AOM

1. Assess for pain. If pain present, treat the pain
2. For severe unilateral or bilateral AOM (moderate or severe otalgia, or otalgia for 48 h, or temperature ≥39°C), prescribe antibiotics if 6 mo or older
3. For nonsevere bilateral AOM (mild otalgia, otalgia <48 h, temperature <39°C), prescribe antibiotics if 6 to 23 mo
4. For nonsevere unilateral AOM, prescribe antibiotics or observe with close follow up based on joint decision making with parents if 6 to 23 mo
5. For nonsevere unilateral or bilateral AOM, prescribe antibiotics or observe with close follow up based on joint decision making with parents if 24 mo or older
6. Antibiotic treatment when given should consist of:
   - amoxicillin if child has not received amoxicillin in past 30 d, child does not have purulent conjunctivitis, or child is not allergic to penicillin
   - add β-lactamase coverage if received amoxicillin in past 30 d, has purulent conjunctivitis, or has history of recurrent AOM not responsive to amoxicillin
   - reassess if symptoms worsen or fail to respond to treatment within 48 to 72 h
   - do NOT prescribe prophylactic antibiotics to reduce frequency of AOM
7. Tympanostomy tubes can be offered for recurrent AOM (3 episodes in 6 mo, 4 episodes in 1 yr) with 1 episode in preceding 6 mo
8. Recommend pneumococcal vaccine and annual influenza vaccine to all children
9. Encourage exclusive breastfeeding for at least 6 mo
10. Avoid tobacco smoke

- antibiotic treatment hastens resolution: 10 d course
  - 1st line:
    - amoxicillin 80-90 mg/kg/d divided into two doses: safe, effective, and inexpensive
    - if penicillin allergic: macrolide (clarithromycin, azithromycin – high resistance), trimethoprim-sulfamethoxazole (Bactrim®)
  - 2nd line:
    - amoxicillin-clavulanic acid (Clavulin®)
    - cefalosporins: cefuroxime axetil (Ceftin®), ceftriaxone (Rocephin®), cefaclor (Ceclor®), cefixime (Suprax®)
  - AOM deemed unresponsive if clinical signs/symptoms and otoscopic findings persist beyond 48 h of antibiotic treatment
  - symptomatic therapy:
    - antipyretics/analgesics (e.g. acetaminophen)
    - decongestants: may relieve nasal congestion but does not treat AOM

- prevention:
  - parent education about risk factors
  - antibiotic prophylaxis: amoxicillin or macrolide shown effective at half therapeutic dose
  - pneumococcal and influenza vaccine
  - surgery:
    - choice of surgical therapy for recurrent AOM depends on whether local factors (Eustachian tube dysfunction) are responsible (use ventilation tubes), or regional disease factors (tonsillitis, adenoid hypertrophy, sinustitis) are responsible

Complications of AOM

- otortic:
  - TM perforation
  - chronic suppurative OM
  - ossicular necrosis
  - cholesteatoma
  - persistent effusion (often leading to hearing loss)

- CNS:
  - meningitis
  - brain abscess
  - facial nerve paralysis

- other:
  - mastoiditis
  - labyrinthitis
  - sigmoid sinus thrombophlebitis

Complications of Tympanostomy Tubes

- Early:
  - Exudation
  - Blockage
- Persistent otitis
- Late:
  - Myringosclerosis
  - Persistent TM perforation
  - Cholesteatoma
Otitis Media with Effusion (OME)

Definition
• presence of fluid in the middle ear without signs or symptoms of ear infection

Epidemiology
• most common cause of pediatric hearing loss
• not exclusively a pediatric disease
• follows AOM frequently in children
• middle ear effusions have been shown to persist following an episode of AOM for 1 mo in 40% of children, 2 mo in 20%, and 3+ mo in 10%

Risk Factors
• same as AOM

Clinical Features
• hearing loss ± tinnitus
  ▪ confirm with audiogram and tympanogram (flat) (see Figure 16B, OT10 and Figure 17B, OT11)
• fullness – blocked ear
• ± pain, low grade fever
• otoscopy of tympanic membrane:
  ▪ discolouration – amber or dull grey with “glue” ear
  ▪ meniscus fluid level behind TM
  ▪ air bubbles
  ▪ retraction pockets/TM atelectasis
  ▪ most reliable finding with pneumatoscopy is immobility

Treatment
• expectant: 90% resolve by 3 mo
• document hearing loss with audiogram
• no statistical proof that antihistamines, decongestants, antibiotics clear disease faster
• surgery: myringotomy ± ventilation tubes ± adenoidectomy (if enlarged or on insertion of second set of tubes after first set falls out)
• ventilation tubes to equalize pressure and drain ear

Complications of Otitis Media with Effusion (OME)
• hearing loss, speech delay, learning problems in young children
• chronic mastoiditis
• ossicular erosion
• cholesteatoma especially when retraction pockets involve pars flaccida or postero-superior TM
• retraction of tympanic membrane, atelectasis, ossicular fixation

Adenoid Hypertrophy

• size peaks at age 5 and resolves by age 12
• increase in size with repeated URTI and allergies

Clinical Features
• nasal obstruction:
  ▪ adenoid facies (open mouth, high arched palate, narrow midface, malocclusion)
  ▪ history of hypernasal voice and snoring
  ▪ long term mouth breather; minimal air escape through nose
• choanal obstruction:
  ▪ chronic rhinosinusitis/rhinitis
  ▪ obstructive sleep apnea
• chronic inflammation:
  ▪ nasal discharge, post-nasal drip, and cough
  ▪ cervical lymphadenopathy

Diagnosis
• enlarged adenoids on nasopharyngeal exam (usually with flexible nasopharyngoscope)
• enlarged adenoid shadow on lateral soft tissue x-ray

Complications
• Eustachian tube obstruction leading to serous otitis media
• interference with nasal breathing, necessitating mouth-breathing
• malocclusion
• sleep apnea/respiratory disturbance
• orofacial developmental abnormalities
Adenoidectomy

Indications for Adenoidectomy
- chronic upper airway obstruction with sleep disturbance/apnea ± cor pulmonale
- chronic nasopharyngitis resistant to medical treatment
- chronic serous otitis media and chronic suppurative otitis media (with 2nd set of tubes)
- recurrent acute otitis media resistant to antibiotics
- suspicion of nasopharyngeal malignancy
- persistent rhinorrhea

Contraindications
- uncontrollable coagulopathy
- recent pharyngeal infection
- short or abnormal palate (cleft or false palate, zona pellucida)

Complications
- bleeding, infection
- velopharyngeal insufficiency (hypernasal voice or nasal regurgitation)
- scarring of Eustachian tube orifice

Sleep-Disordered Breathing in Children

Definition
- spectrum of sleep-related breathing abnormalities ranging from snoring to OSA

Epidemiology
- peak incidence between 2 and 8 yr when tonsils and adenoids are the largest relative to the pharyngeal airway

Etiology
- due to a combination of anatomic and neuromuscular factors:
  - adenotonsillar hypertrophy
  - craniofacial abnormalities
  - neuromuscular hypotonia (i.e. cerebral palsy, Down syndrome)
  - obesity

Clinical Features
- heavy snoring, mouth breathing, pauses or apnea, enuresis, excessive daytime sleepiness, behavioural/learning problems, diagnosis of ADHD, morning headache, failure to thrive

Investigations
- flexible nasopharyngoscopy for assessment of nasopharynx and adenoids
- polysomnography (obstructive apnea-hypopnea index >1/h considered abnormal)

Treatment
- surgical: bilateral tonsillectomy and adenoidectomy
- nonsurgical: CPAP, BiPAP, sleep hygiene

Acute Tonsillitis

Etiology
- Group A β-hemolytic streptococci (most common) and Group C or G streptococci
- S. pneumoniae, S. aureus, H. influenzae, M. catarrhalis
- EBV

Clinical Features
- symptoms:
  - sore throat
  - dysphagia, odynophagia, trismus
  - malaise, fever
  - otalgia (referred)
- signs:
  - tender cervical lymphadenopathy, especially submandibular, jugulodigastric
  - tonsils enlarged, inflammation ± exudates/white follicles
  - strawberry tongue, scarlatiniform rash (scarlet fever)
  - palatal petechiae (infectious mononucleosis)

Trismus: motor disturbance of the trigeminal nerve, leading to spasm of the muscles of mastication, with difficulty in opening the mouth (lockjaw).

DDx Sore Throat
- Streptococcal pharyngitis
- Viral pharyngitis
- Infectious mononucleosis
- Tonsillitis
- Peritonsillar abscess
- Foreign body/trauma
- Leukemia
- Hodgkin’s disease
**Investigations**
- CBC
- swab for C&S
- latex agglutination tests
- Monospot® – less reliable in children <2 yr old

**Treatment**
- soft diet, ample fluid intake
- gargle with warm saline solution
- analgesics and antipyretics
- antibiotics:
  - only after appropriate swab for C&S
  - 1st line penicillin or amoxicillin (erythromycin if penicillin allergy) x 10 d
  - rheumatic fever risk emerges approximately 9 d after the onset of symptoms:
    - antibiotics are utilized mainly to avoid this serious sequela and to provide earlier symptomatic relief
    - no evidence for the role of antibiotics in the avoidance of post-streptococcal glomerulonephritis

---

**Peritonsillar Abscess (Quinsy)**

**Definition**
- cellulitis of space behind tonsillar capsule extending onto soft palate leading to abscess

**Etiology**
- bacterial: Group A strep (GAS) (50% of cases), *S. pyogenes, S. aureus, H. influenzae,* and anaerobes

**Epidemiology**
- can develop from acute tonsillitis with infection spreading into plane of tonsillar bed
- unilateral
- most common in 15 to 30 yr old age group

**Clinical Features**
- fever and dehydration
- sore throat, dysphagia, and odynophagia
- extensive peritonsillar swelling but tonsil may appear normal
- edema of soft palate
- uvular deviation
- involvement of motor branch of CN V (can lead to trismus)
- dysphonia (edema → failure to elevate palate) 2º to CN X involvement
- unilateral referred otalgia
- cervical lymphadenitis

**Complications**
- aspiration pneumonia 2º to spontaneous rupture of abscess
- airway obstruction
- lateral dissection into parapharyngeal and/or carotid space
- bacteremia
- retropharyngeal abscess

**Treatment**
- secure airway
- surgical drainage (incision or needle aspiration) with C&S
- warm saline irrigation
- IV penicillin G x 10 d if cultures positive for GAS
- add PO/IV metronidazole or clindamycin x 10 d if culture positive for *Bacteroides*
- consider tonsillectomy after second episode

**Other Parapharyngeal Space Infection**
- pharyngitis
- parotitis (see *Salivary Glands, OT29*)
- otitis
- mastoiditis (Bezold's abscess)
- odontogenic infection
Tonsillectomy

Absolute Indications
- most common indication: sleep-disordered breathing
- 2nd most common indication: recurrent throat infections
- tonsillar hypertrophy causing upper airway obstruction, obstructive sleep apnea, severe dysphagia, or cardiopulmonary complications such as cor pulmonale
- suspicion of malignancy (e.g. lymphoma, squamous cell carcinoma)
- orofacial/dental deformity
- hemorrhagic tonsillitis

Relative Indications (to reduce disease burden)
- recurrent throat infection with a frequency of at least 7 episodes in the past year, at least 5 episodes per year for 2 yr, or at least 3 episodes per year for 3 yr, with documentation in the medical record for each episode of sore throat and 1 or more of the following: temperature >38.3°C, cervical adenopathy, tonsillar exudate, or positive test for Group A β-hemolytic streptococcus (Paradise Criteria)
- chronic tonsillitis with halitosis (bad breath) or sore throat ± tonsilloliths (clusters of calcified material that form in the crevices of the tonsils)
- complications of tonsillitis: quinsy/peritonsillar abscess, parapharyngeal abscess, retropharyngeal abscess
- failure to thrive

Relative Contraindications
- velopharyngeal insufficiency: overt or submucous/covert cleft of palate, impaired palatal function due to neurological or neuro-muscular abnormalities
- hematologic: coagulopathy, anemia
- infectious: active local infection without urgent obstructive symptoms

Complications
- hemorrhage: early – within 24 h; delayed – 7-10 d
- odynophagia and/or otalgia; dehydration
- infection
- atlantoaxial subluxation (Grisel’s syndrome): rare

Airway Problems in Children

Differential Diagnosis by Age Group

Neonates (obligate nose breathers)
- extralaryngeal:
  - choanal atresia (e.g. CHARGE syndrome)
  - nasopharyngeal dermoid, glioma, encephalocele
  - glossoptosis: Pierre-Robin sequence, Down syndrome, lymphatic malformation, hemangioma
- laryngeal:
  - laryngomalacia: most common cause of stridor in children
  - laryngocele
  - vocal cord palsy (due to trauma or Arnold-Chiari malformation)
  - glottic web
  - subglottic stenosis
  - laryngeal cleft
- tracheal:
  - tracheoesophageal fistula
  - tracheomalacia
  - vascular rings

2 to 3 Months
- congenital:
  - laryngomalacia
  - vascular: subglottic hemangioma (more common), innominate artery compression, double aortic arch
  - laryngeal papilloma
- acquired:
  - subglottic stenosis: post intubation
  - tracheal granulation: post intubation
  - tracheomalacia: post tracheotomy and TEF repair
Infants – Sudden Onset
- foreign body aspiration
- croup
- bacterial tracheitis
- caustic ingestion
- epiglottitis

Children and Adults
- infection:
  - Ludwig's angina
  - peritonsillar/parapharyngeal abscess
  - retropharyngeal abscess
- neoplastic:
  - squamous cell carcinoma (SCC) (adults): larynx, hypopharynx
  - retropharyngeal: lymphoma, neuroblastoma
  - nasopharyngeal: carcinoma, rhabdomyosarcoma
- allergic:
  - angioneurotic edema
  - polyps (suspect cystic fibrosis in children)
- trauma:
  - laryngeal fracture, facial fracture
  - burns and lacerations
  - post-intubation
  - caustic ingestion
- congenital:
  - lingual thyroid/tonsil

Signs of Airway Obstruction

Stridor
- note quality, timing (inspiratory or expiratory)
- body position important:
  - lying prone: subglottic hemangioma, double aortic arch
  - lying supine: laryngomalacia, glossophtosis
- site of stenosis:
  - vocal cords or above: inspiratory stridor
  - subglottis and extrathoracic trachea: biphasic stridor
  - distal tracheobronchial tree: expiratory stridor

Respiratory Distress
- nasal flaring
- supraclavicular and intercostal indrawing
- sternal retractions
- use of accessory muscles of respiration
- tachypnea
- cyanosis
- altered LOC

Feeding Difficulty and Aspiration
- supraglottic lesion
- laryngomalacia
- vocal cord paralysis
- laryngeal cleft g aspiration pneumonia
- TEF

Acute Laryngotracheobronchitis (Croup)
- inflammation of tissues in subglottic space ± tracheobronchial tree
- swelling of mucosal lining and associated with thick, viscous, mucopurulent exudate which compromises upper airway (subglottic space narrowest portion of upper airway)
- normal function of ciliated mucous membrane impaired

Etiology
- viral: parainfluenzae I (most common), II, III, influenza A and B, RSV
Clinical Features
- age: 4 mo to 5 yr
- preceded by URTI symptoms
- generally occurs at night
- biphasic stridor and croupy cough (loud, sea-lion bark)
- appear less toxic than epiglottitis
- supraglottic area normal
- rule out foreign body and subglottic stenosis
- ’steeple-sign’ on AP x-ray of neck
- if recurrent croup, think subglottic stenosis

Treatment
- racemic epinephrine via nebulizer q1-2h, prn (only if in respiratory distress)
- systemic corticosteroids (e.g. dexamethasone, prednisone)
- adequate hydration
- close observation for 3 to 4 h
- intubation if severe
- hospitalize if poor response to steroids after 4 h and persistent stridor at rest
- consider alternate diagnosis if poor response to therapy (e.g. bacterial tracheitis)
- if recurrent episodes of croup-like symptoms, consider bronchoscopy several weeks after acute episode settles to rule out underlying subglottic stenosis

Acute Epiglottitis
- acute inflammation causing swelling of supraglottic structures of the larynx without involvement of vocal cords

Etiology
- H. influenzae type B
- relatively uncommon condition due to Hib vaccine

Clinical Features
- any age, most commonly 1 to 4 yr
- rapid onset
- toxic-looking, fever, anorexia, restlessness
- cyanotic/pale, inspiratory stridor, slow breathing, lungs clear with decreased air entry
- prefers sitting up, open mouth, drooling, tongue protruding, sore throat, dysphagia

Investigations and Management
- investigations and physical examination may lead to complete obstruction, thus preparations for intubation or tracheotomy must be made prior to any manipulation
- stat ENT/anesthesia consult(s)
- WBC (elevated), blood and pharyngeal cultures after intubation
- lateral neck radiograph (only done if patient stable)

Treatment
- secure airway
- IV access with hydration
- antibiotics: IV cefuroxime, cefotaxime, or ceftriaxone
- moist air
- extubate when leak around tube occurs and afebrile
- watch for meningitis

Subglottic Stenosis

Congenital
- diameter of subglottis <4 mm in neonate (due to thickening of soft tissue of subglottic space or maldevelopment of cricoid cartilage)

Acquired
- following prolonged, repeated or traumatic intubation:
  - most commonly due to endotracheal intubation; nasal intubation is less traumatic and preferred in long term intubation as it puts less pressure on the subglottis (tube sits at different orientation) and there is less movement
  - subglottic stenosis is related to duration of intubation and pressure of the endotracheal tube cuff
- can also be due to foreign body, infection (e.g. TB, diphtheria, syphilis) or chemical irritation

Clinical Features
- biphasic stridor
- respiratory distress
- recurrent/prolonged croup

Diagnosis
- rigid laryngoscopy and bronchoscopy
Treatment
• if soft stenosis: divide tissue with knife or laser, dilate with balloon ± steroids
• if firm stenosis: laryngotracheoplasty

Laryngomalacia
• short aryepiglottic folds, omega-shaped epiglottis, pendulous mucosa
• caused by indrawing of supraglottis on inspiration leading to laryngopharyngeal reflux of acid

Clinical Features
• high-pitched inspiratory stridor at 1 to 2 wk
• constant or intermittent and more pronounced supine
• usually mild but when severe can be associated with cyanosis or feeding difficulties, leading to failure to thrive

Treatment
• observation is usually sufficient as symptoms spontaneously subside by 12 to 18 mo in >90% of cases
• in the case of severe laryngomalacia, division of the aryepiglottic folds (supraglottoplasty) provides relief

Foreign Body

Ingested
• usually stuck at cricopharyngeus
• coins, toys, batteries (emergency)
• presents with drooling, dysphagia, stridor if very large

Aspirated
• usually stuck at right mainstem bronchus
• peanuts, carrot, apple core, popcorn, balloons
• presentation
  ▪ stridor if lodged in trachea
  ▪ unilateral "asthma" if bronchial, therefore often misdiagnosed as asthma
  ▪ if totally occludes airway: cough, lobar pneumonia, atelectasis, mediastinal shift, pneumothorax, death

Diagnosis and Treatment
• any patient with suspected foreign body should be kept NPO immediately
• inspiration-expiration chest x-ray (if patient is stable)
• bronchoscopy or esophagoscopy with removal
• rapid onset, not necessarily febrile or elevated WBC

Deep Neck Space Infection

• most commonly arise from an infection of the mandibular teeth, tonsils, parotid gland, deep cervical lymph nodes, middle ear, or the sinuses
• often a rapid onset and may progress to fatal complications

Etiology
• usually mixed aerobes and anaerobes that represent the flora of the oral cavity, upper respiratory tract, and certain parts of the ears and eyes

Clinical Features
• sore throat or pain and trismus
• dysphagia and odynophagia
• stridor and dyspnea
• late findings may include dysphonia and hoarseness
• swelling of the face and neck, erythema
• asymmetry of the oropharynx with purulent oral discharge
• lymphadenopathy

Diagnosis
• lateral cervical view plain radiograph
• CT
• MRI

Treatment
• secure the airway
• surgical drainage
• maximum doses of IV systemic antimicrobials regimens according to the site of infection
### Common Medications

#### Table 20. Antibiotics

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Dose</th>
<th>Indications</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>amoxicillin (Amoxic®, Amoxi®, Amox®)</td>
<td>Adult: 500 mg PO tid Children: 80-90 mg/kg/d in 2 divided doses</td>
<td><em>Streptococcus, Pneumococcus, H. influenzae, Proteus coverage</em></td>
<td>May cause rash in patients with infectious mononucleosis</td>
</tr>
<tr>
<td>piperacillin with tazobactam (Zosyn®)</td>
<td>3 g PO q6h</td>
<td>Gram-positive and negative aerobes and anaerobes plus <em>Pseudomonas</em> coverage</td>
<td>May cause pseudomembranous colitis</td>
</tr>
<tr>
<td>ciprofloxacin (Cipro®, Ciloxan®)</td>
<td>500 mg PO bid</td>
<td><em>Pseudomonas, Streptococci, MRSA, and most Gram-negative; no anaerobic coverage</em></td>
<td>Do not give systemic quinolones to children</td>
</tr>
<tr>
<td>erythromycin (Erythrocin®, EryPed®, Staticin®, T-Stat®, Erybid®, Novorythro Encap®)</td>
<td>500 mg PO qid</td>
<td>Alternative to penicillin</td>
<td>Ototoxic</td>
</tr>
</tbody>
</table>

#### Table 21. Otic Drops

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Dose</th>
<th>Indications</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ciprofloxacin (Ciprodex®)</td>
<td>4 gtt in affected ear bid</td>
<td>For otitis externa and complications of otitis media <em>Pseudomonas, Streptococci, MRSA, and most Gram-negative; no anaerobic coverage</em></td>
<td></td>
</tr>
<tr>
<td>neomycin, polymyxin B sulfate, and hydrocortisone (Cortisporin Otic®)</td>
<td>5 gtt in affected ear tid</td>
<td>For otitis externa Used for inflammatory conditions which are currently infected or at risk of bacterial infections</td>
<td>May cause hearing loss if placed in inner ear</td>
</tr>
<tr>
<td>hydrocortisone and acetic acid (VoSoHC®)</td>
<td>5-10 gtt in affected ear tid</td>
<td>For otitis media</td>
<td>Bactericidal by lowering pH</td>
</tr>
<tr>
<td>tobramycin and dexamethasone (TobraDex®)</td>
<td>5-10 gtt in affected ear bid</td>
<td>For chronic suppurative otitis media</td>
<td>Risk of vestibular or cochlear toxicity</td>
</tr>
</tbody>
</table>

#### Table 22. Nasal Sprays

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Indications</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>flunisolide (Rhinalar®)</td>
<td>Allergic rhinitis</td>
<td>Requires up to 4 wk of consistent use to have effect</td>
</tr>
<tr>
<td>budesonide (Rhinocort®)</td>
<td>Chronic sinusitis</td>
<td>Long term use Dries nasal mucosa; get minor bleeding Patient should stop if epistaxis May sting Flonase® and Nasonex® not absorbed systemically</td>
</tr>
<tr>
<td>triamcinolone (Nasacort®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>beclomethasone (Beconase®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mometasone furoate, monohydrate (Nasonex®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluticasone furoate (Avamys®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihistamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>levocarbastine (Livostin®)</td>
<td>Allergic rhinitis</td>
<td>Immediate effect If no effect by 3 d then discontinue Use during allergy season</td>
</tr>
<tr>
<td>Decongestant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>xylometazoline (Otrivin®)</td>
<td>Acute sinusitis</td>
<td>Careful if patient has hypertension If long term use, can cause decongestant addiction (i.e. rhinitis medicamentosa)</td>
</tr>
<tr>
<td>oxymetazoline (Dristan®)</td>
<td>Rhinitis</td>
<td></td>
</tr>
<tr>
<td>phenylephrine (Neosynephrine®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic/Decongestant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>framycetin, gramicidin, phenylephrine (Soframycin®)</td>
<td>Acute sinusitis</td>
<td></td>
</tr>
<tr>
<td>Anticholinergic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ipratropium bromide (Atrovent®)</td>
<td>Vasomotor rhinitis</td>
<td>Careful not to spray into eyes as can cause burning or precipitation of narrow angle glaucoma Increased rate of epistaxis when combined with topical nasal steroids</td>
</tr>
<tr>
<td>Lubricants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>saline, NeilMed®, Rhinaris®, Secaris®, Polysporin®, Vaseline®</td>
<td>Dry nasal mucosa</td>
<td>Use pm Rhinaris® and Secaris® may cause stinging</td>
</tr>
</tbody>
</table>

Source: Dr. M. M. Carr
References

Textbooks

Journal Articles
Furman JM, Coss SP. Benign paroxysmal positional vertigo. NEJM 1999;341:1190-6.
**Table of Contents**

**Acronyms** ........................................ 3  
**Pediatric Quick Reference Values** ............... 3  
**Primary Care** ...................................... 3  
- Visit Overview  
- Routine Immunization  
- Vaccine Administration  
- Growth and Development  
- Nutrition  
- Injury Prevention Counselling  
**Common Complaints** ............................. 8  
- Breath-Holding Spells  
- Circumcision  
- Crying/Fussing Child  
- Dentition and Caries  
- Enuresis  
- Encopresis  
- Failure to Thrive  
- Infantile Colic  
- Obesity  
- Poison Prevention  
- Rashes  
- Sleep Disturbances  
- Toilet Training  
- Sudden Infant Death Syndrome (SIDS)  
**Child Abuse and Neglect** ......................... 14  
- Physical Abuse  
- Sexual Abuse  
- Neglect  
**Adolescent Medicine** .............................. 15  
**Cardiology** ........................................ 16  
- Congenital Heart Disease (CHD)  
- Acyanotic Congenital Heart Disease  
- Cyanotic Congenital Heart Disease  
- Congestive Heart Failure (CHF)  
- Dysrhythmias  
- Heart Murmurs  
- Infective Endocarditis  
**Development** ...................................... 22  
- Approach to Global Developmental Delay  
- Intellectual Disability  
- Language Delay  
- Fetal Alcohol Spectrum Disorder (FASD)  
- Learning Disabilities  
- Motor Delay  
**Endocrinology** .................................... 26  
- Anti-Diuretic Hormone  
- Diabetes Mellitus (DM)  
- Growth  
- Hypercalcemia/Hypocalcemia/Rickets  
- Hyperthyroidism and Hypothyroidism  
- Sexual Development  
**Gastroenterology** ................................. 34  
- Vomiting  
- Gastroesophageal Reflux  
- Tracheoesophageal Fistula (TEF)  
- Pyloric Stenosis  
- Duodenal Atresia  
- Malrotation of the Intestine  
- Diarrhea  
- Infective Diarrhea  
- Toddler’s Diarrhea  
- Lactase Deficiency (Lactose Intolerance)  
- Irritable Bowel Syndrome  
- Celiac Disease  
- Milk Protein Allergy  
- Inflammatory Bowel Disease (IBD)  
- Cystic Fibrosis  
- Constipation  
- Abdominal Pain  
- Chronic Abdominal Pain  
- Abdominal Mass  
- Upper Gastrointestinal Bleeding  
- Lower Gastrointestinal Bleeding  
**Genetics, Dysmorphisms and Metabolism** ........ 41  
- Genetic Anomalies  
- Approach to the Dysmorphic Child  
- Genetics  
- Genetic Syndromes  
- Muscular Dystrophy (MD)  
- Metabolic Disease  
- Phenylketonuria (PKU)  
- Galactosemia  
**Hematology** ....................................... 46  
- Approach to Anemia  
- Physiologic Anemia  
- Iron Deficiency Anemia  
- Anemia of Chronic Disease  
- Sickle Cell Disease (SCD)  
- Thalassemia  
- Hereditary Spherocytosis  
- Glucose-6-Phosphate Dehydrogenase (GP6)  
- Deficiency  
- Bleeding Disorders  
- Immune Thrombocytopenic Purpura (ITP)  
- Hemophilia  
- von Willebrand’s Disease  
**Oncology** .......................................... 50  
- Leukemia  
- Lymphoma  
- Brain Tumours  
- Wilms’ Tumour (Nephroblastoma)  
- Neuroblastoma  
- Bone Tumours  
- Febrile Neutropenia  
- Tumour Lysis Syndrome  
- Hyperleukocytosis  
- Lymphadenopathy  

---

**Pediatrics**

*Tanvi Agarwal, Nicole Fischer, Suparna Sharma and Wallace Wee, chapter editors*

*Maria Jogova and Howard Meng, associate editors*

*Melini Gupta, EBM editor*

*Dr. Nirit Bernhard, Dr. Sohail Cheema, Dr. Steven Moss, Dr. Sharon Naymark and Dr. Angela Punnett, staff editors*
Pediatrics

Infectious Diseases ........................ 54
Fever
Acute Otitis Media (AOM)
Diphtheria
Gastroenteritis
HIV Infection
Infectious Pediatric Exanthems
Infectious Mononucleosis
Infectious Pharyngitis/Tonsilitis
Meningitis
Mumps
Pertussis
Pneumonia
Periorbital (Preseptal) and Orbital Cellulitis
Sexually Transmitted Infection
Sinusitis
Urinary Tract Infection (UTI)

Neonatology ................................. 66
Gestational Age (GA) and Size
Routine Neonatal Care
Neonatal Resuscitation
Approach to the Depressed Newborn

Common Conditions of Neonates ........ 69
Apnea
Bleeding Disorders in Neonates
Bronchopulmonary Dysplasia (BPD)
Cyanosis
Diaphragmatic Hernia
Hypoglycemia
Intraventricular Hemorrhage (IVH)
Jaundice
Necrotizing Enterocolitis (NEC)
Persistent Pulmonary Hypertension of the Newborn (PPHN)
Respiratory Distress in the Newborn
Retinopathy of Prematurity (ROP)
Common Neonatal Skin Conditions
Sepsis in the Newborn

Nephrology ................................. 79
Approach to Infant/Child with Dehydration
Common Pediatric Renal Disease
Hemolytic Uremic Syndrome (HUS)
Nephritic Syndrome
Nephrotic Syndrome
Hypertension in Childhood

Neurology ................................. 86
Seizure Disorders
Feverile Seizures
Recurrent Headache
Hypotonia
Cerebral Palsy (CP)
Neurocutaneous Syndromes
Acute Disseminated Encephalomyelitis (ADEM)

Neurosurgery ................................ NS35
Spinal Dysraphism
Hydrocephalus
Dandy-Walker Malformation
Chiari Malformations
Craniosynostosis
Brain Tumours

Orthopedics ............................... OR38
Fractures in Children
Stress Fractures
Epiphyseal Injury
Slipped Capital Femoral Epiphysis
Developmental Dysplasia of the Hip
Legg-Calve-Perthes Disease
Osgood-Schlatter Disease
Congenital Talipes Equinovarus (Club Foot)
Scoliosis

Otolaryngology ............................... OT38
Acute Otitis Media (AOM)
Otitis Media with Effusion (OME)
Adenoid Hypertrophy
Adenoidectomy
Sleep-Disordered Breathing
Acute Tonsillitis
Peritonsillar Abscess (Quinsy)
Tonsillectomy
Airway Problems
Signs of Airway Obstruction
Acute Laryngotraechobronchitis (Croup)
Acute Epiglottitis
Subglottic Stenosis
Laryngomalacia
Foreign Body
Deep Neck Space Infection

Plastic Surgery .............................. PL34
Craniofacial Anomalies
Congenital Hand Anomalies

Psychiatry ................................. PS33
The Child Psychiatric Interview
Developmental Concepts
Mood Disorders
Anxiety Disorders
Childhood Schizophrenia
Pervasive Developmental Disorders
Attention Deficit Hyperactivity Disorder
Oppositional Defiant Disorder
Conduct Disorder

Respirology ................................. 92
Approach to Dyspnea
Upper Respiratory Tract Diseases
Lower Respiratory Tract Diseases
Pneumonia
Bronchiolitis
Asthma
Cystic Fibrosis (CF)

Rheumatology ............................... 96
Evaluation of Limb Pain
Growing Pains
Transient Synovitis of the Hip
Septic Arthritis
Juvenile Idiopathic Arthritis (JIA)
Reactive Arthritis
Lyme Arthritis
Systemic Lupus Erythematous (SLE)
Vasculitides

Urology ..................................... U36
Congenital Abnormalities
Nephroblastoma (Wilms’ Tumour)
Cryptorchidism/Ectopic Testes
Disorders of Sexual Differentiation (DSD)
Circumcision

Common Medications ..................... 100

References ................................. 101

P2 Pediatrics

Toronto Notes 2014
### Pediatric Quick Reference Values

**Table 1. Average Vitals at Various Ages**

<table>
<thead>
<tr>
<th>Age</th>
<th>Pulse (bpm)</th>
<th>Respiratory Rate (br/min)</th>
<th>sBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>90-170</td>
<td>40-60</td>
<td>70-90</td>
</tr>
<tr>
<td>3-12 months</td>
<td>80-165</td>
<td>30-55</td>
<td>80-100</td>
</tr>
<tr>
<td>1-2 years</td>
<td>80-125</td>
<td>25-45</td>
<td>90-100</td>
</tr>
<tr>
<td>3-11 years</td>
<td>70-115</td>
<td>18-30</td>
<td>100-110</td>
</tr>
<tr>
<td>12-15 years</td>
<td>60-100</td>
<td>12-18</td>
<td>110-130</td>
</tr>
</tbody>
</table>

### Primary Care

**Visit Overview**

- **schedule:**
  - newborn (within 1 wk post-discharge), 1, 2, 4, 6, 9, 12, 15, 18, 24 mo
  - annually between age 2 to 6; every other year between age 6 to 11
- **content:**
  - history and physical exam including growth, development, and nutrition
  - routine immunization
  - counseling and anticipatory guidance

### Routine Immunization

**Table 2. Publicly Funded Immunization Schedule for Ontario, August 2011**

<table>
<thead>
<tr>
<th>Age</th>
<th>DTaP-IPV-Hib</th>
<th>dTaP-IPV</th>
<th>Pneu-C-13</th>
<th>Rot-1</th>
<th>Men-C-13</th>
<th>Var</th>
<th>MMRV</th>
<th>Men-C-ACYW</th>
<th>HepB</th>
<th>HPV-4</th>
<th>Tdap</th>
<th>Inf</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months</td>
<td>✓/IM</td>
<td>✓/IM</td>
<td>✓/IM</td>
<td>PO</td>
<td>✓/IM</td>
<td></td>
<td></td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 months</td>
<td>✓/IM</td>
<td>✓/IM</td>
<td>✓/IM</td>
<td>PO</td>
<td>✓/IM</td>
<td></td>
<td></td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓/IM</td>
<td></td>
<td></td>
<td>✓/IM</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>✓/IM</td>
<td>✓/IM</td>
<td>✓/IM</td>
<td>SC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 months</td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 months</td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-6 years</td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IM</td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 7</td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IM</td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 8 female</td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-16 years</td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every autumn</td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓/IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IM = intramuscular; PO = per oral; SC = subcutaneous

### Acronyms

**AAP** American Association of Pediatrists  
**ALPS** autoimmune lymphoproliferative syndrome  
**ADHD** attention deficit hyperactivity disorder  
**ARDS** acute respiratory distress syndrome  
**ASD** atrial septal defect  
**ATD** antithyroid drug  
**ATN** acute tubular necrosis  
**CAS** Children's Aid Society  
**CF** cystic fibrosis  
**CHD** congenital heart defect  
**CMV** cytomegalovirus  
**CP** cerebral palsy  
**CPS** Canadian Pediatric Society  
**DI** diabetes insipidus  
**DIC** disseminated intravascular coagulopathy  
**DM** diabetes mellitus  
**DS** Down syndrome  
**EBV** Epstein-Barr virus  
**FASD** fetal alcohol spectrum disorder  
**FSH** follicle stimulating hormone  
**FTD** failure to thrive  
**GA** gestational age  
**GERD** gastroesophageal reflux disease  
**GH** growth hormone  
**GN** glomerulonephritis  
**HE** hypoxic ischemic encephalopathy  
**HSP** Henoch-Schönlein purpura  
**HUS** hemolytic-uremic syndrome  
**IBW** ideal body weight  
**ICH** intracranial hemorrhage  
**IUGR** intra-uterine growth retardation  
**IVH** intraventricular hemorrhage  
**IVIG** intravenous immunoglobulin  
**LCH** luteinizing hormone  
**LLSB** left upper sternal border  
**LRTI** lower respiratory tract infection  
**NICU** neonatal intensive care unit  
**PDA** patent ductus arteriosus  
**PKU** phenylketonuria  
**PUVA** psoralen + UVA  
**RDS** respiratory distress syndrome  
**RUSP** right upper sternal border  
**SLE** systemic lupus erythematosus  
**TPN** total parenteral nutrition  
**UMN** upper motor neuron  
**URTI** upper respiratory tract infection  
**VSD** ventricular septal defect
Table 2. Publicly Funded Immunization Schedule for Ontario, August 2011 (continued)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Adverse Reaction</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP-IPV</td>
<td>Prolonged crying</td>
<td>Evolving unstable neurologic disease</td>
</tr>
<tr>
<td></td>
<td>Hypotonic unresponsive state (rare)</td>
<td>Hyporesponsive/hypotonic following previous vaccine</td>
</tr>
<tr>
<td></td>
<td>Seizure on day of vaccine (rare)</td>
<td>Anaphylactic reaction to neomycin or streptomycin</td>
</tr>
<tr>
<td>Rot-1</td>
<td>Cough</td>
<td>History of intussusception</td>
</tr>
<tr>
<td></td>
<td>Diarrhea, vomiting</td>
<td>Immunocompromised Abdominal disorder (e.g. Meckel’s diverticulum)</td>
</tr>
<tr>
<td></td>
<td>Especially painful injection</td>
<td>Received blood products (e.g. immunoglobulin) within 42 d</td>
</tr>
<tr>
<td>MMR</td>
<td>Measle-like rash (7-14d)</td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Lymphadenopathy, arthralgia, arthritis Parotitis (rare)</td>
<td>Immunocompromised infants (except healthy HIV positive children)</td>
</tr>
<tr>
<td></td>
<td>Especially painful injection</td>
<td>Anaphylactic reaction to gelatin</td>
</tr>
<tr>
<td>Var</td>
<td>Mild varicella-like papules or vesicles</td>
<td>Pregnant or planning to get pregnant within 3 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anaphylactic reaction to gelatin</td>
</tr>
<tr>
<td>HepB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMRV</td>
<td>Same as MMR and Var vaccines</td>
<td>Same as MMR and Var vaccines</td>
</tr>
<tr>
<td>dTAP</td>
<td>I1st trimester pregnancy</td>
<td></td>
</tr>
<tr>
<td>Inf</td>
<td>Malaise, myalgia</td>
<td>Egg-allergic individuals – unless the risk of the disease outweighs the small risk of a systemic hypersensitivity reaction. Referral to an allergy specialist is recommended, as vaccination might be possible after careful evaluation, skin testing and graded challenge or desensitization.</td>
</tr>
<tr>
<td></td>
<td>Febrile seizure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypersensitivity reaction</td>
</tr>
<tr>
<td>HPV-4</td>
<td>Pruritis</td>
<td></td>
</tr>
</tbody>
</table>

Vaccine Administration

- injection site:
  - infants (<12 mo): anterolateral thigh
  - children: deltoid
- timing of injection:
  - DTaP-IPV +Hib given in single injection
  - varicella and MMR vaccines given at either the same visit or separated by >4 wk (MMRV at 4-6 yr)
  - hepatatitis B vaccine given in 3 doses of 0.5 mL (0, 1, 6 mo) either at school in grade 7 (2 adult doses of 1 mL one month apart for teens) (Ontario) or at birth if at increased risk (i.e. endemic country, mother or household contact HBsAg positive)
  - HPV-4 vaccine given in 3 doses (0, 2, 6 mo) to grade 8 females in Ontario schools

Growth and Development

Growth
- growth is not linear:
  - most rapid growth during first two years and at puberty
  - tissues grow at different times
    - first two years = CNS; mid-childhood = lymphoid tissue; puberty = gonads
- measurement of growth:
  - premature infants (<37 wk) use corrected gestational age until age 2 yr
  - body proportion = upper / lower segment ratio (use symphysis pubis as midpoint)
    - newborn = 1.7, adult male = 0.97, adult female = 1.0

Vaccination in Cases of Asplenia or Hyposplenia (such as Sickle Cell Disease)
- Should receive all routine immunizations, including the yearly influenza vaccine
- No vaccines are contraindicated
- Susceptible to infection by encapsulated bacteria (S. pneumoniae, H. influenzae, N. meningitidis)
- For meningococcal, pneumococcal and Haemophilus influenzae b vaccines: regular vaccination in infancy according to recommended immunization schedules, PLUS:
  - Meningococcal vaccination:
    - Meningococcal-C-Conjugate at age ≥2 yr + Quadrivalent Men-P-ACWYW at least 2 wk later
    - Booster of Men-P-ACWYW q2-5 yr
  - Pneumococcal vaccination:
    - Pneumococcal polysaccharide vaccine (Pneu-P-23) at age ≥2 yr
    - Single booster of Pneu-P-23 at age ≥3 yr
  - Haemophilus influenzae type b vaccination:
    - Consider single booster at age ≥5 yr

According to the CDC, the weight of currently available scientific evidence does not support the hypothesis that MMR vaccine causes either autism or IBD. The landmark paper linking autism to the MMR vaccine (Lancet 1998;351:637-641) was retracted due to false claims in the article (Lancet 2010;375:445).

Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis
NEJM 2006;354:11-22
Study: Randomized, double-blind, phase 3 trial. Patients: 83,256 healthy infants from Latin America and Finland.
Intervention: Two oral doses of HRV vaccine vs. placebo at 2 and 4 mo of age.
Outcome: Episodes of gastroenteritis and severity
Results: The vaccine is 85% efficacious against severe rotavirus gastroenteritis and hospitalizations associated with gastroenteritis and 100% efficacious against more severe gastroenteritis.
Average Growth Parameters

Table 3. Parameter of Average Growth

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Growth</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight</td>
<td>3.25 kg (7 lbs)</td>
<td>Gain 20-30 g/d (term neonate)</td>
<td>Weight loss (up to 10% of birth wt) in first 7 d of life is normal. Neoneate should regain birth weight by ~10-14 d of age.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 x birth wt by 4-5 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 x birth wt by 1 yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 x birth wt by 2 yr</td>
<td></td>
</tr>
<tr>
<td>Length/Height</td>
<td>50 cm (20 in)</td>
<td>25 cm in 1st yr</td>
<td>Measure supine length until 2 yr of age, then measure standing height.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 cm in 2nd yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 cm in 3rd yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-7 cm/yr until puberty</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/2 adult height at 2 yr</td>
<td></td>
</tr>
<tr>
<td>Head Circumference</td>
<td>35 cm (14 in)</td>
<td>2 cm/mo for 1st 3 mo</td>
<td>Measure around occipital, parietal, and frontal prominences to obtain the greatest circumference.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 cm/mo at 3-6 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 cm/mo at 6-12 mo</td>
<td></td>
</tr>
</tbody>
</table>

Reflexes

Table 4. Reflexes

<table>
<thead>
<tr>
<th>Reflex</th>
<th>Maneuver to Elicit Reflex</th>
<th>Appropriate Reflex Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moro</td>
<td>Infant placed semi-upright, head supported by examiner’s hand, sudden withdrawal of supported head with immediate resupport</td>
<td>Abduction and extension of the arms, opening of the hands, followed by flexion and adduction of arms</td>
</tr>
<tr>
<td>Galant</td>
<td>Infant held in ventral suspension and one side of back is stroked along paravertebral line</td>
<td>Pelvis will move in the direction of stimulated side</td>
</tr>
<tr>
<td>Grasp</td>
<td>Placement of examiner’s finger in infant’s palm</td>
<td>Flexion of infant’s fingers</td>
</tr>
<tr>
<td>ATNR</td>
<td>Turn infant’s head to one side</td>
<td>“Fencing” posture (extension of ipsilateral arm and arm and flexion of contralateral leg)</td>
</tr>
<tr>
<td>Placing</td>
<td>Dorsal surface of infant’s foot placed touching edge of table</td>
<td>Flexion followed by extension of ipsilateral limb up onto table (remakes primitive walking)</td>
</tr>
<tr>
<td>Rooting</td>
<td>Tactile stimulus near mouth</td>
<td>Infant pursues stimulus with face</td>
</tr>
<tr>
<td>Parachute</td>
<td>Tilt infant to side while in sitting position</td>
<td>Ipsilateral arm extension, present by 6-8 mo</td>
</tr>
</tbody>
</table>

ATNR = asymmetric tonic neck reflex

Abnormal Reflex Response

- Absence may suggest CNS abnormality
- Persistence after 4-6 mo may indicate abnormality (e.g. cerebral palsy)
- Asymmetry suggests focal motor lesions (e.g. brachial plexus injury)
- Upgoing plantar reflex (Babinski’s sign) normal in infants up to age 2 yr

Developmental Milestones

Table 5. Developmental Milestones

<table>
<thead>
<tr>
<th>Age*</th>
<th>Gross Motor</th>
<th>Fine Motor</th>
<th>Speech and Language</th>
<th>Adaptive and Social Skills</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>Turns head side to side when supine</td>
<td>Hands fist, thumb in fist</td>
<td>Cries, startles to loud noises</td>
<td>Calms when comforted</td>
</tr>
<tr>
<td>2 months</td>
<td>Briefly raises head when prone, holds head erect when upright</td>
<td>Pulls at clothes</td>
<td>Variety of sounds (e.g. coos, gurgles)</td>
<td>Smiles responsively, recognizes and calms down to familiar voice, follows movement with eyes</td>
</tr>
<tr>
<td>4 months</td>
<td>Lifts head and chest when prone, holds head steady when supported sitting, rolls prone to supine</td>
<td>Briefly holds object when placed in hand, reaches for midline objects</td>
<td>Turns head towards sounds</td>
<td>Laughs responsively, follows moving toy or person with eyes, responds to people with excitement (e.g. leg movement)</td>
</tr>
<tr>
<td>6 months</td>
<td>Tripod sit, pivots in prone position</td>
<td>Ulnar grasp, transfers objects from hand to hand, brings objects to mouth</td>
<td>Babbles</td>
<td>Stranger anxiety, beginning of object permanence</td>
</tr>
<tr>
<td>9 months</td>
<td>Sits well without support, crawls, pulls to stand, stands with support</td>
<td>Early pincer grasp with straight wrist</td>
<td>“Mama, dada” – appropriate, imitates 1 word, responds to “no” regardless of tone</td>
<td>Plays games (e.g. peek-a-boo), reaches to be picked up</td>
</tr>
<tr>
<td>12 months</td>
<td>Gets into sitting position without help, stands without support, walks while holding on</td>
<td>Neat pincer grasp, releases ball with throw</td>
<td>2 words, follows 1-step command, uses facial expression, sounds, actions to make needs known</td>
<td>Responds to own name, separation anxiety begins</td>
</tr>
</tbody>
</table>

Scoliosis Screening

Despite mass school screening implemented in parts of the USA and Canada in the 1970s-90s, the Canadian (1994) and American (2004) Task Forces on Preventive Health Care do NOT currently recommend routine screening using the Forward Bend Test (FBT). Cohort studies indicate that the forward bend test has poor sensitivity for identifying pathological curves. Furthermore, there is no evidence to suggest that screening and increased bracing lead to better outcomes.

Pediatric Developmental Milestones

- 1 yr: single words
- 2 yr: 2-word sentences; understands 2 step commands
- 3 yr: 3-word combinations; rides tricycle
- 4 yr: counts 4 objects

*Use corrected gestational age until 2 yr
Table 5. Developmental Milestones (continued)

<table>
<thead>
<tr>
<th>Age*</th>
<th>Gross Motor</th>
<th>Fine Motor</th>
<th>Speech and Language</th>
<th>Adaptive and Social Skills</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 months</td>
<td>Walks without support, crawls up stairs/steps</td>
<td>Picks up and eats finger foods, scribbles, stacks 2 blocks</td>
<td>Says 4-5 words, points to needs/wants</td>
<td>Looks to see how others react (e.g. after falling)</td>
</tr>
<tr>
<td>18 months</td>
<td>Runs, walks forward pulling toys or carrying objects</td>
<td>Tower of 3 cubes, scribbling, eats with spoon</td>
<td>10 words, follows simple commands</td>
<td>Show affection towards others, points to show interest in something</td>
</tr>
<tr>
<td>24 months</td>
<td>Climbs up 2 feet per step, runs, kicks ball, walks up and down steps</td>
<td>Tower of 6 cubes, undresses</td>
<td>2-3 word phrases, uses “I, me, you”, 50% intelligible, understands 2-step commands</td>
<td>Parallel play, helps to dress</td>
</tr>
<tr>
<td>3 years</td>
<td>Tricycle, climbs up 1 foot per step, down 2 feet per step, stands on one foot briefly</td>
<td>Copies a circle, turns pages one at a time, puts on shoes, dress/undress fully except buttons</td>
<td>Combines 3 or more words into sentence, recognizes colors, prepositions, plurals, counts to 10, 75% intelligible</td>
<td>Knows sex, age, shares some of the time, plays make-believe games</td>
</tr>
<tr>
<td>4 years</td>
<td>Hops on 1 foot, down 1 foot per step</td>
<td>Copies a cross, uses scissors, buttons clothes</td>
<td>Speech intelligible, uses past tense, 100% intelligible, understands 3-part directions</td>
<td>Cooperative play, fully toilet-trained by day, tries to comfort someone who is upset</td>
</tr>
<tr>
<td>5 years</td>
<td>Skips, rides bicycle</td>
<td>Copies a triangle and square, prints name, ties shoelaces</td>
<td>Fluent speech, future tense, alphabet, retells sequence of a story</td>
<td>Cooperates with adult requests most of the time, separates easily from caregiver</td>
</tr>
</tbody>
</table>

*Use corrected gestational age until 2 yr

**Nutrition**

**Dietary Requirement**

<table>
<thead>
<tr>
<th>Weight</th>
<th>&lt;10 kg</th>
<th>10-20 kg</th>
<th>&gt;20 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>kcal</td>
<td>100 kcal/kg/d</td>
<td>1000 kcal + 50 kcal/kg/d for each kg &gt;10</td>
<td>1500 kcal + 20 kcal/kg/d for each kg &gt;20</td>
</tr>
</tbody>
</table>

**Dietary Recommendations**

- 0 to 6 months: breast milk or formula
  - exclusive breast milk during first 6 mo recommended over formula unless contraindicated
  - breastfed infants require supplements: vitamin K (all babies get at birth, breastfed or not), vitamin D (400-800 IU/d), fluoride (after 6 mo if not sufficient in water), iron (6-12 mo, only if not receiving fortified cereals/meat/meat alternatives)
- >6 months: solid food introduction – do not delay beyond 9 mo
  - 2 to 3 new foods per week with a few days in between each food to allow time for adverse reaction identification
  - suggested order of introduction:
    - meat, meat alternatives, and iron enriched cereal (rice cereal is least allergenic)
    - pureed vegetables
    - fruit
  - 9 to 12 months: finger foods and switch to homogenized (3%) milk
    - foods to avoid:
      - honey until past 12 mo (risk of botulism)
      - added sugar, salt
      - excessive milk (i.e. no more than 16 oz/d after a yr)
      - juice (not nutritious, too much sugar)
      - anything that is a choking hazard (chunks, round foods like grapes)

**Breastfeeding**

- content of breast milk:
  - colostrum (first few days): clear, rich in nutrient (i.e. high protein, low fat), immunoglobulin
  - mature milk: 70:30 whey:casein ratio, fat from dietary butterfat, carbohydrate from lactose
- advantages:
  - easily digested, low renal solute load
  - immunologic
    - contains IgA, macrophages, active lymphocytes, lysozymes, lactoferrin (which inhibits E. coli growth in intestine)
    - lower pH promotes growth of lactobacillus in GI tract
  - parent-child bonding
  - economical, convenient
• contraindicated if mother:
  • is receiving chemotherapy or radioactive compounds
  • has HIV/AIDS, active untreated TB, herpes in breast region
  • is using >0.5 g/kg/d alcohol or illicit drugs
  • is taking medications known to cross to breast milk
  • oral contraceptive pills *not* a contraindication to breastfeeding (estrogen may decrease lactation, but is not dangerous to infant)
  • MotherRisk – valuable research and counselling on reproductive risk or safety of drugs, chemicals, and maternal disease

complications in infant:
• breastfeeding jaundice (first 1-2 wk): due to lack of milk production and subsequent dehydration (see jaundice, P73), likely mechanical problem
• breast milk jaundice (0.5% of newborns, persists up to 4-6 mo): rare, not fully understood, thought to be due to substances in breast milk that inhibit conjugation of bilirubin or increase enterohepatic circulation of bilirubin, likely a biochemical problem. Check bilirubin rule out conjugated hyperbilirubinemia.
  • baby presents healthy and thriving, and jaundice resolves
  • poor weight gain: consider dehydration or failure to thrive
  • oral candidiasis (thrush): check baby’s mouth for white cheesy material that does not scrape off; treat baby with antifungal such as nystatin (Mycostatin®) (treat mother topically to prevent transmission). Can occur in breast or bottle-fed infants.

### Table 6. Formula Compared to Breast Milk

<table>
<thead>
<tr>
<th>Type of Nutrition</th>
<th>Indications</th>
<th>Content (as compared to breast milk)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cow’s milk based</strong> (Enfamil®, Similac®)</td>
<td>Prematurity Transition into breastfeed Contraindication to breastfeed</td>
<td>Lower whey:casein ratio Plant fats instead of dietary butterfat</td>
</tr>
<tr>
<td><strong>Fortified formula</strong></td>
<td>Low birth weight Prematurity</td>
<td>Higher calories and vitamins A, C, D, K May only be used in hospital due to risk of fat-soluble vitamin toxicity</td>
</tr>
<tr>
<td><strong>Soy protein</strong> (Isomil®, Prosobee®)</td>
<td>Galactosemia Lactose intolerance (note: true lactose intolerance rare in children under age 5)</td>
<td>Corn syrup solids or sucrose in place of lactose</td>
</tr>
<tr>
<td><strong>Partially hydrolyzed proteins</strong> (Good Start®)</td>
<td>Delayed gastric emptying Risk of cow’s milk allergy</td>
<td>Protein is 100% whey with no casein</td>
</tr>
<tr>
<td><strong>Protein hydrolysate</strong> (Nutramigen®, Alimentum®, Pregestimil®, Portagen®)</td>
<td>Malabsorption Food allergy</td>
<td>Protein is 100% casein with no whey Cori syrup solids, sucrose or tapioca starch instead of lactose Expensive</td>
</tr>
<tr>
<td><strong>Amino acid</strong> (Neocate®)</td>
<td>Food allergy Short gut</td>
<td>Free amino acids (no protein) Cori syrup solids instead of lactose Very expensive</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>Inborn errors of metabolism</td>
<td>Various different compositions for children with galactosemia, propionic acidemia, etc.</td>
</tr>
</tbody>
</table>

### Injury Prevention Counselling

- injuries are the leading cause of death in children >1 yr of age
- main causes: motor vehicle crashes, burns, drowning, falls, choking, infanticide

### Table 7. Injury Prevention Counselling

<table>
<thead>
<tr>
<th>0-6 months</th>
<th>6-12 months</th>
<th>1-2 years</th>
<th>2-5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not leave alone on bed, on change table or in tub</td>
<td>Install stair barriers</td>
<td>Never leave unattended</td>
<td>Bicycle helmet</td>
</tr>
<tr>
<td>Keep crib rails up</td>
<td>Discourage use of walkers</td>
<td>Keep pot handles turned to back of stove</td>
<td>Never leave unsupervised at home, driveway or pool</td>
</tr>
<tr>
<td>Check water temperature before bathing</td>
<td>Avoid play areas with sharp-edged tables and corners</td>
<td>Caution with whole grapes, nuts, raw carrots, hotdogs, etc. due to choking hazard</td>
<td>Teach bike safety, stranger safety, and street safety</td>
</tr>
<tr>
<td>Do not hold hot liquid and infant at the same time</td>
<td>Cover electrical outlets</td>
<td>No running while eating</td>
<td>Swimming lessons (&gt;4 yr), sunscreen (from 6 mo), toddler seats in the car, fences around pools, dentist by age 3</td>
</tr>
<tr>
<td>Check milk temperature before feeding</td>
<td>Unplug appliances when not in use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate car seats are required before leaving hospital</td>
<td>Keep small objects, plastic bags, cleaning products, and medications out of reach</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Common Complaints

Breath Holding Spells

- epidemiology: 0.1-5% of healthy children 6 mo-4 yr of age, usually start during first year of life
- etiology: child is provoked (usually by anger, injury, or fear) → holds breath and becomes silent
  - spontaneously resolves or loses consciousness
- types:
  - cyanotic (more common), usually associated with anger/frustration
  - pallid, usually associated with pain/surprise
- management:
  - usually resolves spontaneously and rarely progresses to seizure
  - help child control response to frustration and avoid drawing attention to spell

Circumcision

- elective procedure
  - not covered by OHIP in Ontario, but recent evidence shows health benefits outweigh risks and justify access to procedure
  - often for religious or culture reasons
- benefits: prevention of phimosis and slightly reduced incidence of UTI, balanitis, cancer of the penis
- complications (<1%): local infection, bleeding, urethral injury
- contraindications: presence of genital abnormalities (e.g. hypospadias) or known bleeding disorder

Crying/Fussing Child

- history:
  - description of baseline feeding, sleeping, crying patterns
  - infectious symptoms: fever, tachypnea, rhinorrhea, ill contacts
  - feeding intolerance: gastroesophageal reflux with esophagitis, nausea, vomiting, diarrhea, constipation
  - trauma
  - recent immunizations (vaccine reaction) or medications (drug reactions), including maternal drugs taken during pregnancy (neonatal withdrawal syndrome) and drugs that may be transferred via breast milk
  - inconsistent history, pattern of numerous emergency department visits, high-risk social situations all raise concern of abuse

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Examination Findings</th>
<th>Possible Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEENT</td>
<td>Bulging fontanelle</td>
<td>Meningitis, shaken baby syndrome, hydrocephalus</td>
</tr>
<tr>
<td></td>
<td>Blepharospasm, tearing</td>
<td>Corneal abrasion, glaucoma</td>
</tr>
<tr>
<td></td>
<td>Retinal hemorrhage</td>
<td>Shaken baby syndrome</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal infections</td>
<td>Thrush, gingivostomatitis, herpangina, otitis media</td>
</tr>
<tr>
<td>Neurological</td>
<td>Irritability or lethargy</td>
<td>Meningitis, shaken baby syndrome</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Poor perfusion</td>
<td>Sepsis, anomalous coronary artery, meningitis, myocarditis, congestive heart failure (CHF)</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td>Supraventricular tachycardia</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tachypnea</td>
<td>Pneumonia, CHF</td>
</tr>
<tr>
<td></td>
<td>Grunting</td>
<td>Respiratory disease, response to pain</td>
</tr>
<tr>
<td>Abdominal</td>
<td>Mass, empty RLQ</td>
<td>Intussusception</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Scrotal swelling</td>
<td>Incarcerated hernia, testicular torsion</td>
</tr>
<tr>
<td></td>
<td>Penile/clitoral swelling</td>
<td>Hair tourniquet</td>
</tr>
<tr>
<td>Rectal</td>
<td>Anal fissure</td>
<td>Constipation or diarrhea</td>
</tr>
<tr>
<td></td>
<td>Hemoccult positive stool</td>
<td>Intussusception, necrotizing enterocolitis, volvulus</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Point tenderness or decreased movement</td>
<td>Fracture, syphilis, osteomyelitis, toe/finger hair tourniquet</td>
</tr>
</tbody>
</table>
Dentition and Caries

Dentition
- primary dentition (20 teeth)
  - first tooth at 5-9 mo (lower incisor), then 1 per month
  - 6-8 central teeth by 1 yr
  - assessment by dentist 6 mo after eruption of first tooth and certainly by 1 yr of age (Grade B recommendation)
- secondary dentition (32 teeth)
  - first adult tooth is 1st molar at 6 yr, then lower incisors

Caries
- milk caries: decay of superior front teeth and back molars in first 4 yr of life
- cause: often due to prolonged feeding (e.g. put to bed with bottle, prolonged breastfeeding)
- prevention:
  - no bottle at bedtime, clean teeth after last feed
  - minimize juice and sweetened pacifier
  - clean teeth with soft damp cloth or toothbrush and water
  - water fluoridation

Enuresis

Definition
- involuntary urinary incontinence by day and/or night in child >5 yr

General Approach
- should be evaluated if dysuria, change in colour, odour, stream, secondary or diurnal, change in gait, stool incontinence

Primary Nocturnal Enuresis
- definition: wet only at night during sleep, bladder control has never been attained
- epidemiology: boys > girls; 10% of 6 yr olds, 3% of 12 yr olds, 1% of 18 yr olds
- etiology: developmental disorder or maturational lag in bladder control while asleep
- management:
  - time and reassurance (~20% resolve spontaneously each yr)
  - behaviour modification (limiting fluids, voiding prior to sleep), bladder retention exercises, scheduled toileting has limited effectiveness
  - conditioning: "wet" alarm wakes child upon voiding (70% success rate)
  - medications (considered second line therapy, may be used for sleepovers/camp): DDAVP oral tablets (high relapse rate, costly), imipramine ('Tofranil') (rarely used, lethal if overdose, cholinergic side effects)

Secondary Enuresis
- definition: develops after child has sustained period of bladder control (>6 mo)
- etiology: inorganic regression due to stress or anxiety (e.g. birth of sibling, significant loss, family discord), focused on other activities, secondary to organic disease (UTI, DM, DI, neurogenic bladder, cerebral palsy (CP), sickle cell disease, seizures, pinworms)
- management: treat underlying cause

Diurnal Enuresis
- definition: daytime wetting (60-80% also wet at night)
- etiology: micturition deferral (holding urine until last minute) due to psychosocial stressor (e.g. shy), structural anomalies (e.g. ectopic ureteral site, neurogenic bladder), UTI, constipation, CNS disorders
- management: treat underlying cause, behavioural (scheduled toileting, double voiding, good bowel program), pharmacotherapy

Encopresis
- definition: fecal incontinence in a child >4 yr old, at least once per month for 3 months
- prevalence: 1-1.5% of school-aged children (rare in adolescence); M:F = 6:1 in school-aged children
- causes: chronic constipation (retentive encopresis), Hirschsprung disease, hypothyroidism, hypercalcemia, spinal cord lesions, anorectal malformations
Retentive Encopresis
• definition
  • child holds bowel movement, develops constipation, leading to fecal impaction and seepage of soft or liquid stool (overflow incontinence)
• etiology
  • physical: painful stooling often secondary to constipation
  • emotional: disturbed parent-child relationship, coercive toilet training, social stressors
• clinical presentation
  • history
    • crosses legs or stands on toes to resist urge to defecate
    • distressed by symptoms, soiling of clothes
    • toilet training coercive or lacking in motivation
    • may show oppositional behavior
    • abdominal pain
  • physical exam
    • digital rectal exam: large fecal mass in rectal vault
    • anal fissures (result from passage of hard stools)
    • palpable stool in LLQ
• management
  • complete clean-out of bowel: PEG 3350 given orally is most effective, enemas and suppositories may be second line therapies, but these are invasive and often less effective
  • maintenance of regular bowel movements (see Pediatric Gastroenterology, Constipation Treatment, P38)
  • assessment and guidance regarding psychosocial stressors
  • behavioural modification
• complications: recurrence, toxic megacolon (requires >3-12 mo to treat), bowel perforation

Failure to Thrive
• definition
  • weight <3rd percentile, or falls across two major percentile curves, or <80% of expected weight for height and age
  • inadequate caloric intake most common factor in poor weight gain
  • may have other nutritional deficiencies (e.g. protein, iron, vitamin D)
  • factors affecting physical growth: genetics, intrauterine factors, internal time clock, nutrition, endocrine hormones, chronic infections/diseases, psychosocial factors
• clinical presentation
  • history
    • nutritional intake
    • current symptoms
    • past illnesses
    • family history: growth, puberty, parental height and weight including mid-parental height
    • psychosocial history
  • physical exam
    • growth parameters, plotted: height (Ht), weight (Wt), head circumference (HC), arm span
    • vital signs
    • complete head to toe exam
    • dysmorphic features or evidence of chronic disease
    • upper to lower segment ratio
    • sexual maturity staging
    • signs of abuse or neglect
• investigations (as indicated by clinical presentation)
  • CBC, blood smear, electrolytes, T4, TSH, GH, IGF-1
  • bone age x-ray
  • chromosomes/karyotype
  • chronic illness: chest (CXR, sweat Cl-), cardiac (CXR, ECG, ECHO), GI (celiac screen, inflammatory markers, malabsorption), renal (urinalysis), liver (enzymes, albumin)
• Energy Requirements
  • 0-10 kg: 100 kcal/kg/d
  • 1-20 kg: 1,000 kcal + 50 kcal/kg/d for each kg >10
  • >20 kg: 1,500 kcal + 20 kcal/kg/d for each kg >20
• Calculating Upper to Lower (U/L) Segment Ratio
  • Upper segment: Top of head to pubic symphysis
  • Lower segment: Pubic symphysis to floor
  • U/L: upper segment/lower segment
• Upper to Lower (U/L) Segment Ratio
  • Increased in achondroplasia, short limb syndromes, hypothyroid, storage diseases
  • Decreased in Marfan’s, Klinefelter’s, Kallman’s syndromes, and testosterone deficiency
• Mid-Parental Height (MPH)
  • Boys target height = (father ht + mother ht + 13)/2
  • Girls target height = (father ht + mother ht -13)/2

Table 9. Failure to Thrive Patterns

<table>
<thead>
<tr>
<th>Healthy</th>
<th>Medical Illness</th>
<th>Non-Organic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight and height</strong> proportionally small</td>
<td><strong>Weight and height</strong> proportionally small Syndrome Chromosomal</td>
<td><strong>Weight</strong> falls more than height (FTT) Multifactorial</td>
</tr>
<tr>
<td>Familial (BA = CA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constitutional Growth Delay (BA &lt; CA)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BA=bone age; CA=chronological age
**Energy Requirements**
- see Nutrition, P6

**Infantile Colic**
- definition: unexplained paroxysms of irritability and crying for >3 h/d, >3 d/wk for >3 wk in an otherwise healthy, well-fed baby (rule of 3s)
- epidemiology: 10% of infants; usual onset 10 d to 3 mo of age with peak at 6-8 wk
- etiology: lag in development of normal peristaltic movement in gastrointestinal tract; other theories suggest a lack of self-soothing mechanisms or extreme of normal
- management:
  - parental relief, rest and reassurance
  - hold baby, soother, car ride, music, vacuum, check diaper
  - medications (Ovol® drops, gripe water) have no proven benefit, some evidence for probiotics
  - if breastfeeding, elimination of cow's milk protein from mother's diet (effective in very small percentage of cases)
  - try casein hydrosylates formula (Nutramigen®)
  - if breastfeeding is not possible, consider formula
  - time – all resolve, most in the first 2-3 mo of life

**Obesity**
- definition: BMI >95th percentile for age and height
- risk factors: genetic predisposition (e.g. both parents obese – 80% chance of obese child)
- etiology: organic causes are rare (<5%): Prader-Willi, Carpenter, Turner, Cushing syndromes, hypothryoidism
- complications: association with hypertension, dyslipidemia, slipped capital femoral epiphysis, type 2 diabetes, asthma, obstructive sleep apnea, gynecomastia, polycystic ovarian disease, early menarche, irregular menses, psychological trauma (e.g. teasing, decreased self-esteem, unhealthy coping mechanisms, depression)
- childhood obesity is not reliable predictor of adult obesity unless >180% ideal body weight, adolescent obesity good predictor of adult obesity
- management:
  - encouragement and reassurance; engagement of entire family
  - diet: qualitative changes (do not encourage weight loss, but allow for linear growth to catch up with weight), special diets used by adults are not encouraged
  - very low calorie diets for preadolescents are not recommended
  - behaviour modification: increase activity, change eating habits/meal patterns
  - education: multidisciplinary approach, dietitian, counselling
  - surgery and pharmacotherapy are not frequently used in children
  - increase activity; reduce screen time
Poison Prevention

- keep all types of medicines, vitamins, and chemicals locked up in a secure container
- potentially dangerous: drugs, drain cleaners, furniture polish, insecticides, cosmetics, nail polish remover, automotive products
- do not store any chemicals in juice, soft drink, or water bottles
- keep alcoholic beverages out of reach: 3 oz hard liquor can kill a 2-yr-old
- always read labels before administering medicine to ensure correct drug and dose

Rashes

Table 10. Common Pediatric Rashes

<table>
<thead>
<tr>
<th>Type of Rash</th>
<th>Differential</th>
<th>Appearance</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaper Dermatitis</td>
<td>Irritant contact dermatitis</td>
<td>Shiny, red macules/patches, no flexural involvement</td>
<td>Eliminate direct skin contact with urine and feces, allow periods of rest without a diaper, frequent diaper changes, topical barriers (petrolatum, zinc oxide or paste), short-term low-potency topical corticosteroids (severe cases)</td>
</tr>
<tr>
<td></td>
<td>Seborrheic dermatitis</td>
<td>Yellow, greasy macules/plaques on erythema, scales</td>
<td>Short-term topical low-potency corticosteroid</td>
</tr>
<tr>
<td></td>
<td>Candidal dermatitis</td>
<td>Erythematous macerated papules/plaques, satellite lesions</td>
<td>Antifungal agents</td>
</tr>
</tbody>
</table>

Other Dermatitis

- Atopic dermatitis
  - Erythematous papules/plaques, oozing, excoriation, lichenification, classic areas of involvement
  - Eliminate exacerbating factors, maintain skin hydration, corticosteroids, topical calcineurin inhibitor
- Nummular dermatitis
  - Annular erythematous plaques, oozing, crust
  - Avoid irritant if identified, potent topical steroid in emollient base, short-term systemic steroids ± antibiotics (severe)
- Allergic contact dermatitis
  - Red papules/plaques-vesicles/bullaes, only in area of allergen
  - Mild: soothing lotion (i.e. calamine lotion)
  - Moderate: topical moderate/strong potency
  - Severe: systemic corticosteroids and antihistamine
- Irritant contact dermatitis
  - Morphology depends on irritant
  - Avoid skin contact
- Dyshidrotic dermatitis
  - Papulovesicular, cracking/fissuring, hands and feet (“Tapioca pudding”)
  - Mild/Moderate: medium/potent topical corticosteroids
  - Severe: systemic corticosteroids, local PUVA or UVA treatments
- Seborrheic dermatitis
  - See above, sebaceous areas such as nasolabial folds and scalp

Infectious

- Scabies
  - Polyomorphic (red excoriated papules/nodules, burrows), in web spaces/folds, very pruritic
  - Permethrin (Nix) 5% cream for patient and family (2 applications, 1 wk apart)
- Impetigo
  - Honey-coloured crusts or superficial bullae
  - Oral antibiotics (e.g. cephalaxin/erythromycin)
  - Topical if mild: fucidic acid or mupirocin cream
- Tinea corporis
  - Round erythematous plaques, central clearing and scaly border
  - Topical anti-fungal for skin, systemic anti-fungals for nails/head

Pediatric Exanthems (see Infectious Pediatric Exanthems, P58, Dermatology, D40)

Drug Reactions (see Dermatology, D22)

Acne (see Dermatology, D11)

Sleep Disturbances

Types of Sleep Disturbances

- insufficient sleep quantity
  - difficulty falling asleep (e.g. Limit Setting Sleep Disorder)
    - preschool and older children
    - bedtime resistance
    - due to caregiver’s inability to set consistent bedtime rules and routines
    - often exacerbated by child’s oppositional behaviours
• poor sleep quality
  ▪ frequent arousals (e.g. sleep-onset association disorder)
  ▪ child learns to fall asleep only under certain conditions or associations (with parent, held, rocked or fed, with light on, in front of television), and child loses ability to self-soothe
  ▪ during the normal brief arousal periods of sleep (90-120 min), child cannot fall back asleep because same conditions are not present
• obstructive sleep apnea
  ▪ epidemiology: 1-5% of preschool aged children, more common in black children
  ▪ definition: partial or intermittent complete airway obstruction during sleep causing disrupted ventilation and sleep pattern
  ▪ features: snoring/gasping/noisy breathing during sleep and irritable/tired/hyperactive during the day
  ▪ sequelae: cardiovascular (hypertension/LV remodeling due to sympathetic activation), growth, cognitive, and behavioural deficits
  ▪ risk factors: adenotonsillar hypertrophy, obesity
  ▪ management: watchful waiting, weight reduction, airway pressure devices, or surgery depending on the cause
  ▪ adenotonsillectomy does not improve executive function or attention but reduces symptoms and improves behaviour, quality of life, and polysomnographic findings
• parasomnias
  ▪ episodic nocturnal behaviours
  ▪ often involves cognitive disorientation and autonomic/skeletal muscle disturbance
  ▪ e.g. sleep walking, sleep terrors, nightmares

Management of Sleep Disturbances
• set strict bedtimes and “wind-down” routines
• do not send child to bed hungry
• positive reinforcement for limit setting sleep disorder
• always sleep in bed, in a dark, quiet, and comfortable room, without associations
• do not use bedroom for timeouts
• systematic ignoring and gradual extinction for sleep onset association disorder

Nightmares
• epidemiology: common in boys, 4-7 yr old
• associated with REM sleep (anytime during night)
• features: upon awakening, child is alert and clearly recalls frightening dream
  ▪ ± associated with daytime stress/anxiety
• management: reassurance

Night Terrors
• epidemiology: 15% of children have occasional episodes
• abrupt sitting up, eyes open, screaming
• clinical features: occurs in early hours of sleep, stage 4 of sleep; signs of panic and autonomic arousal, no memory of event, unconsolable, stress/anxiety can aggravate them
• course: remits spontaneously at puberty
• management: reassurance for parents, ensure child is safe (e.g. if sleepwalks)

Toilet Training
• 90% of children attain bladder control before bowel control
• generally females train earlier than males
• 25% by 2 yr old (in North America), 98% by 3 yr old have daytime bladder control
• signs of toilet readiness:
  ▪ ambulating independently, stable on potty, desire to be independent or to please caregivers (i.e. motivation), sufficient expressive and receptive language skills (2-step command level), can stay dry for several hours (large enough bladder), can recognize need to go, able to remove clothing

Sudden Infant Death Syndrome (SIDS)

Definition
• sudden and unexpected death of an infant <12 mo of age in which the cause of death cannot be found by history, examination, or a thorough postmortem and death scene investigation

Epidemiology
• 0.5/1000 (leading cause of death between 1-12 mo of age); M:F = 3:2
• more common in children placed in prone position
• in full term infants, peak incidence is 2-4 mo, 95% of cases occur by 6 mo
• increase in deaths during peak respiratory syncytial virus (RSV) season
• most deaths occur between midnight and 8 AM
Risk Factors
• prematurity, smoking in household, socially disadvantaged, higher incidence in aboriginals and African Americans
• risk of SIDS is increased 3-5x in siblings of infants who have died of SIDS

Prevention
• “Back to Sleep, Front to Play” (place infant on back when sleeping)
• allow supervised play time daily in prone position (‘tummy time’)
• alarms, monitors not recommended – increase anxiety, do not prevent life-threatening events
• avoid overheating and overdressing
• appropriate infant bedding (firm mattress, avoid loose bedding and crib bumper pads)
• no smoking
• risks associated with bedsharing: sleeping on a sofa, sleeping with an infant after consumption of alcohol/street drugs, infant sleeping with someone other than primary caregiver
• pacifiers appear to have a protective effect; do not reinsert if falls out

Child Abuse and Neglect

Definition
• an act of commission (physical, sexual, or psychological abuse) or omission (neglect) by a caregiver that harms a child

Legal Duty to Report
• upon reasonable grounds to suspect abuse and/or neglect, physicians are required by legislation to contact the Child Protective Services (CPS) to personally disclose all information relevant to the child safety concern
• duty to report overrides patient confidentiality; physician is protected against liability

Ongoing Duty to Report
• if there are additional reasonable grounds to suspect abuse and/or neglect, a further report to the CPS must be made

Risk Factors
• environmental factors: social isolation, poverty, domestic violence
• caregiver factors: personal history of abuse, psychiatric illness, substance abuse, single parent family, poor social and vocational skills, below average intelligence
• child factors: difficult temperament, disability, special needs (e.g. developmental delay), premature

Physical Abuse

History
• history that is not compatible with physical findings, or history not reproducible
• delay in seeking medical attention that is unexplained by other factors

Physical Exam
• physical findings not explained by underlying medical condition
• growth parameters (weight, height, head circumference)
• recurrent or multiple injuries not explained by accidental injury or child’s development level
• patterned skin injuries: belt buckle, hand prints, burns that do not match provided history
• injury location: bruises on areas with abundant soft-tissue cushioning, such as abdomen, buttocks, genitalia, fleshy part of cheek; bruises on ears; posterior rib/metaphyseal/scapular/vertebral/skeletal fractures (more suspicious for non-accidental injuries); immersion burns (e.g. hot water)
• altered mental status: head injury, poisoning
• head trauma is the leading cause of death in child maltreatment [e.g. acceleration-deceleration forces (shaking), direct force application (blow or impact)]

Investigations
• document all injuries on a body diagram: type, location, size, shape, colour, pattern
  • photography of skin injuries is ideal (police or hospital photography preferred; do not use physician’s personal camera)
• blood tests to rule out medical causes (e.g. thrombocytopenia or coagulopathy)
• screen for abdominal trauma (transaminases and amylase): if increased, abdo CT recommended
• skeletal survey in children <2 yr:
  • bone scan can be beneficial for assessing rib fractures (not helpful for skull or metaphyseal region due to active bone growth) – consider bone scan if equivocal findings on initial skeletal survey
  • dilated eye examination by pediatric ophthalmologist to rule out retinal hemorrhage
• be aware of “red herrings” (e.g. Mongolian blue spots vs. bruises)
• neuroimaging: CT and/or MRI

Apparent Life-Threatening Events (ALTEs)
A group of conditions often marked by an episode of apnea, cyanosis, change in tone, or change in mental status occurring in a child, where an observer fears the child may be dying. There is no clear connection between most ALTEs and SIDS. Evaluating for a cause of the ALTE (e.g. infection, cardiac, neurologic) is guided by history, physical examination and period of observation.

Presentation of Neglect
• Failure to thrive, developmental delay
• Inadequate or dirty clothing, poor hygiene
• Child exhibits poor attachment to parents, no stranger anxiety

“If no cruising, no bruising.”
Sexual Abuse

Epidemiology
• peak ages at 2-6 and 12-16 yr
• most perpetrators are male and known to child
  ▪ in decreasing order: family member, non-relative known to victim, stranger

History
• diagnosis usually depends on child disclosing to someone or forensic interview done by a
  trained individual
• psychosocial: specific or generalized fears, depression, nightmares, social withdrawal, lack of
  trust, low self-esteem, school failure, sexually aggressive behaviour, advanced sexual knowledge,
  sexual preoccupation or play

Physical Exam
• recurrent UTIs, pregnancy, STIs, vaginitis, vaginal bleeding, pain, genital injury, enuresis

Investigations
• depend on presentation, age, sex, and pubertal development of child
  ▪ sexual assault examination kit within 24 h if prepubertal, within 72 h if pubertal
  ▪ rule out STI, UTI, pregnancy (consider STI prophylaxis or emergency contraception)
  ▪ rule out other injuries (vaginal/anal/oral penetration, fractures, head trauma)

Neglect

History
• from child and each caregiver separately (if possible)

Physical exam
• head to toe (do not force), growth parameters, nutrition status
• dental care
• emotional state

Investigations
• blood tests to rule out medical causes (e.g. thrombocytopenia or coagulopathy)

Management of Physical Abuse, Child Abuse and Neglect
• report all suspicions to CPS; request emergency visit if imminent risk to child or any siblings in
  the home
• acute medical care: hospitalize for medical evaluation or treatment of injuries if indicated
• arrange consultation to social work and appropriate follow-up
• may need to discharge child directly to CPS or to responsible guardian under CPS supervision

Adolescent Medicine

Adolescent History (HEEADDSSS)
• tailor your history according to the clinical context

Home: Who do you live with? What kind of place do you live in?

Education/Employment: What grade are you in? What are your favourite subjects? What was
your average on your last report card?

Eating: Tell me about your meals/snacks in a typical day? Have you ever gone on a diet?
(for Eating Disorders – see Psychiatry, PS29)

Activities: What do you do after school? On the weekends? How much time do you spend on
the computer/watching TV every day? Do you use Facebook?

Drugs: Which seems to be more popular at your school, alcohol or drugs? How often do you
drink/smoke marijuana/take other drugs? Do you smoke cigarettes? When you drink, do you usu-
ally get drunk? Have you ever passed out or not been able to remember what happened while you
were drinking? Has anything bad ever happened to you while you were drunk or stoned?
(for Substance Abuse – see Psychiatry; PS21)

Sexuality: Are you romantically interested in anyone? When you think about having sex with
someone, do you think about girls, boys or both? Have you ever had sex with anyone? Whether
the answer is yes or no, the next question is: What activities would you include in the term ‘having
sex’? What do you do to prevent getting a sexually transmitted infection/getting pregnant/getting
someone pregnant? Has anyone ever given you money, drugs or other stuff in exchange for sex?
(for Sexually Transmitted Infections – see Gynecology, GY26)
**Suicidality/Depression:** On a scale of 1 to 10, where 1 is so sad that you might kill yourself and 10 is the happiest you could be, where are you most days? Is there a difference between school days and the weekend? Have you ever thought seriously about suicide? Did you make a plan? (for Depression/Suicide – see Psychiatry, PS9, PS4)

**Safety/Violence:** Do you ever get into a car with a driver who has been drinking? Do you always wear a seatbelt/bicycle helmet? Are you being bullied at school? Has anyone ever touched you in an unwanted way?

For Normal and Abnormal Pubertal Development, P31

## Cardiology

### Congenital Heart Disease (CHD)

#### PRENATAL CIRCULATION

Figure 1. Prenatal circulation

- **Embryologic Development**
  - most critical period of fetal heart development is between 3-8 wk gestation
  - single heart tube grows rapidly forcing it to bend back upon itself and assume the shape of a four chambered heart, insults at this time are most likely to lead to CHD

- **Before Birth**
  - fetal lungs are bypassed by flow through fetal shunts:
    - shunting deoxygenated blood
      - ductus arteriosus: connection between pulmonary artery and aorta
    - shunting oxygenated blood
      - foramen ovale: connection between R and L atria
      - ductus venosus: connecting between umbilical vein and IVC
  - circulation (Figure 1)

- **At Birth**
  - with first breath, lungs open up and pulmonary resistance decreases allowing pulmonic blood flow
  - separation of low resistance placenta → systemic circulation becomes a high resistance system → ductus venosus closure
  - increased pulmonic flow → increased left atrial pressures → foramen ovale closure
  - increased oxygen concentration in blood after first breath → decreased prostaglandins → ductus arteriosus closure
  - closure of fetal shunts and changes in vascular resistance → infant circulation assumes normal adult flow

Prevalence rates of depression: 1-2% in pre-pubertal children and 6-8% in adolescents.

Date rape comprises 80% of sexual assault in teenagers.

Fetal circulation is designed so that oxygenated blood is preferentially delivered to the brain and myocardium.
Epidemiology
- 8/1000 live births have CHD, which may present as a heart murmur, heart failure, or cyanosis; ventricular septal defect is the most common lesion

Investigations
- Echocardiogram, ECG, CXR

CYANOTIC VS. ACYANOTIC CONGENITAL HEART DISEASE
- cyanosis: blue mucous membranes, nail beds, and skin secondary to an absolute concentration of deoxygenated hemoglobin of at least 3 g/dL
- acyanotic heart disease: (i.e. L to R shunt, obstruction occurring beyond lungs) blood passes through pulmonic circulation → oxygenation takes place → low levels of deoxygenated blood in systemic circulation → no cyanosis
- cyanotic heart disease: (i.e. R to L shunt) blood bypasses the lungs → no oxygenation occurs → high levels of deoxygenated hemoglobin enters the systemic circulation → cyanosis

![Figure 2. Common congenital heart diseases](image)

Acyanotic Congenital Heart Disease

1. LEFT TO RIGHT SHUNT LESIONS
- extra blood is displaced through a communication from the left to the right side of the heart → increased pulmonary blood flow → increased pulmonary pressures
- shunt volume is dependent upon three factors: (1) size of defect (2) pressure gradient between chambers or vessels (3) peripheral outflow resistance
- untreated shunts can result in pulmonary vascular disease, left ventricular dilatation and dysfunction, right ventricular hypertension and hypertrophy (RVH), and ultimately R to L shunts

Atrial Septal Defect (ASD)
- 3 types: ostium primum (common in Down syndrome), ostium secundum (most common type, 50-70%), sinus venosus (defect located at entry of superior vena cava into right atrium)
- epidemiology: 6-8% of congenital heart lesions
- natural history:
  - 80-100% spontaneous closure rate if ASD diameter <8 mm
  - if remains patent, congestive heart failure (CHF) and pulmonary hypertension can develop in adult life
- clinical presentation:
  - history: often asymptomatic in childhood
  - physical exam: grade 2-3/6 pulmonic outflow murmur, widely split and fixed S2
- investigations:
  - ECG: right axis deviation (RAD), mild RVH, right bundle branch block (RBBB)
  - CXR: increased pulmonary vasculature
- management: elective surgical or catheter closure between 2-5 yr of age

Ventricular Septal Defect (VSD)
- most common congenital heart defect (30-50%)
- small VSD (majority)
  - clinical presentation:
    - history: asymptomatic, normal growth, and development
    - physical exam: early systolic to holosystolic murmur, best heard at LLSB, thrill
  - investigations: ECG and CXR are normal
  - management: most close spontaneously

Characteristic Chest X-Ray Findings in Congenital Heart Disease
- Boot-shaped heart: tetralogy of Fallot, tricuspid atresia
- Egg-shaped heart: transposition of great arteries
- “Snowman” heart: total anomalous pulmonary venous return
• moderate-to-large VSD
  • epidemiology: CHF by 2 mo; late secondary pulmonary hypertension if left untreated
  • clinical presentation
    • history: delayed growth, decreased exercise tolerance, recurrent URTIs or "asthma" episodes
    • physical exam: holosystolic murmur at LLSB, mid-diastolic rumble at apex, size of VSD is inversely related to intensity of murmur
  • investigations:
    • ECG: left ventricular hypertrophy (LVH), left atrial hypertrophy (LAH), RVH
    • CXR: increased pulmonary vasculature, cardiomegaly, CHF
  • management: treatment of CHF and surgical closure by 1 yr old

Patent Ductus Arteriosus (PDA)
• patent vessel between descending aorta and left pulmonary artery (normally, functional closure within first 15 h of life, anatomical closure within first days of life)
• epidemiology:
  • 5-10% of all congenital heart defects
  • delayed closure of ductus is common in premature infants (1/3 of infants <1750 g); this is different from PDA in term infants
• natural history: spontaneous closure common in premature infants, less common in term infants
• clinical presentation
  • history: asymptomatic, or have apneic or bradycardic spells, poor feeding, accessory muscle use, CHF
  • physical exam:
    • tachycardia, bounding pulses, hyperactive precordium, wide pulse pressure, continuous "machinery" murmur best heard at left infraclavicular area
  • investigations:
    • ECG: may show LAE, LVH, RVH
    • CXR: normal to mildly enlarged heart, increased pulmonary vasculature, prominent pulmonary artery
    • ECHO: diagnostic
• management
  • indomethacin (Indocid®): PGE2 antagonist (PGE2 maintains ductus arteriosus patency) is only effective in premature infants
  • catheter or surgical closure if PDA causes respiratory compromise, FTT, or persists beyond 3rd month of life

2. OBSTRUCTIVE LESIONS
• present with decreased urine output, pallor, cool extremities and poor pulses, shock or sudden collapse

Coarctation of the Aorta
• definition: narrowing of aorta (almost always at the level of the ductus arteriosus)
• epidemiology: commonly associated with bicuspid aortic valve (30%); Turner syndrome (35%)
• clinical presentation
  • history: often asymptomatic
  • physical exam:
    • upper extremity systolic pressures of 140-145 mmHg
    • few have high BP in infancy (160-200 mmHg systolic), but this decreases as collaterals develop
    • decreased blood pressure and weak/absent pulses in lower extremities
    • radial-femoral delay
    • absent or systolic murmur with late peak at apex, left axilla, and left back
    • if severe, presents with shock in the neonatal period when the ductus closes
• investigations: ECG shows RVH early in infancy, LVH later in childhood
• prognosis: can be complicated by hypertension; if associated with other lesions (e.g. PDA, VSD) can lead to CHF
• management: give prostaglandins to keep ductus arteriosus patent for stabilization and perform surgical correction in neonates. For older infants and children balloon arterioplasty may be an alternative to surgical correction.

Aortic Stenosis
• 4 types: valvular (75%), subvalvular (20%), supravalvular and idiopathic hypertrophic subaortic stenosis (IHSS) (5%)
• clinical presentation
  • history: often asymptomatic, but may be associated with CHF, exertional chest pain, syncope or sudden death
  • physical exam: systolic ejection murmur (SEM) at RUSB with aortic ejection click at the apex (only for valvar stenosis)
• management: valvular stenosis is usually treated with balloon valvuloplasty, patients with subvalvar or supravalvular stenosis require surgical repair, exercise restriction required
Pulmonary Stenosis
- 3 types: valvular (90%), subvalvular, or supravalvular
- definition of critical pulmonic stenosis:
  - inadequate pulmonary blood flow, dependent on ductus for oxygenation, progressive hypoxia and cyanosis
- natural history: may be part of other congenital heart lesions (e.g. Tetralogy of Fallot) or in association with syndromes (e.g. congenital rubella, Noonan syndrome)
- clinical presentation
  - history: spectrum from asymptomatic to CHF
  - physical exam: wide split S2 on expiration, SEM at LUSB, pulmonary ejection click (for valvar lesions)
- investigations:
  - ECG: RVH
  - CXR: post-stenotic dilation of the main pulmonary artery
- management: surgical repair if critically ill, or if symptomatic in older infants/children

Cyanotic Congenital Heart Disease
- systemic venous return re-enters systemic circulation directly
- most prominent feature is cyanosis (O₂ sat <75%)
- hyperoxic test differentiates between cardiac and other causes of cyanosis
  - obtain preductal, right radial ABG in room air, then repeat after the child inspires 100% O₂
  - if PaO₂ improves to greater than 150 mmHg, cyanosis less likely cardiac in origin

1. RIGHT TO LEFT SHUNT LESIONS
Tetralogy of Fallot
- epidemiology: 10% of all CHD, most common cyanotic heart defect diagnosed beyond infancy with peak incidence at 2-4 mo of age
- pathophysiology:
  - embryological defect due to anterior and superior deviation of the outlet septum leading to:
    - VSD, RVOTO (e.g. pulmonary stenosis), over-riding aorta and RVH
    - infants may initially have a L → R shunt (therefore no cyanosis); however, RVOTO is progressive, leading to increasing R → L shunting with hypoxemia and cyanosis
  - degree of RVOTO determines the direction and degree of shunt and, therefore, the extent of clinical cyanosis and degree of RVH
- clinical presentation
  - history: hypoxic "tet" spells
  - during exertional states (crying, exercise) the increasing pulmonary vascular resistance and decrease in systemic resistance causes an increase in right-to-left shunting
  - clinical features include paroxysm of rapid and deep breathing, irritability and crying, increasing cyanosis, decreased intensity of murmur (decreased flow across RVOTO)
  - if severe, can lead to decreased level of consciousness, seizures, death
  - physical exam
    - single loud S2 due to severe pulmonary stenosis (i.e. RVOTO), systolic ejection murmur (LSB)
- investigations:
  - ECG: RAD, RVH
  - CXR: boot shaped heart, decreased pulmonary vasculature, right aortic arch (in 20%)
- management of spells: O₂, knee-chest position, fluid bolus, morphine sulfate, propanolol
- treatment: surgical repair at 4-6 mo of age; earlier if marked cyanosis or "tet" spells

2. OTHER CYANOTIC CONGENITAL HEART DISEASES
Transposition of the Great Arteries (TGA)
- epidemiology: 3-5% of all congenital cardiac lesions, most common cyanotic CHD in neonate
- pathophysiology: parallel pulmonary and systemic circulations
  - systemic: body → RA → RV → aorta → body
  - pulmonary: lungs → LA → LV → pulmonary artery → lungs
- survival is dependent on mixing through PDA and/or atrial or ventricular septal defects
- physical exam:
  - neonates: ductus arteriosus closure causes rapidly progressive severe hypoxemia unresponsive to oxygen therapy, acidosis, and death
  - VSD present: cyanosis is not prominent; CHF within first weeks of life
  - VSD absent: no murmur
- investigations:
  - ECG: RAD, RVH, or may be normal
  - CXR: egg-shaped heart with narrow mediastinum ("egg on a string")
- management:
  - symptomatic neonates: prostaglandin E1 infusion to keep ductus open until balloon atrial septostomy
  - surgical repair: arterial switch performed in the first two weeks in those without a VSD while LV muscle is still strong

Total Anomalous Pulmonary Venous Connection
- epidemiology: 1-2% of CHD
- pathophysiology:
  - all pulmonary veins drain into right-sided circulation (systemic veins, RA)
  - no direct oxygenated pulmonary venous return to left atrium
  - often associated with obstruction at connection sites
  - ASD must be present for oxygenated blood to shunt into the LA and systemic circulation
- management: surgical repair in all cases and required urgently for severe cyanosis

Truncus Arteriosus
- pathophysiology:
  - single great vessel gives rise to the aorta, pulmonary and coronary arteries
  - truncal valve overlies a large VSD
  - potential for coronary ischemia with fall in pulmonary vascular resistance
- management: surgical repair within first 6 wk of life

Hypoplastic Left Heart Syndrome (HLHS)
- epidemiology: 1-3% of CHD; commonest cause of death from CHD in first month of life
- pathophysiology: LV hypoplasia may include atretic or stenotic mitral and/or aortic valve, small ascending aorta, and coartation of the aorta with resultant systemic hypoperfusion
- systemic circulation is dependent on ductus patency; upon closure of the ductus, infant presents with circulatory shock and metabolic acidosis
- management:
  - intubate and correct metabolic acidosis
  - IV infusion of PGE1 to keep ductus open
  - surgical palliation (overall survival 50% to late childhood) or heart transplant

Congestive Heart Failure (CHF)
- see Cardiology, C30

Etiology
- CHD
- arteriovenous malformations (AVMs)
- cardiomyopathy
- arrhythmias
- acute hypertension
- anemia
- cor pulmonale
- myocarditis

History
- infant: feeding difficulties, early fatigability, diaphoresis while sleeping or eating, respiratory distress, lethargy, FTT
- child: decreased exercise tolerance, fatigue, decreased appetite, failure to thrive, respiratory distress, frequent URTIs or “asthma” episodes
- orthopnea, paroxysmal nocturnal dyspnea, pedal/dependent edema are all uncommon in children

Physical Findings
- 4 key features: tachycardia, tachypnea, cardiomegaly, hepatomegaly
- FTT
- alterations in peripheral pulses, four limb blood pressures (in some CHDs)
- dysmorphic features associated with congenital syndromes

Investigations
- CXR: cardiomegaly, pulmonary venous congestion

Management
- general: sitting up, O2, sodium and water restriction, increased caloric intake
- pharmacologic: diuretics, afterload reduction (i.e. ACE inhibitor), digoxin rarely used
- curative: correction of underlying cause
**Dysrhythmias**

- see [Cardiology, C12](#)
- can be transient or permanent, congenital (structurally normal or abnormal) or acquired (toxin, infection, infarction)

**Sinus Arrhythmia**
- phasic variations with respiration (present in almost all normal children)

**Sinus Tachycardia**
- rate of impulses arising from sinus node is elevated (>150 bpm in infants, >100 bpm in older children)
- etiology: hypertension, fever, anxiety, sepsis, anemia/hypoxia, PE, drugs, etc.
- differentiate from SVT (see below) by slowing the sinus rate (vagal massage, β-blockers) to identify sinus P waves

**Premature Atrial Contractions (PACs)**
- may be normal variant or can be caused by electrolyte disturbances, hyperthyroidism, cardiac surgery, digitalis toxicity

**Premature Ventricular Contractions (PVCs)**
- common in adolescents
- benign if single, uniform, disappear with exercise, and no associated structural lesions
- if not benign, may degenerate into more severe dysrhythmias

**Supraventricular Tachycardia (SVT)**
- abnormally rapid heart rhythm originating above the ventricles – most frequent sustained dysrhythmia in children
- not life-threatening, but can lead to symptoms

**Complete Heart Block**
- congenital heart block can be caused by maternal anti-Ro or anti-La (e.g. mother with SLE)
- often diagnosed in utero (may lead to development of fetal hydrops)
- clinical symptoms related to level of block (the lower the block, the slower the heart rate and greater the symptoms of inadequate cardiac output)
- symptomatic patients need a pacemaker

---

**Heart Murmurs**

- 50-80% of children have audible heart murmurs at some point in their childhood
- most childhood murmurs are functional (e.g. "innocent") without associated structural abnormalities and have normal ECG and radiologic findings
- in general, murmurs can become audible or accentuated in high output states, e.g. fever, anemia

**Table 11. Differentiating Heart Murmurs**

<table>
<thead>
<tr>
<th></th>
<th>Innocent</th>
<th>Pathological</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History and Physical</strong></td>
<td>Asymptomatic</td>
<td>Symptoms and signs of cardiac disease (FTT, exercise intolerance)</td>
</tr>
<tr>
<td><strong>Timing</strong></td>
<td>SEM</td>
<td>All diastolic, pansystolic, or continuous (except venous hum)</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td>&lt;3/6</td>
<td>≥3/6 (palpable thrill)</td>
</tr>
<tr>
<td><strong>Splitting</strong></td>
<td>Physiologic S2</td>
<td>May have fixed split or single S2</td>
</tr>
<tr>
<td><strong>Extra sounds/Clicks</strong></td>
<td>None</td>
<td>May be present</td>
</tr>
<tr>
<td><strong>Change of Position</strong></td>
<td>Murmur varies</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

---

**Pediatric vs. Adult ECG**

Pediatric ECG findings that may be normal:
- HR >100 bpm
- Shorter PR, QT intervals and QRS duration
- Inferior and lateral small Q waves
- RV larger than LV in neonates, so normal to have:
  - Right axis deviation
  - Large precordial R waves
  - Upright T waves
  - Inverted T waves in the anterior precordial leads from early infancy to teen years
Table 12. Five Innocent Heart Murmurs

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Age</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Pulmonic Stenosis</td>
<td>Neonates, low-pitched, radiates to axilla and back</td>
<td>Neonates, usually disappears by 3-6 mo</td>
<td>Patent Ductus Arteriosus Pulmonary stenosis</td>
</tr>
<tr>
<td>Still’s Murmur</td>
<td>Vibratory, LL SB or apex, SEM</td>
<td>3-6 yr</td>
<td>Subaortic stenosis</td>
</tr>
<tr>
<td>Venous Hum</td>
<td>Infraclavicular hum, continuous, R&gt;L</td>
<td>3-6 yr</td>
<td>Patent Ductus Arteriosus</td>
</tr>
<tr>
<td>Pulmonary Ejection</td>
<td>Soft, blowing, USB, SEM</td>
<td>8-14 yr</td>
<td>Atrial septal defect</td>
</tr>
<tr>
<td>Supraclavicular Arterial Bruit</td>
<td>Low intensity, above clavicles</td>
<td>Any age</td>
<td>Aortic stenosis</td>
</tr>
</tbody>
</table>

**Infective Endocarditis**
- see Infectious Diseases, ID17

**Development**

**Approach to Global Developmental Delay**
- also known as Early Developmental Impairment (EDI)

**Definition**
- performance significantly below average in two or more areas of development (i.e. gross motor, fine motor, language, cognitive, social, adaptive)
- when persistent, these become developmental disabilities which are lifelong impairments

**Epidemiology**
- 5-10% of children have neurodevelopmental delay
- careful evaluation can reveal a cause in 50-70% of cases

**Etiology**
- CNS abnormalities (meningitis/encephalitis, brain malformation, trauma, etc.)
- sensory deficits (hearing, vision)
- environmental (psychosocial neglect, lead exposure, antenatal drug or alcohol exposure, etc.)
- genetic/chromosomal disorders (Down syndrome, Fragile X, etc.)
- metabolic disorders (inborn errors of metabolism, hypothyroidism, etc.)
- obstetrical (prematurity, hypoxic ischemic encephalopathy, TORCH infections, etc.)

**Clinical Presentation**
- history
  - intrauterine exposures, perinatal events
  - detailed developmental milestones: rate of acquisition, regression of skills
  - associated problems: feeding, seizures, behaviour, sleep
  - family history, consanguinity
  - social history
- physical
  - dysmorphic features, hepatosplenomegaly, neurocutaneous markers, growth parameters, detailed neurological examination
- investigations
  - neurodevelopmental assessment, vision and hearing test, psychosocial evaluation, OT, PT and/or SLP assessments, genetics consultation
  - laboratory testing and imaging (guided by history and physical exam)
    - microarray, chromosomes, FISH, Fragile X testing, neuroimaging, metabolic workup, neuroelectrophysiologic testing

**Management**
- dependent on specific area of delay
- therapy services (e.g. speech and language therapy for language delay, OT and/or PT for motor delay), early intervention services (e.g. infant development services, Ontario Early Years Centres)
**Intellectual Disability**

**Definition**
- state of functioning that begins in childhood and is characterized by limitations in both intelligence and adaptive skills
- referred to as mental retardation in DSM-IV, not a term used in clinical settings
- historically defined as an IQ <70

**Epidemiology**
- 1% of general population; M:F = 1.5:1

**Etiology**
- any disorder that interferes with brain development and functioning
- prenatal (majority): TORCH infections, fetal alcohol syndrome
- genetic/metabolic: DS, Fragile X, PKU, untreated or delayed diagnosis of congenital hypothyroidism, CNS abnormalities, other chromosomal/metabolic disorders

**Risk Factors**
- male, consanguineous parents, family history, older maternal age, decreasing maternal education, certain ethnicities
- prenatal: pre-eclampsia, maternal malnutrition or DM
- perinatal: prematurity, low birth weight, birth trauma/hypoxia
- postnatal: intracranial hemorrhage, CNS or other serious infection, hypoxia, environmental toxins, psychosocial deprivation, malnutrition

**Clinical Presentation**
- history
  - well below average general intellectual functioning
  - significant deficits in adaptive functioning in at least two of: communication, self-care, home-living, social skills, self-direction, academic skills, work, leisure, health, safety
- physical
  - check growth, dysmorphic features, complete physical exam
- investigations
  - standardized psychology assessment (includes IQ test and measure of adaptive functioning)
  - vision, hearing, and neurologic assessment
  - genetic and metabolic testing as indicated

**Management**
- main objective: enhance adaptive functioning level
- requires an interprofessional team with strong case co-ordination
- emphasize community-based treatment and early intervention
- individual/family therapy, behaviour management services, therapy services (e.g. OT, SLP), medications for associated conditions
- education: life skills, vocational training, communication skills, family education
- psychosocial support for individual and family; respite care

**Prognosis**
- higher rates of sensory deficits, motor impairment, behavioural/emotional disorders, seizures, psychiatric illness

**Language Delay**

**Definition**
- no universally accepted definition, but often identified around 18 mo of age with enhanced well baby visit
- if formally tested, performance on a standardized assessment of language is at least one standard deviation below mean of age
- can be expressive, receptive, or both
- expressive language: ability to produce or use language
- receptive language: ability to understand language

**Epidemiology**
- ~10-15% of 2 yr old children have a language delay, but only 4-5% remain delayed after 3 yr of age
- ~6-8% of school-aged children have specific language impairment (many of whom were not identified before school entry)
Etiology
- cognitive disability
- constitutional language delay
- genetic/metabolic: DS, Fragile X syndrome, Williams syndrome, hypothyroidism, PKU, etc.
- hearing impairment
- mechanical problems: cleft palate, cranial nerve palsy
- medical condition: seizure disorder (includes acquired epileptic aphasia), CP, TORCH infection, iron deficiency, lead poisoning, etc.
- autism spectrum disorder (ASD)
- psychosocial: neglect or abuse
- selective mutism

Risk Factors
- male, positive family history, prematurity, psychosocial (poverty, low parental education, maternal depression)

Clinical Presentation
- history
  - concerns about hearing, delay in language development or regression in previously normal language development
  - delayed language milestones on well-child check up; presence of red flags
  - must determine if language delay is expressive, receptive or mixed
  - children with expressive language delays may have concurrent behaviour problems or drooling (because of abnormal oral musculature)
  - risk factors for hearing loss (hereditary, recurrent AOM) and language delay
- physical
  - guided by history: look for abnormal growth, dysmorphisms, unusual social interactions (lack of eye contact, not pointing)
  - include full exam of the external/internal ear (e.g. TM scarring), oral pharynx (e.g. cleft palate) and neurologic system (including tone)
- investigations
  - use of language specific screens in primary care setting: The Early Language Milestone, CAT/CLAMS, MCHAT, etc.
  - all children with suspected language delay MUST be referred to an audiologist for a hearing assessment
  - CBC (to rule out anemia), venous blood lead levels, genetic/metabolic workup as indicated

Management
- specific to etiology
- often multidisciplinary and requires appropriate referrals: early intervention services, special education services, SLP, ENT and dental professionals, general support services
- primary care provider can help reinforce family’s understanding of delay and provide follow-up and care coordination
- prevention: parents can read aloud to their child, engage in dialogic reading, avoid baby talk, narrate daily activities, etc.

Prognosis
- depends on etiology
- if language delay persists beyond 5 yr old then more likely to have difficulties in adulthood
- persistent language delay is associated with poor academic performance, behavioural problems, social isolation

Fetal Alcohol Spectrum Disorder (FASD)

Definition
- term describing the range of effects of prenatal exposure to alcohol, including physical, mental, behavioural and learning disabilities
- no “safe” level of alcohol consumption during pregnancy has been established
- spectrum includes: Fetal Alcohol Syndrome (FAS), partial Fetal Alcohol Syndrome (pFAS), Alcohol-Related Birth Defects (ARBD), and Alcohol-Related Neurodevelopmental Disorder (ARND)

Epidemiology
- prevalence of FAS and FASD is 0.1% and 1.0%, respectively
- most common preventable cause of intellectual disability

Pathogenesis
- specific mechanism of FASD is unknown, but hypothesis include nutritional deficits, toxic effects of acetaldehyde, alteration of placental transport, abnormal protein synthesis, and altered cerebral neurotransmitter
Diagnosis
- often misdiagnosed or missed entirely
- diagnosis of FAS, ARBD and ARND all require evidence of maternal drinking during pregnancy
- criteria for diagnosis of FAS
  a) growth deficiency: low birth weight and/or decelerating weight over time not due to nutrition
  b) characteristic pattern of facial anomalies: short palpebral fissures, flattened philtrum, thin upper lip, flat midface
  c) central nervous system dysfunction: microcephaly and/or neurobehavioral dysfunction (hyperactivity, fine motor problems, attention deficits, learning disabilities, cognitive disabilities, difficulties in adaptive functioning, etc.)
- criteria for diagnosis of ARBD
  a) congenital anomalies, including malformations and dysplasias of the cardiac, skeletal, renal, ocular, and auditory systems
- criteria for diagnosis of ARND
  a) central nervous system dysfunction (similar to FAS)
  b) complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level that cannot be explained by familial background or environment alone

Management
- early diagnosis is essential to prevent secondary disabilities
- no cure, but individuals with FASD and their families should be linked to community resources and services to improve outcome

Prognosis
- secondary disabilities include unemployment, mental health problems, difficulties with the law, inappropriate sexual behaviour, disrupted school experience, peer problems

Learning Disabilities

Definition
- specific and persistent failure to acquire academic skills despite conventional instruction, adequate intelligence, and sociocultural opportunity
- a significant discrepancy between a child's intellectual ability and their academic performance
- several types or ADLs: learning disabilities in reading, writing, mathematics

Epidemiology
- prevalence: 2-10%
- high incidence of psychiatric comorbidity: anxiety, dysthymia, conduct disorder (CD), major depressive disorder (MDD), oppositional defiant disorder (ODD), attention deficit hyperactivity disorder (ADHD)

Etiology
- pathogenesis is unknown, likely genetic factors involved
- learning disabilities may be associated with a number of conditions:
  - genetic/metabolic: Turner syndrome, Klinefelter syndrome
  - perinatal: prematurity, low birth weight, birth trauma/hypoxia
  - postnatal: CNS damage, hypoxia, environmental toxins, FAS, psychosocial deprivation (understimulation), malnutrition
- poor visual acuity is NOT a cause

Risk Factors
- positive family history, prematurity, other developmental and mental health conditions, neurologic disorders (e.g. seizure disorders, neurofibromatosis), history of CNS infection/irradiation/traumatic injury

Clinical Presentation
- history and physical
  - school difficulties (academic achievement, behaviour, attention, social interaction)
  - development of negative self-concept → reluctance to participate even in areas of strength
  - social issues: overt hostility towards parents/teachers; difficulties making friends for several reasons (problems remembering names, difficulties with language to engage in conversations, inability to understand games and complex rules, etc.), bullying and anxiety
- look for dysmorphisms, complete physical exam
- investigations
  - standardized tests for IQ
  - individual scores on achievement tests in reading, mathematics or written expression (WISC III, WRAT) >2 SD below that expected for age, education, and IQ
Management
• provide quality instruction for specific learning disability
• support student by modifying the curriculum and/or providing accommodations (e.g. scribe for writing, extra time for tests, photocopied notes, etc.)
• consider grade retention in certain students (no guidelines exist, very rare in Ontario)
• specialized education placements that can provide educational remediation

Prognosis
• limited information available about persistence of learning disabilities over time
• low self-esteem, poor social skills, 40% school drop-out rate

Motor Delay
• see Cerebral Palsy, P90 and Muscular Dystrophy, P44

Endocrinology

Anti-Diuretic Hormone

Diabetes Insipidus (DI)
• see Endocrinology, E19 and Nephrology, NP11

Syndrome of Inappropriate Antidiuretic Hormone (SIADH)
• see Endocrinology, E19 and Nephrology, NP9

Diabetes Mellitus (DM)

DM Type 1
• insulin deficiency following destruction of the pancreatic β cells

Epidemiology
• most common form of diabetes mellitus in children, M=F
• variable prevalence internationally, affects ~1:4000 children in Canada
• can present at any age, but bimodal peaks at 5-7 yr old and at puberty

Etiology
• type 1A: cell-mediated autoimmune destruction of β-cells of the pancreas
• type 1B: rare, non-immune variation; unknown cause
• disease results from some level of genetic predisposition and an environmental trigger
  ▪ HLA locus confers ~50% of genetic susceptibility
  ▪ trigger likely infectious and/or hormonal (as suggested by bimodal peaks in age of onset)

Risk Factors
• positive family history of DM1, personal or family history of other autoimmune diseases

Clinical Presentation
• history
  ▪ initially presents as polyuria, often manifested as nocturia or secondary enuresis
  ▪ polydipsia, weight loss (lack of insulin leading to a catabolic state) and polyphagia
  ▪ diabetic ketoacidosis on initial presentation (~20%): vomiting, abdominal pain, confusion/lethargy
• physical
  ▪ tachypnea, signs of dehydration, ↓ LOC, Kussmaul’s respiration, ketone breath
• investigations
  ▪ initial tests: urine dipstick (glucose, ketones), random blood glucose (>11.1)
  ▪ DKA bloodwork: venous/arterial blood gas, osmolarity, plasma glucose, bicarbonate, HbA1C, serum ketones, BUN, Cr, electrolytes, CBC
  ▪ if etiology is unclear, consider ordering autoimmune antibodies (anti-Gad, anti-islet)

Management
• disclose diagnosis and prompt patient education around survival skills, meal plans and insulin injections
• refer patient to facility capable of managing DM1
• management is multi-disciplinary and family-centered
• initial insulin dosing
  ▪ 2/3 of total daily insulin dose in AM (1/3 rapid acting + 2/3 intermediate-acting)
  ▪ 1/3 of total daily insulin dose in PM (1/3 rapid acting + 2/3 intermediate-acting)

Diagnostic Criteria for Diabetes Mellitus (Types 1 and 2)
One of:
• HbA1C 6.5% (not validated in children)
• Fasting glucose ≥7.0 mmol/L
• 2 h plasma glucose during OGTT ≥11.1 mmol/L
• Random glucose ≥11.1 mmol/L with classic symptoms of hyperglycemia (polyuria, polydipsia, weight loss)

Blood Glucose Targets by Age

<table>
<thead>
<tr>
<th>Age range</th>
<th>Pre-meal blood glucose target</th>
<th>HbA1c target</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>6-12</td>
<td>&lt;8.5%</td>
</tr>
<tr>
<td>6-12</td>
<td>6-10</td>
<td>&lt;8%</td>
</tr>
<tr>
<td>&gt;12</td>
<td>4-7</td>
<td>&lt;7%</td>
</tr>
</tbody>
</table>
• blood glucose monitoring
  ▪ tight glycemic control decreases rate of long term complications
  ▪ target glucose range: in infants/toddlers from 6-10 mmol/L, in children 4-10 mmol/L, in adolescents 4-7 mmol/L
  ▪ for tighter control, may consider continuous subcutaneous insulin infusion (CSII) pump or MDI (multiple daily injections regimen: basal insulin plus analog for meals)
  ▪ young children are more susceptible to hypoglycemia

• if DKA present: ABCs, admit, correct dehydration, correct acidosis (start insulin infusion), restore normal blood glucose, identify/treat precipitating event
  ▪ low threshold to investigate (CT/MRI) and treat DKA, as cerebral edema is a major concern

• screen for micro- and macrovascular complications (regular ophthalmology assessments, blood pressure, urine microalbuminemia), concurrent autoimmune diseases (thyroiditis, celiac disease, etc.) and mental health issues (depression, eating disorders)

Prognosis
• no cure currently
• short-term complications
  ▪ hypoglycemia: due to missed/delayed meals, excess insulin or exercise, illness; can lead to seizures and/or coma; reversed with PO/IV glucose or IM glucagon
  ▪ hyperglycemia: due to intercurrent illness, diet-to-insulin mismatch, ↑ risk of end-organ damage
  ▪ DKA: due to missed insulin doses, infection; most common cause of death
• long-term complications
  ▪ microvascular: retinopathy, nephropathy, neuropathy
  ▪ macrovascular: metabolic syndrome
  ▪ increased risk of other autoimmune diseases

DM Type 2
• see Family Medicine, FM22, Endocrinology, E6
• impaired glucose metabolism due to increased peripheral insulin resistance
• rare before 10 yr of age, but more common in older children/adolescents
• prevalence is rising mainly due to the increased incidence of childhood obesity
• risk factors: obesity, positive family history, female gender, certain ethnic groups
• clinical presentation may be similar to that of DM1, though most children are asymptomatic
• may present in DKA or hyperglycemic hyperosmotic nonketotic (HONK) state
• management: diet, physical activity (60 min of moderate to intense exercise per day, limit non-academic screen time to 2 h/d), weight loss, oral hypoglycemics (metformin used in children because it does not cause hypoglycemia), insulin
• prognosis: includes microvascular and macrovascular complications similar to DM1

Growth

APPROACH TO SHORT STATURE

Definition
• short stature – height <3rd percentile
• poor growth evidenced by growth deceleration (height crosses major percentile lines, growth velocity <25th percentile)

Epidemiology
• ~2.5% of the population by definition

Etiology
• see sidebar

Clinical Presentation
• history and physical
  ▪ plot on growth curve (special growth charts available for Turner syndrome, achondroplasia, DS)
  ▪ decreased growth velocity may be more worrisome than actual height
  ▪ see Figure 7 for the approach to short stature
• investigations
  ▪ calculate mid-parental height: children are usually in a percentile between their parents’ height (see Mid-Parental Height sidebar, P10)
  ▪ AP x-ray of left hand and wrist for bone age
  ▪ remaining investigations guided by history and physical (e.g. TSH, sweat chloride, etc.)
**Management**
- depends on severity of problem as perceived by parents/child
- no treatment for non-pathological short stature, except for idiopathic short stature
- GH therapy if requirements met (see *Growth Hormone Deficiency*, below)
- other conditions that are treated: Turner, Prader-Willi, chronic renal failure
- support and management of resultant self-image issues, social anxiety, etc.

**GROWTH HORMONE (GH) DEFICIENCY**
- a rare but treatable cause of short stature in children

**Epidemiology**
- 1/10,000-1/4,000 children

**Etiology**
- GH important for chondrocyte proliferation and IGF-1 release → IGF-1 acts at long bones, liver
- congenital GH deficiency: idiopathic, embryologic CNS malformation (associated with midline facial anomalies, neurologic defects, micropenis in males, hypoglycemia), perinatal asphyxia, rare mutations
- acquired GH deficiency: tumours (e.g. craniopharyngioma), trauma, cranial infection, irradiation, post-surgical

**Risk Factors**
- previous head trauma, history of intracranial bleed or infection, head surgery or irradiation, positive family history, breech delivery

**Clinical Presentation**
- history and physical
  - congenital: growth may be normal in first 6 mo (insulin main growth factor), growth deceleration after; look for microgeni
  - acquired: severe growth failure, ↑ weight/height ratio (short and chubby), infantile fat distribution, immature face with underdeveloped nasal bridge and frontal bossing, high-pitched voice, sparse and thin hair growth, delayed puberty
  - hypothalamic: pituitary dysfunction (micropenis, cryptorchidism, optic nerve hypoplasia, etc.)
  - investigations
    - blood glucose (hypoglycemia), AP x-ray of left hand and wrist for bone age (delayed), IGF-1
    - testing for GH deficiency (stimulation testing), only performed when
      - height <3rd percentile
      - decreased growth velocity
      - midline craniofacial anomalies
      - episodes of hypoglycemia
      - delayed bone age, puberty

---

**Figure 7. Approach to the child with short stature**

- IUGR
  - Primordial
    - Ht, Wt, and HC are affected
    - Chromosomal (e.g. Turner, Dawn)
    - Teratogen, placental insufficiency, infection
  - Proportionate
  - Disproportionate
    - Skeletal dysplasia
  - Normal Growth Velocity
  - Constitutional Growth Delay
    - Delayed puberty
    - May have family history of delayed puberty
    - May need short-term therapy with androgens/estrogens
    - Delayed bone age
    - Often mid-parental height is normal
  - Familial
    - Normal bone age
    - Treatment not indicated
    - Family Hx of short stature
  - Slow Growth Velocity
  - Endocrine (height affected more than weight)
    - GH deficiency
    - Hypothyroidism/Hyperthyroidism
    - Hypercortisolism
    - Hyperpituitarism
    - Adrenal insufficiency
  - Chronic disease (weight affected more than height)
    - Cyanotic congenital heart disease
    - Celiac disease, inflammatory bowel disease, CF
    - Chronic infections
    - Chronic renal failure (often height more affected)
  - Psychosocial neglect (psychosocial dwarfism)
    - Usually decreased height and weight (decreased head circumference if severe)
physiologic increase in GH with arginine, clonidine, insulin, dopamine, or propranolol
positive test if failure to raise GH >5.7 ng/mL post-stimulation

Management
• GH therapy indicated if
  • GH shown to be deficient by 2 different stimulation tests
  • growth velocity <3rd percentile or height <<3rd percentile
  • bone age x-rays show unfused epiphyses/delayed bone age
  • Turner syndrome, Noonan syndrome, Prader-Willi syndrome, chronic renal failure, idiopathic short stature
• support and management of resultant self-image issues, social anxiety, etc.

Prognosis
• if administered at an early age, GH therapy can help patients achieve adult height
• children treated with recombinant GH are at a slightly increased risk of developing pseudotumor cerebri, slipped capital femoral epiphysis and worsening scoliosis
• rare side effects: pancreatitis, transient gynecomastia, increase of growth/pigmentation of nevi

TALL STATURE
• height greater than two SD above the mean for a given age, sex and race

Etiology
• constitutional/familial
• endocrine: Beckwith-Wiedemann syndrome, hyperthyroidism, hypophyseal gigantism, precocious puberty
• genetic: homocystinuria, Klinefelter syndrome, Marfan syndrome, Sotos syndrome

Hypercalcemia/Hypocalcemia/Rickets
• see Endocrinology, E39, E40, E45

Hyperthyroidism and Hypothyroidism
• may be congenital or acquired (for acquired causes, see Endocrinology, E22 and 27)

CONGENITAL HYPERTHYROIDISM
• also known as neonatal Graves’ disease

Epidemiology
• ~1:25,000 neonates, M=F

Etiology
• results from transplacental passage of maternal thyroid stimulating antibodies from mother with a history of Graves’ disease

Clinical Presentation
• history and physical
  • clinical manifestations may be masked if mother on antithyroid treatment
  • may present with tachycardia with congestive heart failure, heart murmur, goiter, craniosynostosis, irritability, poor feeding, FTT
• investigations
  • serum levels of TSH and free T4 in all infants with suspected congenital hypothyroidism or infants born to mothers with Graves’ disease

Management
• methimazole until antibodies cleared
• symptomatic treatment as needed (e.g. β-blockers to control tachycardia)

Prognosis
• if prompt and adequate treatment given, most neonates improve rapidly
• antibodies usually spontaneous cleared by 2-3 mo of life
• fetal or neonatal hyperthyroidism may have adverse effects on CNS development, leading to developmental and behavioural problems
CONGENITAL HYPOTHYROIDISM

**Epidemiology**
- incidence: 1:4000-1:2000 newborns; F:M=2:1
- one of the most common preventable causes of intellectual disability

**Etiology**
- may be classified as permanent primary, central and transient hypothyroidism
- ~85% of primary cases are sporadic (mostly thyroid dysgenesis), remaining 15% hereditary (mostly inborn errors of thyroid synthesis)
- causes of transient hypothyroidism: maternal antibody-mediated, iodine deficiency (rare in developed countries), prenatal exposure to antithyroid medications

**Clinical Presentation**
- history and physical
  - usually asymptomatic in neonatal period because maternal T4 crosses the placenta
  - may have: prolonged jaundice, constipation, sluggish, hoarse cry, lethargy, poor feeding, macroglossia, coarse facial features, large fontanelles, umbilical hernia
- investigations
  - diagnosis through newborn screening of TSH or free T4; abnormal results should be confirmed with serum levels from venipuncture

**Management**
- thyroxine replacement

**Prognosis**
- excellent outcome if treatment started within 1-2 mo of birth
- if treatment started after 3-6 mo of age, may result in permanent developmental delay and/or disability (mild to profound)

## Sexual Development

AMBIGUOUS GENITALIA

**Definition**
- newborn or child whose gender is difficult to assign based on the appearance of genitalia
- subtype of disorders of sex differentiation (DSD): a condition in which development of chromosomal, gonadal or anatomic sex is atypical
- subtypes: 46,XX DSD, 46,XY DSD, ovotesticular DSD (true hermaphrodite)

**Epidemiology**
- incidence of genital abnormalities at birth is as high as 1:300
- prevalence of complex anomalies with true sexual ambiguity much lower at ~1:5000

**Etiology**
- 46,XY DSD
  - inborn error of testosterone biosynthesis or Leydig cell hypoplasia
  - 5-a-reductase deficiency, androgen receptor deficiency or insensitivity
  - luteinizing hormone (LH)/hCG unresponsiveness
- 46,XX DSD
  - virilizing congenital adrenal hyperplasia (CAH) (most common)
  - maternal source: virilizing ovarian or adrenal tumours, untreated maternal CAH, placental aromatase deficiency
  - ovotesticular DSD
    - both ovarian follicles and seminiferous tubules in the same patient with a 46,XX karyotype
    - mixed gonadal dysgenesis

**Risk Factors**
- parental consanguinity, positive family history of ambiguous genitalia, early childhood illness/death or primary amenorrhea, maternal medications during pregnancy (androgens-progestogens, danazol, phenytoin, aminoglutethimide, endocrine disruptors)

**Clinical Presentation**
- history
  - thorough obstetrical history, including prenatal screens and maternal medications
  - family history: autosomal recessive pattern may suggest CAH, X-linked recessive pattern may suggest androgen insensitivity syndrome
• physical
  • male pseudohermaphrodite (XY): small phallus, hypospadias, undescended testicles
  • female pseudohermaphrodite (XX): clitoral hypertrophy, labioscrotal fusion
  • look for concurrent midline defects, dysmorphic features and congenital abnormalities
• investigations
  • karyotype and genetic work-up as indicated
  • blood work: electrolytes and renin (evidence of salt-wasting in CAH); 17-OH-progesterone, androgens, FSH and LH
  • imaging: abdominal U/S to look for uterus, testicles, ovaries

Management
• depends on underlying etiology
• avoid announcement of probable sex or use of personal pronouns until all tests are complete
• continuous psychosocial support for parents and child during development
• elective surgical reconstruction of genitalia is sometimes possible

CONGENITAL ADRENAL HYPERPLASIA (CAH)

Definition
• autosomal recessive disorder characterized by the partial or total defect of various synthetic enzymes of the adrenal cortex required for cortisol and aldosterone production

Epidemiology
• occurs in ~1:15,000 live births
• most common cause of ambiguous genitalia

Etiology
• for biosynthetic pathways of adrenal cortex, see Endocrinology, E29
• 21-hydroxylase deficiency (21-OH) responsible for ~95% of CAH cases
• results in ↓ cortisol and aldosterone production with shunting toward ↑ androgens
• cortisol deficiency leads to elevated ACTH, which causes adrenal hyperplasia
• rarer causes include deficiencies in 11-OH, cholesterol desmolase, 17-OH and 3-HSD

Clinical Presentation
• depends on which enzyme in cortisol synthesis pathway is defective
• presentation of 21-OH deficiency can be divided into:
  • classic deficiency with salt wasting: inadequate aldosterone resulting in FTT, hyperkalemia, hyponatremia, hypoglycemia, acidosis
  • classic deficiency without salt wasting: simple virilizing type
  • non-classic: signs/symptoms of androgen excess (amenorrhea, precocious puberty, etc.)
• 21-OH deficiency screening is part of many newborn screening programs across North America
• high serum levels of 17-OH progesterone in random blood sample diagnostic for 21-OH deficiency

Management
• correct any abnormalities in fluids, electrolytes or serum glucose
• provide glucocorticoids/mineralcorticoids as necessary, extra glucocorticoids in times of stress
• psychosocial support

Prognosis
• complications if untreated include virilization, acne, salt wasting, hypotension

NORMAL PUBERTAL DEVELOPMENT

Physiology
• puberty occurs with the maturation of the hypothalamic–pituitary–gonadal (HPG) axis
• ↑ pulsatile release of GnRH → ↑ release of LH and FSH → maturation of gonads, release of sex steroids → secondary sexual characteristics
• adrenal production of androgens also required

Females
• onset: age 8-13 yr old (may start as early as 7 yr in girls of African descent)
• usual sequence (Figure 8)
  1. thelarche: breast budding
  2. pubarche: axillary hair, body odour, mild acne
  3. growth spurt
  4. menarche: mean age 12.5 yr; indicates that growth spurt is almost complete; menses may be irregular in duration and length of cycle
• early puberty is common and often constitutional, late puberty is rare (rule out organic causes)
Males
- onset: age 9-14 yr old
- usual sequence
  1. testicular enlargement
  2. penile enlargement
  3. pubarche: axillary and facial hair, body odour, mild acne
  4. growth spurt: occurs later in boys
- early puberty is uncommon (rule out organic causes), late puberty is common and often constitutional
- gynecomastia (transient development of breast tissue) is a common self-limited condition seen in 50% of male during puberty (but any discharge from nipple or fixed mass should be investigated)

Tanner Staging
- scale used in paediatrics that defines physical measurements of development based on external primary and secondary sex characteristics

**Figure 8. Tanner staging**

**PREOCIOUS PUBERTY**

**Definition**
- development of secondary sexual characteristics 2-2.5 SD before population mean
- < 8 yr old for females, < 9 yr old for males

**Epidemiology**
- 1/10,000, F>M

**Etiology**
- usually idiopathic in females (90%), more suggestive of pathology in males (50%)
- central (GnRH dependent)
  - hypergonadotrophic hypergonadism; hormone levels as in normal puberty
  - premature activation of the HPG axis
  - differential diagnosis: idiopathic or constitutional (most common), CNS disturbances (tumours, hamartomas, post-meningitis, increased ICP, radiotherapy), neurofibromatosis (NF), primary severe hypothyroidism
- peripheral (GnRH independent)
  - hypogonadotrophic hypergonadism
  - differential diagnosis: adrenal disorders (CAH, adrenal neoplasm), testicular/ovarian tumour, gonadotropin/bCG secreting tumour (hepatoblastoma, intracranial teratoma, germinoma), exogenous steroid administration, McCune-Albright syndrome, aromatase excess syndrome, rarely hypothyroidism (Van-Wyk-Grumbach syndrome)
Clinical Presentation
- history
  - symptoms of puberty, family history of precocious puberty, medical illness
- physical
  - growth velocity: prepubertal: 4 to 6 cm/yr, growth spurt: boys 8-10 cm/yr, girls 6-8 cm/yr
  - complete physical exam, including Tanner staging and neurological assessment
- investigations
  - initial screening tests: bone age, serum hormone levels (estradiol, testosterone, LH, FSH, TSH, free T4, DHEA-S, 17-OH progesterone)
  - secondary tests: MRI head, pelvic U/S, β-hCG, GnRH and/or ACTH stimulation test

Management
- indications for medical intervention to delay progression of puberty: rapid advancement of puberty, early age, risk of compromise of final adult height, psychological
- central causes: goals are to preserve height and alleviate psychosocial stress; GnRH agonists (e.g. leuprolide) most effective
- peripheral causes: goal is to limit effects of elevated sex steroids; treat underlying cause; medications that decrease the production of a specific sex steroid or blocks its effects (e.g. ketoconazole, spiranloactone, tamoxifen, anastrozole), surgical intervention

DELAYED PUBERTY

Definition
- failure to develop secondary sex characteristics by 2-2.5 SD beyond the population mean
  - for males: lack of testicular enlargement by 14 yr old
  - for females: lack of breast development by 13 yr old OR absence of menarche by 16 yr old or within 5 yr of pubertal onset

Epidemiology
- M>F

Etiology
- usually constitutional delay in males, more suggestive of pathology in females
- central causes
  - constitutional delay in activation of hypothalamic-pituitary-gonadal axis (most common)
  - hypogonadotropic hypogonadism
- peripheral causes
  - hypergonadotropic hypogonadism (e.g. primary gonadal failure, gonadal damage, Turner syndrome, hormone deficiency, androgen insensitivity syndrome, etc.)

Clinical Presentation
- history
  - weight loss, short stature, family history of puberty onset, medical illness, high performance athletes (females)
- physical
  - growth velocity (minimum 4 cm/yr), Tanner staging, neurological exam, complete physical exam
- investigations
  - initial screening tests: bone age, serum hormone levels (estradiol, testosterone, LH, FSH, TSH, free T4, IGF-1), CBC, electrolytes, BUN, Cr, liver function tests, liver enzymes, ESR, CRP, urinalysis
  - secondary tests: MRI head, pelvic U/S, karyotype, IBD panel, celiac disease panel, LH levels following GnRH agonist

Management
- identify and treat underlying cause
- hormonal replacement: cyclic estradiol and progesterone for females, testosterone for males
**Vomiting**

**History**
- characteristic of emesis (e.g. projectile, bilious, bloody)
- pattern of emesis (e.g. association with feeds, cyclic, morning)
- associated symptoms (e.g. anorexia, diarrhea, etc.)
- red flags: bilious or bloody emesis, projectile vomit, abdominal distension and tenderness, high fever, signs of dehydration

**Physical Findings**
- vital signs to determine clinical status and hydration state
- dictated by suspected differential (see Table 13)

**Investigations**
- CBC, electrolytes, BUN, Cr, amylase, lipase done routinely
- in sick child, add: ESR, venous blood gases, culture and sensitivity (blood, stool), imaging
- dictated by suspected differential (see Table 13)

| Table 13. Common Differential Diagnosis, Associated Findings and Diagnostic Approach Based on Age |
|-----------------|-----------------|-----------------|
| **Cause**       | **Suggestive Findings** | **Diagnostic Approach** |
| **NEONATES – NON-BILIOUS** | | |
| Tracheoesophageal fistula | Vomiting, excessive secretions soon after birth (e.g. drooling, choking, respiratory distress), inability to feed, inability to advance through NG tube | Inability to advance NG tube, CXR, upper GI series with water-soluble contrast |
| Pyloric stenosis | Projectile vomiting immediately after feeding, dehydrated, palpable "olive" in RUQ, decreased stools, hunger | U/S of pylorus, upper GI study Electrolytes, blood gas (hypokalemic, hypochloremic metabolic alkalosis) |
| GERD | Fussiness after feeds, spit ups, arching of back, poor weight gain | Empiric trial of acid suppression, pH monitoring study, UGI, endoscopy |
| Sepsis | Fever, lethargy, tachycardia, tachypnea, widening pulse pressure | CBC, cultures (blood, urine, CSF), CXR |
| Inborn error of metabolism | Poor feeding, failure to thrive, jaundice, hepatosplenomegaly, cardiomyopathy, dysmorphia, developmental delay | Electrolytes, blood gas (hyponatremic, hyperkalemic metabolic acidosis), lactate, ammonia, LFTs, BUN, Cr, serum Glu, bilirubin, PT/PTT, CBC |
| **NEONATES – BILIOUS** | | |
| Duodenal atresia | Bilious vomiting, abdominal distension, often seen in Down’s syndrome, jaundice, polyhydramnios during pregnancy | AXR, upper GI series (‘double bubble’ sign) |
| Malrotation with volvulus | Bilious emesis, abdominal distension, pain, bloody stool, shock | AXR, upper GI series, contrast enema |
| Hirschsprung’s disease | Bilious emesis, abdominal distension, pain, failure to pass stool | AXR, upper GI series, contrast enema, rectal biopsy |
| **CHILDREN AND ADOLESCENTS** | | |
| Gastroenteritis | Diarrhea, fever, sick contact, recent travel | CBC, stool culture |
| Appendicitis | Periumbilical discomfort that later localizes to RLQ, fever, anorexia | Abdominal U/S |
| Intussusception | Colicky progressive abdominal pain, drawing of leg up to chest, lethargy, bloody stool | Abdominal U/S |
| Non-GI infection (e.g. meningitis) | Fever, localized findings depending on cause | Cultures (CSF, blood, urine), brain imaging |
| Increased intracranial pressure | Nocturnal wakening, progressive recurrent headache worse with Valsalva, nuchal rigidity | Brain CT without contrast Therapeutic LP in idiopathic intracranial hypertension |
| Toxic ingestion | Finding possibly varying by substance- toxidrome, often a history of ingestion | Qualitative and sometimes quantitative levels (urine, blood) |
| Pregnancy | Amenorrhea, morning sickness, bloating, breast tenderness | Urine β-HCG |
| Cyclic vomiting | At least 3 self-limited episodes of vomiting lasting 12 h, 7 d between episodes, no organic cause of vomiting | Diagnosis of exclusion |
Management
- rehydration (see Nephrology, P79)
- treat underlying cause (see detailed differential diagnosis above)

**Gastroesophageal Reflux**

**Epidemiology**
- extremely common in infancy (up to 50%)

**Clinical Presentation**
- vomiting typically soon after feeding, non-bilious, rarely contains blood, small volume (<30 mL)

**Investigations**
- thriving baby requires no investigation
- investigations required if concomitant FTT, feeding aversion, recurrent cough, pneumonia or bronchospasm, GI blood loss or symptoms persist after 18 mo

**Management**
- conservative: thickened feeds, frequent and smaller feeds
- medical:
  - short-term parenteral (NG) feeding to enhance weight gain
  - ranitidine, omeprazole: decreases gastric acidity, decreases esophageal irritation
  - domperidone, metoclopramide: improves gastric emptying and GI motility
- surgical: indicated for failure of medical therapy (Nissen fundoplication)

**Complications**
- esophagitis, strictures, Barrett's esophagus, FTT, aspiration, oral feeding aversion

**Tracheoesophageal Fistula (TEF)**
- see General Surgery, GS64

**Pyloric Stenosis**
- see General Surgery, GS61

**Duodenal Atresia**
- see General Surgery, GS63

**Malrotation of the Intestine**
- see General Surgery, GS62

**Diarrhea**
- definition of diarrhea varies with diet and age (stool normalcy difficult to define in children)
  - infants → increase in stool frequency to twice as often per day; older children → 3+ loose or watery stools/d
  - duration: acute: <2 wk; chronic: >2 wk

**Pathophysiology**
- osmotic: due to non-absorbable solutes in GI tract (e.g. lactose intolerance)
- secretory: increased secretion of Cl- ions and water in intestinal lumen (e.g. bacterial toxin)
- malabsorption: decreased GI surface area (e.g. short bowel syndrome)

**History**
- frequency, duration, quality of diarrhea
- associated symptoms (e.g. fever, abdominal pain, hematochezia, etc.)
- recent antibiotic use or recent travel
- elements of diet

**Physical Findings**
- vital signs to determine clinical status and hydration state
- dictated by suspected differential (see Tables 14 and 15, P36)

Diarrhea is defined as an increase in frequency and/or decreased consistency of stools compared to normal.

Normal stool volume:
Infants: 5-10 g/kg
Children: 200 g/d

Diarrhea Red Flags
- Bloody stool, fever, petechiae or purpura, signs of severe dehydration, weight loss/FTT.
Investigations

- **Acute diarrhea:**
  - stool for culture and sensitivity, ova and parasites, electron microscopy for viruses, *C. difficile* toxin, microscopy (leukocytes suggestive of invading pathogen), blood and urine cultures, bloodwork

- **Chronic diarrhea:**
  - serial heights, weights, growth percentiles
  - if child growing well and thriving, workup is limited (stool cultures as above, stool reducing substances)
  - red flags: poor growth, chronic rash, other serious infections, hospitalizations for dehydration
    - require full work-up (as per below)
  - stool: consistency, pH, reducing substances, microscopy, occult blood, O&P, C&S, *C. difficile* toxin, 3 d fecal fat, α-1 antitrypsin clearance, fecal elastase
  - urinalysis, urine culture
  - CBC, differential, ESR/CRP, smear, electrolytes, total protein, albumin, Ca²⁺, PO₄³⁻, Mg²⁺, Fe, ferritin, folate, fat-soluble vitamins, PTT, INR

- sweat chlorides, celiac screen, thyroid function tests, urine vanillyl mandellic acid (VMA) and homovanillic acid (HVA), HIV test, lead levels

- CXR, upper GI series and follow-through

- specialized tests: endoscopy, small bowel biopsy

**Differential Diagnosis**

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Non-infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td></td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Salmonella</td>
</tr>
<tr>
<td>Norwalk</td>
<td>Campylobacter</td>
</tr>
<tr>
<td>Enteric Adenovirus</td>
<td>Shigella, Pathogenic <em>E. coli</em></td>
</tr>
<tr>
<td></td>
<td><em>Entamoeba histolytica</em></td>
</tr>
<tr>
<td></td>
<td><em>C. difficile</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chronic</th>
<th>0 – 3 months</th>
<th>3 months – 3 years</th>
<th>3 – 18 years</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>ØFFT</td>
<td>GI infection</td>
<td>GI infection</td>
<td>GI infection</td>
<td>Drug-induced</td>
</tr>
<tr>
<td></td>
<td>Toddler’s diarrhea</td>
<td>Lactase deficiency</td>
<td>Irritable bowel syndrome</td>
<td></td>
</tr>
<tr>
<td>FFT</td>
<td>Disaccharidase deficiency</td>
<td>Celiac disease</td>
<td>IBD</td>
<td>Short bowel syndrome</td>
</tr>
<tr>
<td></td>
<td>Cow’s milk protein intolerance</td>
<td></td>
<td>Endocrine (thyrotoxicosis, Addison’s)</td>
<td>Schwachman-Diamond syndrome</td>
</tr>
<tr>
<td></td>
<td>Cystic fibrosis</td>
<td></td>
<td>Neoplastic (pheochromocytoma, lymphoma)</td>
<td></td>
</tr>
</tbody>
</table>

**Infective Diarrhea**

<table>
<thead>
<tr>
<th>Viral Infection</th>
<th>Bacterial Infection</th>
</tr>
</thead>
</table>
| **Etiology**   | Most common cause of gastroenteritis
Commonly: rotaviruses, astroviruses, Norwalk virus (typically older children) |

| **Presentation Clinical** | | |
|---------------------------|-------------------|
| Associated with URIs      | Severe abdominal pain |
| Resolves in 3-7 d         | High fever |
| Slight fever, malaise, vomiting, vague abdominal pain | Bloody diarrhea |

| **Risk Factors** | |
|------------------| |
| Day care         | Travel |
| Poorly cooked meat | Poorly refrigerated foods |
| Prolonged antibiotics |

| **Management** | |
|----------------| |
| Prevention and treatment of dehydration most important (see Dehydration, P79) | |
| Early refueling advisable, start with small amounts of easily digested carbohydrates, postpone dairy and fibrous vegetables | |
| Antibiotic therapy when indicated, antidiarrheal medications not indicated | |
| Notify Public Health authorities if appropriate | |
**Toddler’s Diarrhea**

**Epidemiology**
- most common cause of chronic diarrhea during infancy
- onset between 6-36 mo of age, ceases spontaneously between 2-4 yr

**Clinical Presentation**
- diagnosis of exclusion in thriving child
- 4-6 bowel movements per day
- diet history (e.g. excess juice intake overwhelms small bowel resulting in disaccharide malabsorption)
- stool may contain undigested food particles
- excoriated diaper rash

**Management**
- reassurance that it is self-limiting
- 4Fs (adequate Fibre, normal Fluid intake, 35-40% Fat, discourage excess Fruit juice)

**Lactase Deficiency (Lactose Intolerance)**

**Clinical Presentation**
- chronic, watery diarrhea and abdominal pain, bloating associated with dairy intake
- primary lactose intolerance: crampy abdominal pain with loose stool (older children, usually of East Asian and African descent)
- secondary lactose intolerance: older infant, persistent diarrhea (post viral/bacterial infection, Celiac disease, or IBD)

**Diagnosis**
- trial of lactose-free diet
- watery stool, acid pH, positive reducing sugars
- positive breath hydrogen test if >6 yr

**Management**
- lactose-free diet, soy formula
- lactase-containing tablets/capsules/drops (e.g. Lacteeze®, Lactaid®)

**Irritable Bowel Syndrome**

- diagnosis of exclusion in older child/adolescent; may be similar to recurrent abdominal pain
- management: encourage high fibre diet, reassurance, medications (cAMP inhibitors) rarely for refractory cases

**Celiac Disease**

- see Gastroenterology, G18
- in children: presents at any age, usually 6-24 mo with the introduction of gluten in the diet
- FTT with poor appetite, irritability, apathy, rickets, wasted muscles, flat buttocks, rarely distended abdomen
- GI symptoms: anorexia, nausea, vomiting, edema, anemia, abdominal pain
- non-GI manifestations: iron-deficiency anemia, dermatitis herpetiformis, dental enamel hypoplasia, osteopenia/osteoporosis, short stature, delayed puberty, behavioural changes
- associated with other autoimmune disorders

**Milk Protein Allergy**

**Pathophysiology**
- immune-mediated mucosal injury (IgE and non-IgE-mediated)

**Clinical Presentation**
- up to 50% of children intolerant to cow’s milk may be intolerant to soy protein as well
- often history of atopy
- can present as:
  - proctocolitis: mild diarrhea, small amounts of bloody stools (common presentation in young infant)
  - enterocolitis: vomiting, diarrhea, anemia, hematochezia
  - enteropathy: chronic diarrhea, hypoalbuminemia
Management
• casein hydrolysate formula (dairy-free e.g. Nutramigen®, Pregestimil®) or mother may remove all milk protein from diet and continue breastfeeding (with adequate calcium and vit D intake)

Inflammatory Bowel Disease (IBD)
• see Gastroenterology, G19

Cystic Fibrosis (CF)
• see Respirology, P95

Constipation
• decreased stool frequency (<3 stools/wk) and/or stool fluidity (hard, pellet-like)

FUNCTIONAL CONSTIPATION
• 99% of cases of constipation

Pathophysiology
• lack of fibre in diet or change in diet, poor fluid intake, behavioural
  • infants: often occurs when introducing cow's milk after breast milk due to high fat and solute content, lower water content
  • toddlers/older children: can occur during toilet training, or due to pain on defecation, stool withholding

Management
• clean out: PEG 3350 flakes, picosalax, biscodyl, PEGlyte
• maintenance: adequate fluid intake (if <6 mo, 150 mL/kg/d), adequate dietary fibre, stool softening (PEG 3350, mineral oil), appropriate toilet training technique
• months of maintenance treatment is often required

Complications
• pain retention cycle: anal fisses + pain → withhold passing stool → chronic dilatation ± overflow incontinence

HIRSCHSPRUNG’S DISEASE (Congenital Aganglionic Megacolon)
• see General Surgery, GS63

OTHER ORGANIC DISORDERS CAUSING CONSTIPATION
• endocrine: hypothyroidism, DM, hypercalcemia
• neurologic: spina bifida
• anatomic: bowel obstruction, anus (imperforate, atresia, stenosis)
• drugs: lead, chemotherapy, opioids

Abdominal Pain

ACUTE ABDOMINAL PAIN

History
• description of pain (location, radiation, duration, constant vs. colicky, relation to meals)
• associated symptoms: nausea, vomiting, diarrhea, fever

Physical Examination
• abdominal exam, peritoneal signs, bowel sounds, rectal exam, rash

Investigations
• CBC, differential, urinalysis to rule out urinary tract infection (UTI)
# Table 16. Differential Diagnosis of Acute Abdominal Pain

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Hepatobiliary Tract</th>
<th>Genitourinary</th>
<th>Hematologic</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenteritis</td>
<td>Cholecystitis</td>
<td>UTI</td>
<td>Henoch-Schönlein Purpura</td>
<td>DKA</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>Pancreatitis</td>
<td>Nephrolithiasis</td>
<td>Sickle cell crisis</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Meckel’s diverticulum</td>
<td></td>
<td>Testicular torsion</td>
<td></td>
<td>Somatization</td>
</tr>
<tr>
<td>Mesenteric adenitis</td>
<td></td>
<td>Ovarian torsion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileus</td>
<td></td>
<td>Ectopic pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal obstruction (incarcerated hernia, intussusception, volvulus)</td>
<td></td>
<td>PID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malabsorption</td>
<td></td>
<td>Endometriosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBS</td>
<td></td>
<td>Menstruation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholecystitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testicular torsion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian torsion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PID</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstruation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henoch-Schönlein Purpura</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DKA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## APPENDICITIS
- see [General Surgery], GS28
- most common cause of acute abdomen after 5 yr of age
- clinical features: low grade fever, abdominal pain, anorexia, N/V (after onset of pain), peritoneal signs (generalized peritonitis is a common presentation in infants/young children)
- treatment: surgical
- complications: perforation (common in young children), abscess

## INTUSSUSCEPTION
- telescoping of segment of bowel into distal segment causing ischemia and necrosis

### Epidemiology
- 90% idiopathic, children with CF or GJ tube at significantly increased risk
- 50% between 3-12 mo, 75% before 2 yr of age

### Pathophysiology
- usual site: ileocecal junction; jejunum in children with GJ tubes
- lead point of telescoping segment may be swollen Peyer’s patches, Meckel’s diverticulum, polyp, malignancy, Henoch-Schönlein Purpura

### Clinical Presentation
- “classic triad” (only in 10-15% of patients)
- sudden onset of recurrent, paroxysmal, severe periumbilical pain with pain-free intervals
- later vomiting (may be bilius) and rectal bleeding (late finding)
- shock and dehydration

### Diagnosis
- U/S, air enema

### Management
- air enema can be therapeutic (reduces intussusceptions in 75% of cases), reduction under hydrostatic pressure, surgery rarely needed

## Chronic Abdominal Pain

### Epidemiology
- prevalence: 10% of school children (peak at 8-10 yr), F>M

### Etiology
- organic (<10%)
  - gastrointestinal
    - constipation (cause vs. effect), infectious
    - IBD, esophagitis, peptic ulcer disease, lactose intolerance
    - anatomic anomalies, masses
    - pancreatic, hepatobiliary
  - genitourinary causes
  - recurrent urinary tract infections, nephrolithiasis, chronic PID, Mittelschmerz
  - neoplastic
  - Functional/Recurrent Abdominal Pain (RAP) (90%)
Clinical Presentation
- clustering episodes of vague, crampy periumbilical/epigastric pain, vivid pain description
- seldom awakens child from sleep, less common on weekends
- aggravated by exercise, alleviated by rest
- psychological factors related to onset and/or maintenance of pain, school avoidance
- psychiatric comorbidity: anxiety, somatoform, mood, learning disorders, sexual abuse, eating disorders, elimination disorders
- diagnosis of exclusion

Investigations
- CBC, ESR, urinalysis, stools for O&P, C&S, occult blood

Management
- continue to attend school
- manage any emotional or family problems, counselling
- trial of high fibre diet, trial of lactose-free diet
- reassurance

Prognosis
- pain resolves in 30-50% of kids within 2-6 wk of diagnosis
- 30-50% of kids with RAP have functional pain as adults (e.g. irritable bowel syndrome)

Abdominal Mass

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal (note: 50% of abdominal masses in newborn are renal in origin)</td>
<td>Nephroblastoma (Wilms’ tumour)</td>
</tr>
<tr>
<td>Polycystic kidney disease (PKD)</td>
<td>Renal cell carcinoma (RCC)</td>
</tr>
<tr>
<td>Hamartoma</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Ovarian tumours</td>
</tr>
<tr>
<td>Ovarian cysts</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
<td>Retroperitoneal sarcoma</td>
</tr>
<tr>
<td>Abdominal hernia</td>
<td></td>
</tr>
<tr>
<td>Teratoma</td>
<td></td>
</tr>
<tr>
<td>Fecal impaction</td>
<td></td>
</tr>
</tbody>
</table>

Upper Gastrointestinal Bleeding
- see Gastroenterology, G25

Lower Gastrointestinal Bleeding
- see Gastroenterology, G27

Epidemiology
- acute:
  - infectious (bacterial, parasitic)
  - antibiotic-induced (C. difficile)
  - necrotizing enterocolitis in preterm infants
  - anatomic
  - malrotation/volvulus, intussusception
  - Meckel's diverticulitis
  - anal fissures, hemorrhoids
  - vascular/hematologic
  - Henoch-Schönlein Purpura (HSP)
  - hemolytic uremic syndrome (HUS)
  - coagulopathy
- chronic:
  - anal fissures (most common)
  - colitis
  - inflammatory bowel disease (IBD)
  - allergic (milk protein)
  - structural
  - polyps (most are hamartomas)
  - neoplasms (rare)
  - coagulopathy

Physical Examination
- hemodynamic status, evidence of FTT, fever
- anal and rectal exam: tags, fissures, anal fistulas, polyps, foreign body, blood per rectum
- stool appearance
- NG aspirate
- lower GI bleed may present as melena (if it involves the small bowel) or hematochezia
Investigations
- stool cultures (C&S, *C. difficile* toxin)
- urinalysis and microscopy
- CBC, smear, differential, ESR, CRP, electrolytes, urea, creatinine, INR, PTT, albumin, iron studies, amoeba titers
- radiologic investigations
- abdominal x-ray to rule out obstruction
- Meckel's radionucleide scan

Management
- acute stabilization: ABCs, volume and blood replacement, bowel rest (NPO, NG tube)
- once stable, endoscopy and/or surgery as indicated

Genetics, Dysmorphisms and Metabolism

Genetic Anomalies

Minor and Major Anomalies
- minor anomaly: an unusual anatomic feature that is of no serious medical or cosmetic consequence to the patient
- major anomaly: anomaly that creates significant medical, surgical or cosmetic problems for the patient

Mechanism for Anomalies
- malformation: results from an intrinsically abnormal developmental process (e.g. polydactyly)
- disruption: results from the extrinsic breakdown of, or interference with, an originally normal developmental process (e.g. amniotic band disruption sequence)
- deformation: alteration of the final form of a structure by mechanical forces (e.g. Potter deformation sequence)
- dysplasia: abnormal development that results in abnormal organization of cells into tissues (e.g. bone dysplasia)

Multiple Anomalies
- association: non-random occurrence of multiple independent anomalies that appear together more than would be predicted by chance but are not believed to have a single etiology (e.g. VACTERL)
- sequence: related anomalies that come from a single initial major anomaly or precipitating factor that changes the development of other surrounding or related tissues or structures (e.g. Potter sequence)
- syndrome: a pattern of anomalies that occur together and are caused by a single known or unknown cause (e.g. Down syndrome)

Approach to the Dysmorphic Child
- genetic disorders are the most common cause of infant death in developed countries

General Approach to the Dysmorphic Child
- Are the anomalies major or minor?
- What is the mechanism underlying the anomaly?
- Do the anomalies fit as part of an association, sequence or syndrome?

History
- prenatal/obstetrical history (see Obstetrics, OB2)
- complete 3 generation family pedigree: consanguinity, stillbirths, neonatal deaths, specific illnesses, intellectual disability, multiple miscarriages, ethnicity
Physical Examination

Investigations
- prenatal counselling and assessing risk of recurrence
- serial photographs if child is older
- x-rays for bony abnormalities
- cytogenetic studies
  - karyotype if recognized syndrome
  - chromosome microarray analysis (array comparative genomic hybridization) if developmental delay with multiple congenital anomalies
  - fluorescent in situ hybridization (FISH) if microdeletion syndrome or trisomy suspected
  - chromosomes in skin fibroblasts if mosaicism suspected and microarray is normal
- biochemistry: specific enzyme assays
- single gene testing

Genetics

MECHANISMS OF INHERITANCE

Mendelian Inheritance
- disorders caused by mutation of one or both copies of a gene, inherited in one of two patterns:
  - autosomal: encoded by genes on one of 22 pairs of autosomes (chromosomes 1-22)
  - X-linked: encoded by a gene on the X chromosome

Triplet Repeat Expansions
- disorder in which trinucleotide repeats in certain genes exceed the normal number and result in altered expression of the gene or production of an abnormal protein (e.g. Fragile X syndrome, spinocerebellar ataxias, myotonic dystrophy, Huntington disease)

Imprinting Disorders
- imprinting: epigenetic process that involves methylation or acetylation of DNA, affecting gene expression
- imprinted genes are expressed differently depending on whether they are inherited from the mother or the father (parent-of-origin gene expression)
- occur when imprinted alleles are silenced (e.g. Prader-Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome)

Mitochondrial Inheritance
- disorders caused by mutations of the DNA present in mitochondria
- inheritance pattern: mother passes on the defect to all her children; father does not pass on the defect since embryo only receives mitochondria from the mother (in the egg)

METHODS OF GENETIC TESTING
- microarray analysis
  - a microarray is a collection of DNA probes attached to a solid surface
  - microarray analysis can identify small deletions or duplications of genetic material anywhere in the genome
  - indicated when there is developmental delay + one or more major malformations
- **FISH**
  - usually to identify a gain or loss of chromosomal material
- **karyotype**
  - microscopic analysis of all 46 chromosomes with a special stain that shows large changes in the number or structure of chromosomes

### Genetic Syndromes

#### Table 18. Common Genetic Syndromes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Trisomy 21</th>
<th>Trisomy 18</th>
<th>Trisomy 13</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>1:600-800 births</td>
<td>1:600 live births</td>
<td>1:10,000 live births</td>
</tr>
<tr>
<td><strong>Most common abnormality of autosomal chromosomes</strong></td>
<td>47,XXY (most common) 46,XX or 46,XY</td>
<td>47,XXY (most common)</td>
<td>46,XX or 46,XY</td>
</tr>
<tr>
<td><strong>Genotype</strong></td>
<td>X-linked</td>
<td>CGG trinucleotide repeat on X chromosome measurable by molecular analysis</td>
<td>Autosomal dominant (not a sex chromosome disorder) with variable expression</td>
</tr>
<tr>
<td><strong>Hypertonia at birth</strong></td>
<td></td>
<td>Hypertonia</td>
<td>Higher transmission of affected maternal gene</td>
</tr>
<tr>
<td><strong>Low IQ, developmental delay, hearing problems</strong></td>
<td></td>
<td>Hypo- or hypertonia</td>
<td></td>
</tr>
<tr>
<td><strong>Onset of Alzheimer’s disease in 40s</strong></td>
<td></td>
<td>Seizures, deafness</td>
<td></td>
</tr>
<tr>
<td><strong>Other Features</strong></td>
<td>Transverse palmar crease, clinodactyly and absent middle phalanges of the 5th finger</td>
<td>Small for gestational age (SGA) Rocker-bottom feet</td>
<td>Severe developmental delay</td>
</tr>
<tr>
<td><strong>Cardiac Defect</strong></td>
<td>50%, particularly AVSD</td>
<td>60% (VSD, PDA, ASD)</td>
<td>80% (VSD, PDA, ASD)</td>
</tr>
<tr>
<td><strong>Gl</strong></td>
<td>Duodenal/esophageal/anus atresia, TE fistula, Hirschsprung’s disease, chronic constipation</td>
<td>Hemia, TEF</td>
<td></td>
</tr>
<tr>
<td><strong>GU</strong></td>
<td>Cryptorchidism, rarely fertile</td>
<td>Polycystic kidneys, cryptorchidism</td>
<td>Polycystic kidneys</td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td>Hypotonia at birth</td>
<td>Hypertonia</td>
<td></td>
</tr>
<tr>
<td><strong>Eyes</strong></td>
<td>Upslanting palpebral fissures, inner epicanthal folds, speckled iris (Brushfield spots), refractive errors (myopia), acquired cataracts, nystagmus, strabismus</td>
<td>Microophthalmia, hypotelorism, iris coloboma, retinal anomalies</td>
<td>Microophthalmia, corneal abnormalities</td>
</tr>
<tr>
<td><strong>Ears</strong></td>
<td>Low-set, small, overfolded upper helix, frequent AOM, hearing loss</td>
<td>Low-set, malformed</td>
<td>Low-set, malformed</td>
</tr>
<tr>
<td><strong>Facial Features</strong></td>
<td>Protruding tongue, large cheeks, low flat nasal bridge, small nose</td>
<td>Cleft lip/palate Small mouth, micrognathia</td>
<td>60-80% cleft lip and palate</td>
</tr>
<tr>
<td><strong>Skeletal/MSK</strong></td>
<td>Short stature</td>
<td>Clenched fist with overlapping digits, hypoplastic nails, clinodactyly, polydactyly</td>
<td>Severe growth retardation Polydactyly, clenched hand</td>
</tr>
<tr>
<td><strong>Seizures, scoliosis, mitral valve prolapse</strong></td>
<td></td>
<td>Severe growth retardation</td>
<td></td>
</tr>
<tr>
<td><strong>Complications:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Seizures, scoliosis, mitral valve prolapse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prognosis/Management</strong></td>
<td>Per AAP Guidelines (Health Supervision of Children with Down syndrome), recommend chromosomal analysis, CBC, echo, yearly thyroid test, atlanto-occipital x-ray at 2 yr, sleep study, hearing test, and ophthalmology assessment</td>
<td>44% die in 1st month 10% survive past 1 yr (profound intellectual disability in survivors)</td>
<td>33% die in 1st month, 50% by 2nd month, 90% by 1 yr from FTT Profound intellectual disability in survivors</td>
</tr>
</tbody>
</table>

#### Table 19. Most Common Sex Chromosome Disorders

<table>
<thead>
<tr>
<th>Fragile X Syndrome</th>
<th>Klinefelter Syndrome</th>
<th>Turner Syndrome</th>
<th>Noonan Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genotype</strong></td>
<td>X-linked</td>
<td>Genetic anticipation</td>
<td>47,XXY (most common)</td>
</tr>
<tr>
<td><strong>CGG trinucleotide repeat on X chromosome measurable by molecular analysis</strong></td>
<td>CGG trinucleotide repeat on X chromosome</td>
<td>CGG trinucleotide repeat on X chromosome</td>
<td>Autosomal dominant (not a sex chromosome disorder) with variable expression</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>1:3600 males, 1:6000 females</td>
<td>1:1000 live male births</td>
<td>1:4000 live female births</td>
</tr>
<tr>
<td><strong>Most common heritable cause of intellectual disability in boys</strong></td>
<td>Increased risk with advanced maternal age</td>
<td>Risk not increased with advanced maternal age 1:4000 live female births</td>
<td></td>
</tr>
<tr>
<td><strong>Phenotype</strong></td>
<td>Tall, slim, underweight No features prepuberty Postpuberty: male may suffer from developmental delay, long limbs, gynecomastia, lack of facial hair</td>
<td>Short stature, short webbed neck, low posterior hairline, wide carrying angle Broad chest, widely spaced nipples Hypertelorism, low set eyes, epicanthal folds, ptosis</td>
<td>Certain phenotypic features similar to females with Turner syndrome; therefore, sometimes called the “male Turner syndrome”, although it affects both males and females</td>
</tr>
<tr>
<td><strong>Complications:</strong></td>
<td></td>
<td>Severe growth retardation</td>
<td></td>
</tr>
<tr>
<td><strong>Seizures, scoliosis, mitral valve prolapse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 19. Most Common Sex Chromosome Disorders**

- **Fragile X Syndrome**
  - X-linked
- **Klinefelter Syndrome**
  - CGG trinucleotide repeat on X chromosome measurable by molecular analysis
- **Turner Syndrome**
  - 47,XXY (most common) 46,XX or 46,XY
- **Noonan Syndrome**
  - Autosomal dominant (not a sex chromosome disorder) with variable expression

**Table 18. Common Genetic Syndromes**

- **Incidence**
  - 1:600-800 births
- **Genotype**
  - X-linked
- **Management**
  - Prognosis
  - **Other Features**
    - Transverse palmar crease, clinodactyly and absent middle phalanges of the 5th finger
    - 1% lifetime risk of leukemia
    - Increased risk with advanced maternal age 1:1000 male and female live births
    - 45,X (most common) 46,XX or 46,XY
    - Autosomal dominant (not a sex chromosome disorder) with variable expression
Table 19. Most Common Sex Chromosome Disorders (continued)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>IQ and Behaviour</th>
<th>Gonad and Reproductive Function</th>
<th>Diagnosis/Prognosis/Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragile X Syndrome</td>
<td>Mild to moderate intellectual disability, 20% of affected males have normal IQ</td>
<td>Premutation carrier females at risk of developing premature ovarian failure</td>
<td>Molecular testing of FMR1 gene: overamplification of the trinucleotide repeat, length of segment is proportional to severity of clinical phenotype (genetic anticipation)</td>
</tr>
<tr>
<td>Klinefelter Syndrome</td>
<td>Milder intellectual disability Behavioural or psychiatric disorders – anxiety, shyness, aggressive behaviour, antisocial acts</td>
<td>Infertility due to hypogonadism/ hypospermia</td>
<td>Increased risk of germ cell tumours and breast cancer Management: Testosterone in adolescence</td>
</tr>
<tr>
<td>Turner Syndrome</td>
<td>Mildly deficient to normal intelligence</td>
<td>Streak ovaries with deficient follicles, infertility, primary amenorrhea, impaired development of secondary sexual characteristics</td>
<td>Normal life expectancy if no complications Increased risk of X-linked diseases Management: ECHO, ECG to screen for cardiac malformation GH therapy for short stature Estrogen replacement at time of puberty for development of secondary sexual characteristics</td>
</tr>
<tr>
<td>Noonan Syndrome</td>
<td>Moderate intellectual disability in 25% of patients</td>
<td>Delayed puberty</td>
<td>Management: Affected males may require testosterone replacement therapy at puberty ECHO, ECG</td>
</tr>
</tbody>
</table>

Table 20. Other Genetic Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genotype</th>
<th>Incidence</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>DiGeorge Syndrome</td>
<td>Microdeletions of chromosome region 22q11</td>
<td>1:15,000</td>
<td>&quot;CATCH 22&quot; C: Cyanotic CHD (may account for up to 5% of all cases of CHD)</td>
</tr>
<tr>
<td>Prader-Willi Syndrome</td>
<td>Due to deletion of paternal chromosome 15q11 or two maternal chromosome 15s (maternal uniparental disomy)</td>
<td>1:10,000</td>
<td>A: Anomalies: craniofacial anomalies typically micrognathia and low set ears</td>
</tr>
<tr>
<td>Angelman Syndrome</td>
<td>Due to maternally derived deletion of the usually maternally expressed genes The paternal copy is silenced epigenetically</td>
<td></td>
<td>T: Thymic hypoplasia “immunodeficiency” recurrent infections</td>
</tr>
<tr>
<td>CHARGE Syndrome</td>
<td>2/3 of children with CHARGE have been found to have a CHD7 mutation on chromosome 8</td>
<td></td>
<td>H: Hypoparathyroidism, hypocalcemia</td>
</tr>
</tbody>
</table>

Muscular Dystrophy (MD)

- group of inherited diseases characterized by progressive skeletal and cardiac muscle degeneration

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Epidemiology
- 1:4000 males

Etiology
- X-linked recessive: 1/3 spontaneous mutations, 2/3 inherited mutations
- missing structural protein (dystrophin) ➔ muscle fibre fragility ➔ fibre breakdown ➔ necrosis and regeneration

Clinical Presentation
- proximal muscle weakness by age 3, positive Gower’s sign, waddling gait, toe walking
- pseudohypertrophy of calf muscles (muscle replaced by fat) and wasting of thigh muscles
- decreased reflexes
- non-progressive delayed motor and cognitive development (dysfunctional dystrophin in brain)
- cardiomyopathy

Gower’s Sign
Child uses hands to “climb up” the legs to move from a sitting to a standing position.
Diagnosis
- molecular genetic studies of dystrophin gene (DMD) (first line)
- family history (pedigree analysis)
- increased CK (50-100x normal) and lactate dehydrogenase
- elevated transaminases
- muscle biopsy, electromyography (EMG)

Management
- supportive (e.g. physiotherapy, wheelchairs, braces), prevent obesity
- cardiac health monitoring and early intervention
- bone health monitoring and intervention (vit D, bisphosphonates)
- steroids (e.g. prednisone or deflazacort)
- surgical (for scoliosis)
- gene therapy trials underway

Complications
- patient usually wheelchair-bound by 12 yr of age
- early flexion contractures, scoliosis, osteopenia of immobility, increased risk of fracture
- death due to pneumonia/respiratory failure or CHF in 2nd-3rd decade

Metabolic Disease
- an inherited disorder of metabolism; often autosomal recessive
- infants and older children may present with failure to thrive (FTT) or developmental delay
- in Ontario, universal newborn screening looks for: 9 organic acid disorders, 6 amino acid disorders, 5 fatty acid oxidation defects, 3 hemoglobinopathies, 2 endocrinopathies, galactosemia, biotinidase deficiency, cystic fibrosis, and hearing loss
- types of disorders
  - proteins: PKU, tyrosinemia, organic acid disorders, urea cycle defects
  - carbohydrates: galactosemia, glycogen storage diseases
  - fats: fatty acid oxidation defects
  - organelle disorders: congenital disorders of glycosylation, mucopolysaccharidosis

Clinical Manifestations
- vomiting and acidosis after feeding initiation (amino acid or carbohydrate metabolic disorder)
- hepatosplenomegaly (metabolites accumulate in the liver)
- neurologic syndrome: acute and chronic encephalopathy, intellectual disability, megalencephaly (mucopolysaccharide disorders)
- severe acidosis (aminoaciduria), hyperammonemia (urea cycle and organic acid disorders)
- growth retardation, seizures, coma, hypoglycemia
- autonomic manifestations (e.g. pallor, sweating, tremor)

Physical Exam
- odour: burnt sugar, sweaty feet, musty, ammonia-like
- skin: hypo/hyperpigmentation, rash, xanthomas
- hair: alopecia, hirsutism, abnormal architecture, fair colouring
- eyes: cornea (clouding, crystals), lens (cataracts, dislocation), retina (macular cherry red spot, pigment retinopathy, optic atrophy)

Initial Investigations
- important to send lab studies at initial presentation in order to facilitate immediate diagnosis and treatment
- check newborn screening results
- electrolytes, ABGs (calculate anion gap, rule out acidosis)
- CBC with differential and smear
- blood glucose (hypoglycemia seen with organic acidemia, fatty acid oxidation defects and glycogen storage diseases)
- lactate, ammonium (hyperammonemia with urea cycle defects), plasma Ca$^{2+}$ and Mg$^{2+}$
- routine urinalysis: ketonuria must be investigated
- carnitine levels with acylcarnitine profile
- others: urate, urine nitroprusside, plasma amino acid screen, urine organic acids, CSF glycine, free fatty acids (3-β-hydroxybutyrate ratio >4 in fatty acid oxidation defect)
- storage diseases: urine mucopolysaccharide and oligosaccharide screen

Metabolic disease must be ruled out in any newborn who becomes acutely ill after a period of normal behaviour and development or with a family history of early infant death even if the newborn screen is negative.
**Phenylketonuria (PKU)**

**Epidemiology**
- 1:10,000; autosomal recessive disease

**Etiology**
- deficiency of phenylalanine hydroxylase prevents conversion of phenylalanine to tyrosine leading to build up of toxic metabolites
- mothers who have PKU may have infants with congenital abnormalities

**Clinical Presentation**
- baby is normal at birth, then develops a musty odour, eczema, hypertonia, tremors, and mental retardation
- hypopigmentation due to low tyrosine (fair hair, blue eyes)

**Management**
- PKU screening at birth
- dietary restriction of phenylalanine starting within the first 10 d of life
- duration of dietary restriction controversial – lifelong or until end of puberty; should be resumed during pregnancy to maintain normal phenylalanine levels

**Galactosemia**

**Epidemiology**
- 1:60,000; autosomal recessive disease

**Etiology**
- most commonly due to deficiency of galactose-1-phosphate uridylyltransferase leading to an inability to process lactose/galactose

**Clinical Presentation**
- signs of liver and renal failure, jaundice, FTT and cataracts with ingestion of lactose/galactose

**Management**
- elimination of galactose from the diet (e.g. dairy, breast milk)
- most infants are fed a soy-based diet

**Complications**
- increased risk of sepsis, especially E. coli
- if the diagnosis is not made at birth, liver and brain damage may become irreversible

**Hematology**

**Approach to Anemia**

![Figure 10. Anemia](image)

- Decreased reticulocytes:
  - Microcytic: Iron deficiency anemia, Thalassemia, Anemia of chronic disease, Lead poisoning, Sideroblastic anemia
  - Normocytic: Anemia of chronic disease, renal failure, marrow infiltration
  - Macrocytic: Megaloblastic anemia, marrow failure

- Increased reticulocytes:
  - Hemolysis: Hemoglobinopathies, Membrane problem, Enzyme problem, Immune hemolysis
  - Extrinsic to RBC: Antibody mediated
  - Intrinsic to RBC: Membrane problem, Enzyme problem

- Sickle cell disease, Thalassemia
- Hemolytic anemia, Membrane problem

- G6PD deficiency
- TTP, HUS

*Figure 10. Anemia*
**Physiologic Anemia**

- high Hb (>170 g/L) and reticulocyte count at birth is caused by a hypoxic environment in utero
- after birth, levels start to fall due to shorter fetal RBC lifespan, decreased RBC production (during first 6-8 wk of life, there is virtually no erythropoiesis due to new O₂ rich environment), and increasing blood volume secondary to growth
- lowest levels about 100 g/L at 8-12 wk age (earlier and more exaggerated in premature infants); levels rise spontaneously with activation of erythropoiesis
- no treatment usually required

**Iron Deficiency Anemia**

- most common cause of childhood anemia
- full term infants exhaust iron reserves by 6 mo of age
- premature infants have lower reserves, therefore exhausted by 2-3 mo of age
- common diagnosis between 6 mo-3 yr and 11-17 yr due to periods of rapid growth and increased iron requirements; adolescents also have poor diet and menstrual losses

**Etiology**

- dietary risk factors
- age >6 mo: <2 servings/d of iron-fortified cereal, red meat, or legumes
- age <12 mo: use of low-iron formula (<10 mg/L), primary diet of cow, goat or soy milk
- age 1-5 yr: >20 oz/d of non-fortified milk
- blood loss
  - iatrogenic: repeated blood sampling (especially in hospitalized neonates)
  - allergic: cow’s milk protein-induced colitis

**Clinical Manifestation**

- usually asymptomatic until marked anemia, pallor, fatigue, pica (eating non-food materials), tachycardia, systolic murmur

**Investigations**

- CBC: low Hb, MCV and MCH, reticulocyte count normal or high (absolute number low)
- Mentzer index (MCV/RBC) can help distinguish iron deficiency anemia from thalassemia
  - ratio <13 suggests thalassemia; ratio >13 suggests iron deficiency
- blood smear: hypochromic, microcytic RBCs, pencil shaped cells, poikilocytosis
- iron studies: low ferritin, other (low iron, high TIBC)
- initial therapy: trial of iron

**Prevention**

- breastfed term infants: begin iron supplementation (1 mg/kg/d) at 4-6 mo, continuing until able to eat ≥2 feeds/d of iron-rich foods
- non-breastfed (<50% of diet) term infants: give iron-fortified formula from birth
- premature infants: give iron supplements from 1 mo through to 1 yr of age
- no cow’s milk until 9-12 mo, early introduction of red meat and iron-rich vegetables: total daily iron should be 11 mg (age 6-12 mo), 7 mg (age 1-3 yr)
- universal screening of Hb levels recommended at 9 mo
- children at risk (premature, LBW, low SES, First Nations, etc.) fed whole cow’s milk in their first year

**Management**

- encourage diverse, balanced diet, limit homogenized milk to 16-20 oz/d
- oral iron therapy: 6 mg/kg/d elemental iron, divided bid to tid, for 3 mo
  - increased reticulocyte count in 2-3 d (peaks day 5-7)
  - increased hemoglobin in 4-30 d
  - repletion of iron stores in 1-3 mo
  - repeat hemoglobin levels after 1 mo of treatment
- poor response to oral iron therapy: non-compliance, medication intolerance, ongoing blood loss, IBD, celiac disease, incorrect diagnosis

**Complications**

- can cause irreversible effects on development if untreated (behavioural and intellectual deficiencies)
- angular chelitis, glossitis, koilonychia (spoon nails)
**Anemia of Chronic Disease**

- most often normocytic, normochromic (microcytic, hypochromic may occur with chronic infection/malignancy)
- multifactorial in origin
- chronic inflammatory states including juvenile idiopathic arthritis (JIA), chronic infections, chronic renal failure, and malignancies
- iron stores are variable and ferritin levels are unreliable (acute phase reactant); therefore bone marrow assessment may be necessary for diagnosis
- anemia of chronic renal failure predominantly caused by decreased erythropoietin (EPO) production; treat with EPO if necessary

**Sickle Cell Disease (SCD)**

- see Hematology, H19
- identification of specific genotypes important due to differences in frequency, type and severity of clinical complications (most severe: SS, less severe: SC, S-β thalassemia, rare: SD)

**Epidemiology**
- increased incidence in people of African and Mediterranean heritage

**Pathophysiology**
- caused by a genetic defect at position 6 of the β-globin genes
  - HbS: single amino acid replacement (glutamic acid → valine)
  - RBCs sickle under conditions of stress (low pO₂, dehydration, fever, acidosis)
  - acute intravascular sickling results in infarction of tissue (capillary occlusion and thrombosis of spleen, lungs, bones, brain, digits)
  - hemolysis causes chronic, well-compensated, normochromic normocytic anemia

**Presentation**
- clinical disease presents at 5-6 mo of age after fall in fetal Hb
- anemia, fever (medical emergency – infection is leading cause of death in SCD), jaundice, splenomegaly, crisis (dactylitis is often the first presentation)
- sickle cell trait: asymptomatic (may have microscopic hematuria and later isothenuria)

**Types of Crises**
- vaso-occlusive crisis
  - due to obstruction of blood vessels by rigid, sickled cells → tissue hypoxia → cell death; presents as fever and pain in any organ; most commonly in long bones of arms and legs, chest, abdomen, CNS (stroke), dactylitis (in young children), priapism
  - acute chest crisis: fever, chest pain, progressive respiratory distress, increased WBC count, pulmonary infiltrates
  - aplastic crisis: depression of erythropoiesis (decreased reticulocyte count to <1%, decreased Hb), generally associated with infection (especially parvovirus B19)
  - acute splenic sequestration: sudden, massive pooling of red cells in spleen, splenomegaly, tender spleen, acute fall in hemoglobin, shock, increased reticulocyte count

**Functional Asplenia**
- splenic dysfunction usually by 5 yr of age secondary to auto-infarction
- susceptible to infection by encapsulated organisms (especially S. pneumoniae)
- all individuals with SCD should be on prophylactic antibiotics, and be vaccinated against pneumococcal/meningococcal/H. influenzae type b, along with hepatitis B and influenza
- febrile episodes require immediate evaluation: rule out bacteremia, meningitis, acute chest syndrome, and osteomyelitis (commonly due to Salmonella in SCD)

**Other Manifestations**
- long term complications: growth delay, bony abnormalities (e.g. avascular necrosis (AVN) of femoral head), gallstones, retinopathy, restrictive lung disease (screen with PFTs), cardiomyopathy (screen with Echo), and pulmonary hypertension

**Management**
- acute crises
  - fluids (1.5x maintenance; 1x maintenance only if in chest crisis), analgesia (opioid, multi-modal), antibiotics (e.g. 3rd generation cephalosporins), incentive spirometry and ambulation to decrease risk of chest crisis
  - straight transfusions for symptomatic/significant anemia, evolving chest crisis
  - RBC exchange transfusion for impending stroke, severe chest crisis, persistent priapism
  - O₂ if respiratory distress or chest crisis (with incentive spirometry)
  - cultures and CBC if febrile, reticulocyte counts, CXR or LP if indicated
• chronic
  ▪ early aggressive treatment of infections, prophylactic antibiotics (daily oral penicillin)
  ▪ pneumococcal, meningococcal, hepatitis B, Hib, and influenza vaccines
  ▪ folate supplementation
  ▪ hydroxyurea if frequent crises, history of acute chest syndrome (raises HbF level)
  ▪ transcranial Doppler to assess risk of stroke
  ▪ chronic transfusion program if history of stroke or abnormal transcranial Doppler
  ▪ genetic counselling and education
  ▪ annual fundoscopic exam (after 10 yr old)
  ▪ bi-annual screening for pulmonary hypertension (after 12 yr old)
  ▪ bi-annual chemistry and urinanalysis to monitor organ dysfunction

Thalassemia

• see Hematology, H18

Hereditary Spherocytosis

• see Hematology, H21

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

• see Hematology, H22

Bleeding Disorders

• see Hematology, H25

Coagulation Defects
• bleeding into joints (hemarthroses) and muscles
• large spreading ecchymoses and hematomas

Platelet Abnormalities
• petechiae, purpura, bruises, mucocutaneous bleeding (e.g. epistaxis, gingival bleeding), menorrhagia, prolonged bleeding from superficial cuts

Table 21. Classification of Bleeding Disorders

<table>
<thead>
<tr>
<th>Site of Pathophysiology</th>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Vessels</td>
<td>Vasculitis</td>
<td>Henoch-Schönlein purpura</td>
</tr>
<tr>
<td>Platelets</td>
<td>Decreased production</td>
<td>Drugs, marrow infiltration, leukemia/lymphoma</td>
</tr>
<tr>
<td></td>
<td>Increased destruction</td>
<td>Immune thrombocytopenic purpura, infection, drugs</td>
</tr>
<tr>
<td></td>
<td>Increased consumption</td>
<td>DIC, giant hemangioma, hypersplenism</td>
</tr>
<tr>
<td></td>
<td>Dysfunctional</td>
<td>von Willebrand disease, drugs (ASA), uremia</td>
</tr>
<tr>
<td>Coagulation Pathway</td>
<td>Vitamin K deficiency</td>
<td>Hemorrhagic disease of the newborn</td>
</tr>
<tr>
<td></td>
<td>Factor VIII deficiency</td>
<td>Hemophilia A</td>
</tr>
<tr>
<td></td>
<td>Factor IX deficiency</td>
<td>Hemophilia B</td>
</tr>
<tr>
<td></td>
<td>Abnormal vWF</td>
<td>von Willebrand disease</td>
</tr>
</tbody>
</table>

Immune Thrombocytopenic Purpura (ITP)

Epidemiology
• most common cause of thrombocytopenia in childhood
• peak age: 2-6 yr, M=F
• incidence 5:100,000 children per year

Etiology
• caused by autoantibodies that bind to platelet membranes → Fc-receptor mediated splenic uptake → destruction of platelets
Clinical Presentation

- 50% present 1-3 wk after viral illness (URTI, chicken pox)
- sudden onset of petechiae, purpura, epistaxis in an otherwise well child
- clinically significant bleed in only 3% (severe bleed more likely with platelet count <10) with <0.5% risk of intracranial bleed
- no lymphadenopathy, no hepatosplenomegaly
- labs: thrombocytopenia with normal RBC, WBC
- bone marrow aspirate only if atypical presentation (≥1 cell line abnormal, hepatosplenomegaly)
- differential diagnosis: leukemia, drug-induced thrombocytopenia, HIV, infection (viral), autoimmune (SLE, ALPS)

Management

- observation vs. pharmacologic intervention highly debated; spontaneous recovery in >70% of cases within 3 mo
- treatment with IVIg or prednisone if mucosal or internal bleeding, platelets <10, or at-risk of significant bleeding (surgery, dental procedure, concomitant vasculitis or coagulopathy)
- life-threatening bleed: additional platelet transfusion ± emergency splenectomy
- persistent (>3-12 mo) or chronic (>12 mo): re-evaluate; treat if symptoms persist
- supportive: avoid contact sports and ASA/NSAIDs

Hemophilia

- see Hematology. H29

von Willebrand’s Disease

- see Hematology. H28

Table 22. Evaluation of Abnormal Bruising/Bleeding

<table>
<thead>
<tr>
<th></th>
<th>PFA</th>
<th>PT</th>
<th>PTT</th>
<th>VIII:C</th>
<th>vWF</th>
<th>Platelets</th>
<th>Fibrinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>von Willebrand</td>
<td>↑</td>
<td>N</td>
<td>N or ↑</td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIC</td>
<td>N or ↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Vitamin K Deficiency</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>↑</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>↓</td>
</tr>
</tbody>
</table>

BT = bleeding time; VIII:C = Factor VIII coagulant activity; vWF = von Willebrand’s Factor; DIC = disseminated intravascular coagulation

Oncology

- cancer is the second most common cause of death after injuries in children after 1 yr of age
- cause is rarely known, but increased risk for:
  - chromosomal syndromes (e.g. Trisomy 21)
  - prior malignancy
  - neurocutaneous syndromes
  - immunodeficiency syndromes
  - family history
  - exposure to radiation, chemicals, biologic agents
- leukemias are the most common type of pediatric malignancy (40%), followed by brain tumours (20%), and lymphomas (15%)
- some malignancies are more prevalent in certain age groups
  - newborns: neuroblastoma, Wilms’ tumour, retinoblastoma
  - <1yr: infancy and childhood: leukemia, neuroblastoma, Wilms’ tumour, retinoblastoma
  - adolescence: lymphoma, gonadal tumours, bone tumours
- unique treatment considerations in pediatrics because radiation, chemotherapy, and surgery can impact growth and development, endocrine function and fertility
- good prognosis: treatments have led to remarkable improvements in overall survival and cure rates for many pediatric cancers (>80%)

Corticosteroids versus Intravenous Immune Globulin for the Treatment of Acute Immune Thrombocytopenic Purpura in Children: A Systematic Review and Meta-analysis of Randomized Controlled Trials

J Pediatr 2005;147:521-527

Study: Meta-analysis of 10 RCTs from 1985-2003. RCTs compared corticosteroids and IVIG in the treatment of pediatric ITP, and had to include patient platelet counts.

Patients: 596 children 3 mo-18 yr of age who were presenting for the first time with primary acute ITP, with no other underlying condition.

Intervention: Corticosteroids and IVIG at any dose. Corticosteroid treatments included methylprednisolone 10-30 g/kg/d and prednisone 2-4 g/m²/d. IVIG dosing ranged from 0.5-1 g/kg/d.

Main Outcome: Primary outcome was platelet levels >20,000/mm³ (20 x 10⁹/L) at 48 h after treatment. (This outcome was chosen because intracranial hemorrhage rarely occurs at platelet above 20). Secondary outcomes included incidence of ICH.

Results: The relative risk (RR) of reaching a platelet count >20,000/mm³ at 48 h was 0.74 (95% CI 0.65-0.85) for corticosteroids versus IVIG (at any dose), with a NNT of 4.55 (95% CI 3.23-7.69).

Subgroup analyses by dosing favoured IVIG in 6/10 dose comparisons. Only 3/586 children developed ICH – two were treated with corticosteroids and one with IVIG.

Summary: Children treated with corticosteroids are less likely to have a platelet count >20,000/mm³ than children treated with IVIG after 48 h of therapy. However, optimal dosing of IVIG is unclear, and impact of IVIG versus corticosteroids on ICH and mortality are unclear.

Extensive bruising in the absence of lab abnormalities: consider child abuse.
Leukemia

- see Hematology, H35, H38, H41, H46

Epidemiology
- mean age of diagnosis 2-5 yr but can occur at any age
- heterogeneous group of diseases:
  - acute lymphoblastic leukemia (ALL) (80%)
  - acute myeloblastic leukemia (AML) (15%)
  - chronic myelogenous leukemia (CML) (<5%)
- children with Down syndrome are 15x more likely to develop leukemia

Clinical Presentation
- infiltration of leukemic cells into bone marrow results in bone pain, and bone marrow failure (anemia, neutropenia, thrombocytopenia)
- infiltration into tissues results in lymphadenopathy, hepatosplenomegaly, CNS manifestations, testicular disease
- fever, fatigue, weight loss, bruising, and easy bleeding

Management
- combination chemotherapy using non-cross resistant chemotherapy agents

Prognosis
- 80-90% 5-yr event-free survival for ALL, 50-60% 5-yr survival for AML
- patients are stratified into standard risk and high risk based on WBC and age; other prognostic factors include presence of CNS/testicular disease, immunophenotype, cytogenetics, and initial response to therapy (most important prognostic variable)

Lymphoma

- see Hematology, H42

Epidemiology
- Hodgkin lymphoma: incidence is bimodal, peaks at ages 15-34 and >50 yr old
- Non-Hodgkin lymphoma: incidence peaks at 7-11 yr

Clinical Presentation
- Hodgkin lymphoma:
  - most common presentation is persistent, painless, firm, cervical or supraclavicular lymphadenopathy
  - can present as persistent cough or dyspnea (secondary to mediastinal mass) or less commonly as splenomegaly, axillary or inguinal lymphadenopathy
  - constitutional symptoms (B symptoms) in 30% of children
- Non-Hodgkin lymphoma:
  - generally categorized into lymphoblastic, large cell, and Burkitt’s/Burkitt’s-like lymphoma
  - rapidly growing tumour with distant metastases (unlike adult non-Hodgkin lymphoma)
  - signs and symptoms related to disease site: most commonly abdomen, chest (mediastinal mass), head and neck region

Management
- Hodgkin lymphoma:
  - combination chemotherapy and radiation
  - aimed at limiting cumulative doses of anthracyclines (toxic to heart) and alkylators (risk of second malignancy, infertility) and limiting dose and field of radiation
  - increasing role for use of PET scanning to assess early disease response and plan therapy.
- Non-Hodgkin lymphoma:
  - combination chemotherapy
  - no added benefit of radiation in pediatric protocols.

Prognosis
- Hodgkin lymphoma: >90% 5-yr survival
- Non-Hodgkin lymphoma: 75-90% 5-yr survival

Brain Tumours

- see Neurosurgery, NS10, NS38
**Wilms’ Tumour (Nephroblastoma)**

**Epidemiology**
- usually diagnosed between 2-5 yr; M=F
  - most common primary renal neoplasm of childhood
  - 5-10% of cases both kidneys are affected (simultaneously or in sequence)

**Differential Diagnosis**
- hydronephrosis, polycystic kidney disease, renal cell carcinoma, neuroblastoma

**Clinical Presentation**
- 80% present with asymptomatic, unilateral abdominal mass
- may also present with hypertension, gross hematuria, abdominal pain, vomiting
- may have pulmonary metastases at time of diagnosis (respiratory symptoms)

**Associated Congenital Abnormalities**
- WAGR syndrome (Wilms’ tumour, Aniridia, Genital anomalies, mental Retardation) with 11p13 deletion
- Beckwith-Wiedemann syndrome
  - characterized by enlargement of body organs (especially tongue), hemihypertrophy, renal medullary cysts, and adrenal cytomegaly
  - also at increased risk for developing hepatoblastoma, and less commonly adrenocortical tumours, nephroblastomas and rhabdomyosarcomas
- Denys-Drash syndrome
  - characterized by gonadal dysgenesis and nephropathy leading to renal failure

**Management**
- staging ± nephrectomy
- chemotherapy; radiation for higher stages

**Prognosis**
- 90% long-term survival

---

**Neuroblastoma**

**Epidemiology**
- most common cancer occurring in first year of life
- neural crest cell tumour arising from sympathetic tissues (neuroblasts)

**Clinical Presentation**
- can originate from any site in sympathetic nervous system, presenting as mass in neck, chest or abdomen mass (most common site is adrenal gland)
- signs and symptoms of disease vary with location of tumour
  - thoracic: dyspnea, Horner's syndrome
  - abdomen: palpable mass
  - spinal cord compression
- metastases are common at presentation (>50% present with advanced stage disease)
  - usually to bone or bone marrow (presents as bone pain, limp)
  - can also present with periorbital ecchymoses, abdominal pain, emesis, fever, weight loss, anorexia, hepatomegaly, “blueberry muffin” skin nodules
- paraneoplastic: hypertension, palpitations, sweating (from excessive catecholamines), diarrhea, FTT (from vasoactive intestinal peptide secretion), opsomyoclonus
- diagnostic criteria (either of the following):
  - unequivocal histologic diagnosis from tumour tissue biopsy
  - evidence of metastasis to bone marrow (“rosettes”) on aspirate analysis, with concomitant elevation of urine or serum catecholamine metabolite (VMA, HVA) levels

**Management**
- depends on prognostic factors and may include combination of: surgery, radiation, chemotherapy, bone marrow transplantation

**Prognosis**
- prognosis is often poor due to late detection
- good prognostic factors:
  - “age and stage” are important determinants of better outcome: 12-18 mo, stage I, II, IV-S disease (“S” designates a “Special” classification only pertaining to infants)
  - primary site: posterior mediastinum and neck
  - low serum ferritin
  - specific histology
  - tumour cell markers: aneuploidy, absent MYCN oncogene amplification
**Bone Tumours**

- see Orthopedics, OR42

**Febrile Neutropenia**

- see Infectious Diseases, ID39

**Tumour Lysis Syndrome**

- see Hematology, H50

**Hyperleukocytosis**

- total WBC >100 x 10^9/L
- common presenting feature of leukemia
- medical emergency
- leukostasis = symptomatic hyperleukocytosis
  - presents clinically with respiratory or neurological distress caused by hyperviscosity of blood
  - risk of intracerebral hemorrhage, pulmonary leukostasis syndrome, tumour lysis syndrome
- management: fluids, allopurinol/rasburicase, fresh frozen plasma/platelets to correct thrombocytopenia, induction chemotherapy, avoid transfusing RBCs unless symptomatic (and then use very small volumes)

**Lymphadenopathy**

**Clinical Presentations**

- features of malignant lymphadenopathy (LAD): firm, discrete, non-tender, enlarging, immobile, ± suspicious mass/imaging findings, ± 'B' symptoms
- fluctuance, warmth or tenderness are more suggestive of benign nodes (infection)

**Differential Diagnosis**

- infection:
  - viral: URTI, EBV, CMV, adenovirus, HIV
  - bacterial: S. aureus, GAS, anaerobes, *Mycobacterium* (e.g. TB), cat scratch disease (*Bartonella*)
  - other: fungal, protozoan, *Rickettsia*
- auto-immune: rheumatoid arthritis, SLE, serum sickness
- malignancy: lymphoma, leukemia, metastatic solid tumours
- storage diseases: Niemann-Pick, Gaucher’s
- other: sarcoidosis, Kawasaki disease, histiocytoses

**Investigations**

- generalized LAD
  - CBC and differential, blood culture
  - uric acid, LDH
  - ANA, RF, ESR
  - EBV/CMV/HIV serology
  - toxoplasma titre
  - fungal serology
  - CXR
  - TB tests
  - biopsy
- regional LAD
  - period of observation if asymptomatic
  - trial of oral antibiotics
  - ultrasound
  - biopsy (especially if persistent >6 wk and/or 'B' symptoms)

Most common cause of acute bilateral cervical LAD is viral illness.
Infectious Diseases

Fever

Definition
- fever: no generally accepted definition, a practical definition is >38°C oral or rectal
- fever without a source/focus: acute febrile illness (typically <10 d duration) with no cause of fever even after careful history and physical
- fever of unknown origin: daily or intermittent fevers for at least 2 consecutive weeks of uncertain cause after careful history and physical and initial laboratory assessment

Etiology
- infectious: anatomic approach (CNS, ears, upper and lower respiratory tract, GI, GU, skin, soft tissue, bones and joints, etc.)
- inflammatory: mainly autoimmune (Kawasaki Disease, JIA, IBD, SLE, etc.)
- malignancy: childhood cancers (leukemia, lymphoma, neuroblastoma, etc.)
- miscellaneous: dehydration, drugs and toxins, post-immunization, familial dysautonomia, factitious disorder, etc.

Diagnosis
- history: duration, height and pattern of fever, associated symptoms, exposures, constitutional symptoms, ethnic or genetic background, day care, sick contacts, travel
- physical: toxic vs. non-toxic, vitals, growth, complete exams of the: skin, HEENT, chest, abdomen, lymph nodes, genitalia
- investigations: guided by history, physical exam and clinical suspicion; see Figure 11 for guidelines for children from 0-3 yr old

Evaluation of Neonates and Infants with Fever
- several protocols exist that attempt to identify neonates and young infants at low risk of serious bacterial infection (e.g. Rochester Criteria)
  - such protocols are not as sensitive in the 1-28 d age group; therefore, febrile neonates should be considered high risk regardless of clinical presentation and laboratory findings

Management
- admit to hospital if appropriate
- treat the source if known
- replace fluid losses (e.g. from vomiting, diarrhea, etc.); maintenance fluid needs are higher in febrile child
- reassure parents that most fevers are benign and self-limited
- antipyretics are not necessary in most cases, but can be given if child is uncomfortable (acetaminophen and/or ibuprofen)

NOTES
1. Full Septic Workup (SWU) – blood C&S, CBC and differential, urine R&B, C&S, LP, CR if respiratory symptoms, stool C&S if GI symptoms
2. Follow-up is crucial – if adequate F/U is not assured, a more aggressive diagnostic and therapeutic approach may be indicated
3. Low-Risk (Rochester) Criteria
4. Considerable practice variation exists in terms of empiric antibiotics treatment
5. Important Principles – the younger the child, the greater the difficulty to clinically assess the degree of illness

Figure 11. Approach to the febrile child

Rochester Criteria – developed to identify infants ≤60 d of age with fever at low risk of serious bacterial infection

<table>
<thead>
<tr>
<th>Clinically</th>
<th>Well</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count</td>
<td>5-15 x 10⁹/L</td>
</tr>
<tr>
<td>Bands</td>
<td>&lt;1.5 x 10⁹/L</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>10 WBC/HPF</td>
</tr>
<tr>
<td>Stool (if diarrhea)</td>
<td>5 WBC/HPF</td>
</tr>
<tr>
<td>Past Health</td>
<td>Born &gt;37 wk</td>
</tr>
<tr>
<td></td>
<td>Home with/before mom</td>
</tr>
<tr>
<td></td>
<td>No hospitalizations</td>
</tr>
<tr>
<td></td>
<td>No prior antibiotic use</td>
</tr>
<tr>
<td></td>
<td>No prior treatment</td>
</tr>
<tr>
<td></td>
<td>for unexplained</td>
</tr>
<tr>
<td></td>
<td>hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td>No chronic disease</td>
</tr>
</tbody>
</table>
Acute Otitis Media (AOM)

Definition
All of:
1. presence of middle ear effusion (MEE)
2. presence of middle ear inflammation (MEI)
3. acute onset of symptoms of MEE and MEI

Epidemiology
- most frequent diagnosis in sick children visiting clinicians' offices and most common reason for antibiotic administration
- peak incidence between 6-15 mo; ~85% of children have >1 episode by 3 yr old
- seasonal variability: peaks in winter

Etiology
- primary defect causing AOM: Eustachian tube dysfunction/obstruction → stasis/colonization by pathogens
- bacterial: S. pneumoniae, non-typable H. influenzae, M. catarrhalis, Group A Streptococcus, S. aureus
- viral: RSV, influenza, parainfluenza, adenovirus
- commonly due to bacterial/viral co-infection

Risk Factors
- non-modifiable: young age, family history of OM, prematurity, orofacial abnormalities, immunodeficiencies, Down syndrome, race and ethnicity
- modifiable: lack of breastfeeding, day care attendance, household crowding, exposure to cigarette smoke and air pollution, pacifier use

Diagnosis
- history
  - acute onset of otalgia or ear tugging in a preverbal child, otorrhea, decreased hearing
  - unexplained irritability, fever, upper respiratory symptoms, poor sleeping, anorexia, nausea, vomiting and diarrhea
- physical
  - febrile
  - MEE on otoscopy: immobile tympanic membrane, acute otorrhea, loss of bony landmarks, opacification of TM, air-fluid level behind TM
  - MEI on otoscopy: bulging TM with marked discolouration (hemorrhagic, red, grey, or yellow)

Management
- observation for 48-72 h without antimicrobials may be appropriate since >80% of AOM in children resolve spontaneously
- criteria for watchful waiting approach:
  - child is >6 mo old
  - child does not have immunodeficiency, chronic cardiac or pulmonary disease, anatomical abnormalities of the head or neck, a history of complicated otitis media (suppurative complications of chronic perforation) or Down syndrome
  - the illness is not severe – otalgia appears to be mild and fever is <39ºC in the absence of antipyretics
  - parents are capable of recognizing signs of worsening illness and can readily access medical care if the child does not improve
- antimicrobials are indicated if child does not meet the criteria for watchful waiting or does not improve/worsens during observation (Table 23)
- maintain hydration
- symptomatic relief: acetaminophen, ibuprofen
- referral to otolaryngology for myringotomy and tympanostomy tubes may be warranted for recurrent infections (see Otolaryngology, OT39 for indications)

Table 23. Treatment of AOM

<table>
<thead>
<tr>
<th>Antimicrobial Agents for Acute Otitis Media (AOM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line treatment (no penicillin allergy):</strong></td>
</tr>
<tr>
<td>Amoxicillin: 75 mg/kg/d to 90 mg/kg/d divided three times per day</td>
</tr>
</tbody>
</table>

| **Second-line treatment:** |
| Cefuroxime axetil: 30 mg/kg/d divided twice per day |
| Clarithromycin: 15 mg/kg/d divided twice per day |
| Azithromycin: 10 mg/kg OD x 1 dose, then 5 mg/kg OD x 4 doses |
| Ceftriaxone: 50 mg/kg intramuscularly (or intravenously) x 1 dose |

If initial therapy fails (i.e. no symptomatic improvement after 2-3 d):
- Amoxicillin-clavulanate: 90 mg/kg/d amoxicillin, 6.4 mg/kg/d clavulanate divided twice per day for 10 d
- If AOM-related symptoms do not resolve with amoxicillin/clavulanate, a course of ceftriaxone 50 mg/kg/d intramuscularly (or intravenously) once per day x 3 doses could be considered

Management of Acute Otitis Media
Paediatr Child Health 2009;14:457-460
**Purpose:** Updates a previous document published in 1998.
**Study:** Evidence-based guideline by the Canadian Pediatric Society (CPS).
**Recommendations:** The watchful waiting approach (observation for 48-72 h without antibiotics) is appropriate except for:
- Children ≤ 6 mo
- Children with immunodeficiency
- Children with chronic cardiac or pulmonary disease
- Children with anatomical abnormalities of the head or neck
- History of complicated otitis media
- Children with Down syndrome
- Parent are incapable of recognizing signs of worsening illness or cannot readily access medical care if child does not improve
- If the child’s status worsens or fails to improve in 48-72 h, antibiotic treatment must be started.
Complications
- extracranial:
  - hearing loss and speech delay (secondary to persistent MEE), TM perforation, extension of suppurative process to adjacent structures (mastoiditis, petrositis, labyrinthitis), cholesteatoma, facial nerve palsy, middle ear atelectasis, ossicular necrosis, vestibular dysfunction
- intracranial:
  - meningitis, epideral and brain abscess, subdural empyema, lateral and cavernous sinus thrombosis, carotid artery thrombosis

Diphtheria

Definition
- upper respiratory bacterial illness caused by *Corynebacterium diptheriae*
- characterized by pharyngitis, low-grade fever, and nasopharyngeal pseudomembranes released by bacteria (with possible dermatologic, cardiac and/or nervous system involvement)

Epidemiology
- routine immunization has significantly reduced morbidity and mortality
- diphtheria now very rare

Etiology
- caused by lysogenized phage
- transmitted by direct contact or droplet spread; incubation period is 2-5 d

Risk Factors
- unvaccinated, immunocompromised, travel to or inhabitants of endemic countries

History
- early symptoms similar to a common cold: low-grade fever, sore throat, anorexia, malaise
- later symptoms (due to Diphtheria toxin): pallor, diaphoresis, stupor, coma

Physical
- grey membranes may cover tonsils and soft palate (at day 2-3); becomes greenish or black with hemorrhage
- cervical lymphadenopathy; “bull neck” secondary to submandibular edema in severe disease

Investigations
- throat culture (specifically state that diphtheria is suspected as some labs only look for group A *Streptococcus* on routine throat cultures)

Management
- treat based on clinical suspicion; awaiting culture results will postpone treatment and worsen prognosis
- diphtheria antitoxin
- penicillin G or erythomycin (halts furthers toxin production and prevents carrier state)

Prognosis
- 5-10% mortality for respiratory diphtheria
- complications: airway obstruction, recurrent laryngeal nerve palsy
- associated conditions: diphtheritic peripheral neuritis, myocarditis

Gastroenteritis

Definition
- inflammation (generally of infectious etiology) of the stomach and small intestine leading to illness characterized by nausea, vomiting and diarrhea

Epidemiology
- cause of 3-5 million childhood deaths annually worldwide
- viral gastroenteritis most commonly affects children aged 6 mo – 5 yr

Etiology
- viral (rotavirus, adenovirus, astrovirus), bacterial (*E. coli, Salmonella, Shigella, Campylobacter*) or parasitic (*Giardia lamblia*)
- rotavirus in ~50% of cases; primarily transmitted fecal-oral; incubation period of ~2 d
- antibiotic-associated (*Clostridium difficile*)

Risk Factors
- young age, day care attendance, infected household member, immunocompromised, antibiotic use (*Clostridium difficile*)
History
- non-specific: diarrhea, vomiting, fever, anorexia, headache, myalgias, abdominal cramps
- bacterial and parasitic agents more common in older children (2-4 yr): blood and/or mucous in stool, recent travel, consumption of unprocessed meats, recent antibiotic use or hospitalization
- recent infectious contacts: symptoms usually begin 24-48 h after exposure

Physical
- febrile
- dehydrated: must assess extent (see Dehydration, P79)

Investigations
- not usually necessary in young children
- stool analysis: leukocytes/erythrocytes suggests bacterial or parasitic etiology; pH <6 and presence of reducing substances suggests viral etiology

Management
- rehydration: replace deficits, ongoing loses and maintenance needs (see P79)
- oral rehydration therapy (ORT) preferred for mild-moderate dehydration in acute gastroenteritis
- antiemetics may reduce vomiting, but increase diarrhea
- regular diet of small frequent feeds recommended in mild illness
- may return to age-appropriate diet once re-hydrated and vomiting stops
- antibiotics or antiparasitic agents sometimes indicated in bacterial or parasitic gastroenteritis
- promote regular hand-washing and return to school 24 h after last diarrheal episode to prevent transmission
- oral rotavirus vaccine now available in Canada

Complications
- viral gastroenteritis usually self-limiting (lasts 3-7 d in most cases)
- adverse effects related to hypovolemia, shock, tissue acidosis, and rapid onset and over-correction of electrolyte imbalances
- death in severe dehydration (rare in developed countries)

HIV Infection
- see Infectious Diseases, ID41

Epidemiology
- 20-30% risk of vertical transmission in untreated HIV infected women, <1% with antiretroviral treatment during pregnancy and perinatally

Transmission
- infants and children: most often vertical (transplacentally in majority, maternal blood, exposure to infected secretions during delivery, breast milk)
- adolescents: sexual intercourse, needles (IV drug use and tattoos), blood products (rare)

Risk Factors
- HIV positive mother or mother with HIV positive partner
- IV illicit drug use (IVDU)
- unprotected sex
- sexual abuse
- receipt of blood products (rare)

Clinical Features of AIDS in Infants and Children
- signs and symptoms occur often within the first year, most within 2 yr of age
- encephalopathy, recurrent/persistent thrush, persistent diaper candidiasis, chronic interstitial pneumonitis (relatively common), opportunistic infections (especially Pneumocystis jiroveci (PJP) pneumonia), hepatomegaly, lymphadenopathy, failure to thrive

Management
- adequate nutrition (breastfeeding contraindicated in developed countries)
- suppression of HIV with HAART
- prompt treatment of infections
- prophylaxis:
  - TMP/SMX for PJP, azithromycin for mycobacterium avium complex (MAC); nystatin, ketoconazole, acyclovir if indicated
  - all routine immunizations (including live vaccines if well), but avoid oral-polio vaccine and BCG
<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen(s)</th>
<th>Incubation period</th>
<th>Communicability</th>
<th>Mode of Transmission</th>
<th>Rash</th>
<th>Associated Features</th>
<th>Management</th>
<th>Outcomes and complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema Infectiosum (aka Fifth Disease)</td>
<td>Parvovirus B19</td>
<td>4-14 d</td>
<td>Low risk of transmission once symptomatic</td>
<td>Respiratory secretions or infected blood</td>
<td>Appearance: uniform, erythematous maculopapular &quot;lacy&quot; rash</td>
<td>Initial 7-10 d of flu-like illness and fever</td>
<td>Supportive</td>
<td>Rash fades over days to week, but may reappear months later with sunlight, exercise</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Timing: 10-17 d after symptoms (immune response)</td>
<td>Rash may be warm, non-tender, and pruritic</td>
<td></td>
<td>Aplosic crisis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Distribution: bilateral cheeks (&quot;slapped cheeks&quot;) with circumsoral sparing; may affect trunk and extremities</td>
<td>Less common presentations include 'gloves and socks syndrome' or STAR complex (sore throat, arthritis, rash)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Appearance: asymptomatic symmetric papules Distribution: face, cheeks, extremities, spares trunk bilateral cheeks</td>
<td>Viral prodrome May have lymphadenopathy and/or hepatosplenomegaly</td>
<td>Supportive</td>
<td>Resolves in 3-12 wk</td>
</tr>
<tr>
<td>Gianotti-Crosti Syndrome (aka Papular Acrodermatitis)</td>
<td>EBV and Hep B (majority)</td>
<td>Variable</td>
<td>None</td>
<td>—</td>
<td>Appearance: vesicles and pustules on an erythematous base Distribution: acral</td>
<td>Enanthem: vesicles in the POSTERIOR oral cavity (pharynx, tongue)</td>
<td>Supportive</td>
<td>Mainly dehydration</td>
</tr>
<tr>
<td>Hand, Foot and Mouth Disease</td>
<td>Coxsackie group A</td>
<td>3-5 d</td>
<td>Likely 1-7 d after symptoms but may be up to months</td>
<td>Direct and indirect contact with infected bodily fluids, fecal-oral</td>
<td>Appearance: vesicles and pustules on an erythematous base Distribution: acral</td>
<td>Enanthem: vesicles in the POSTERIOR oral cavity (pharynx, tongue)</td>
<td>Supportive</td>
<td>Mainly dehydration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Timing: 1-2 d before rash Desquamation</td>
<td>Enanthem: vesicles/or erosions in the ANTERIOR oral cavity (buccal mucosa, tongue)</td>
<td>Mainly supportive</td>
<td>Consider oral or topical antivirals</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Distribution: starts at hairline and spreads downwards with sparing of palms and soles</td>
<td>May present with herpetic whitlow (autonoculation)</td>
<td>Local: secondary skin infections, keratitis, gingivostomatitis</td>
<td>CNS: encephalitis Disseminated hepatitis, DIC</td>
</tr>
<tr>
<td>Herpes Simplex</td>
<td>HSV 1,2</td>
<td>1-26 d</td>
<td>Direct contact, often through saliva for HSV-1 and sexual contact for HSV-2</td>
<td>Direct contact with infected secretions or mucuous membranes</td>
<td>Appearance: vesicles on an erythematous base</td>
<td>Enanthem: vesicles/or erosions in the ANTERIOR oral cavity (buccal mucosa, tongue)</td>
<td>Mainly supportive</td>
<td>Consider oral or topical antivirals</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Timing: 3 d after start of symptoms Distribution: starts at hairline and spreads downwards with sparing of palms and soles</td>
<td>May present with herpetic whitlow (autonoculation)</td>
<td>Local: secondary skin infections, keratitis, gingivostomatitis</td>
<td>CNS: encephalitis Disseminated hepatitis, DIC</td>
</tr>
<tr>
<td>Measles</td>
<td>Morbillivirus</td>
<td>8-13 d</td>
<td>4 d before and after rash</td>
<td>Airborne</td>
<td>Appearance: erythematous maculopapular</td>
<td>Prodome of cough, coryza, conjunctivitis (3 Cs) Enanthem: Koplik’s spots 1-2 d before rash Desquamation</td>
<td>Infected: symptomatic Unimmunized contacts: measles vaccine within 72 h of exposure or IgG within 6 d of exposure</td>
<td>Secondary bacterial infections: AOM, sinusitis, pneumonia Encephalitis Rare: myocarditis, pericarditis, trombocytopenia, Stevens-Johnson syndrome, glomerulonephritis, subacute sclerosing panencephalitis</td>
</tr>
<tr>
<td>Kawasaki Disease</td>
<td>See P100</td>
<td></td>
<td></td>
<td></td>
<td>Timing: 3 d after start of symptoms Distribution: starts at hairline and spreads downwards with sparing of palms and soles</td>
<td>Prodome of cough, coryza, conjunctivitis (3 Cs) Enanthem: Koplik’s spots 1-2 d before rash Desquamation</td>
<td>Infected: symptomatic Unimmunized contacts: measles vaccine within 72 h of exposure or IgG within 6 d of exposure</td>
<td>Secondary bacterial infections: AOM, sinusitis, pneumonia Encephalitis Rare: myocarditis, pericarditis, trombocytopenia, Stevens-Johnson syndrome, glomerulonephritis, subacute sclerosing panencephalitis</td>
</tr>
<tr>
<td>Disease</td>
<td>Pathogen(s)</td>
<td>Incubation period</td>
<td>Communicability</td>
<td>Mode of Transmission</td>
<td>Rash</td>
<td>Associated Features</td>
<td>Management</td>
<td>Outcomes and complications</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------------------</td>
<td>-------------------</td>
<td>-----------------</td>
<td>-----------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Non-Specific Enteroviral Exanthems</td>
<td>Enteroviruses</td>
<td>Variable</td>
<td>Variable</td>
<td>Direct and indirect contact with infected bodily fluids</td>
<td>Polymorphous rash (macules, papules, vesicles, petechiae, urticaria)</td>
<td>Systemic involvement is rare, but possible</td>
<td>Supportive Diagnosis confirmed using viral cultures (NP and rectal swabs)</td>
<td>Self-limiting</td>
</tr>
<tr>
<td>Rosela</td>
<td>HHV 6</td>
<td>5-15 d</td>
<td>Unknown</td>
<td>—</td>
<td>Appearance: blanching, pink, maculopapular Timing: appears once fever subsides Distribution: starts at the neck and trunk and spreads to the face and extremities</td>
<td>High grade fever Common: irritability, anorexia, lymphadenopathy, erythematous TM and pharynx, Nagayama sign Less common: cough, coryza, bulging fontanelles</td>
<td>Supportive</td>
<td>CNS: febrile seizures (10-25%), aseptic meningitis Thrombocytopenia</td>
</tr>
<tr>
<td>Rubella</td>
<td>Rubivirus</td>
<td>14-21 d</td>
<td>7 d before and after eruptions</td>
<td>Droplet</td>
<td>Appearance: pink, maculopapular Timing: 1-5 d after start of symptoms Distribution: starts on face and spreads to neck and trunk</td>
<td>Prodrome of low grade fever and occipital/retroauricular nodes  STAR complex (sore throat, arthritis, rash) Positive serology for rubella IgM</td>
<td>Infected: symptomatic Prevention: MMR vaccine Report to public health</td>
<td>Excellent prognosis with acquired disease Arthritis may last days to weeks Encephalitis Irreversible defects in congenitally infected patients (i.e. congenital rubella syndrome)</td>
</tr>
<tr>
<td>Scarlet Fever</td>
<td>See P61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>Varicella zoster virus</td>
<td>0-21 d</td>
<td>1-2 d pre-eruptions and 5 d post-eruption</td>
<td>Mainly airborne, but also through direct contact with vesicle fluid</td>
<td>Appearance: crops of skin lesions, polymorphic, from macules to papules to vesicles to crusts Timing: 1-3 d after start of symptoms Distribution: generalized</td>
<td>Significant pruritis Enanthem: vesicular lesions which may become pustular or ulcerate</td>
<td>Supportive Avoid salicylates (due to risk of Reye syndrome) Consider antivirals Respiratory and contact isolation, report to public health Prevention: varicella vaccine</td>
<td>Skin: bacterial suprainfection, necrotizing fasciitis CNS: acute encephalitis and cerebellar ataxia Systemic: hepatitis, DIC Congenital varicella syndrome if intrapartum infection</td>
</tr>
</tbody>
</table>
Infectious Mononucleosis

Definition
- systemic viral infection caused by Epstein-Barr virus (EBV) with multivisceral involvement; often called "the great imitator"

Epidemiology
- peak incidence between 15-19 yr old
- ~50% of children in developed countries have a primary EBV infection by 5 yr old, but <10% of children develop clinical infection

Etiology
- EBV: a member of herpesviridae
- transmission is mainly through infected saliva ("kissing disease") and sexual activity (less commonly); incubation period of 1-2 mo

Risk Factors
- infectious contacts, sexually active, multiple sexual partners in the past

History
- prodrome: 2-3 d of malaise, anorexia
- infants and young children: often asymptomatic or mild disease
- older children and adolescents: malaise, fatigue, fever, sore throat, abdominal pain (often LUQ), headache, myalgia

Physical
- classic triad: febrile, generalized non-tender lymphadenopathy, pharyngitis/tonsillitis (exudative)
- ± hepatosplenomegaly
- ± periorbital edema, ± rash (urticarial, maculopapular or petichial) – more common after inappropriate treatment with β lactam antibiotics
- any “-itis” (including arthritis, hepatitis, nephritis, myocarditis, meningitis, encephalitis, etc.)

Investigations
- heterophil antibody test (Monospot® test)
  - 85% sensitive in adults and older children, but only 50% sensitive if <4 yr of age
  - false positive results with HIV, SLE, lymphoma, rubella, parvovirus
- EBV titres
- CBC and differential, blood smear: atypical lymphocytes, lymphocytosis, Downey cells, ± anemia, ± thrombocytopenia
- throat culture to rule out streptococcal pharyngitis

Management
- supportive: adequate rest, hydration, saline gargles and analgesics for sore throat
- splenic enlargement is often not clinically apparent so all patients should avoid contact sports for 6-8 wk
- if airway obstruction secondary to nodal and/or tonsillar enlargement is present (especially younger children), admit for steroid therapy
- acyclovir does NOT reduce duration of symptoms or result in earlier return to school/work

Prognosis
- most acute symptoms resolve in 1-2 wk, though fatigue may last for months
- short-term complications: splenic rupture, Guillain-Barré syndrome

Infectious Pharyngitis/Tonsillitis

Definition
- inflammation of the pharynx, especially the tonsils if present, causing a sore throat

Etiology
- viral (~80%): adenoviruses, enteroviruses, coxsackie, upper respiratory tract viruses, EBV, CMV
- bacterial (~20%): mainly Group A Streptococcus, M. pneumonia (older children), N. gonorrhoea (sexually active), C. diptheriae (unvaccinated)
- fungal: Candida

Epidemiology
- season: GAS pharyngitis more common in late winter or early spring; viral all yr long
- age: GAS pharyngitis peak incidence at 5-12 yr of age and uncommon <3 yr; viral pharyngitis affects all ages
History
• GAS: sore throat (may be severe), fever, malaise, headache, abdominal pain, N/V, absence of other URTI symptoms
• viral: sore throat (often mild), conjunctivitis, cough, rhinorrhea, hoarseness, diarrhea, flu-like symptoms (fever, malaise, myalgias)

Physical
• GAS: febrile, pharyngeal/tonsillar erythema and exudates, enlarged (>1 cm) and tender anterior cervical lymph nodes, palatal petechiae, strawberry tongue, scarlatiniform rash
• viral: afebrile, absent/mild tonsillar exudates, minor and non-tender adenopathy, viral exanthems

Investigations
• no single sign or symptom reliably identifies GAS as the causative organism in children with sore throat
• scores are used to predict if throat culture will be positive (e.g. McIsaac Criteria)
  ▪ these score systems have not been found to be sensitive or specific enough to diagnose GAS in children and adolescents with sore throat
• suspected diagnosis of GAS pharyngitis should be confirmed with a rapid streptococcal antigen test and a follow-up throat culture if the rapid test is negative

Management
• antibiotics (for group A Streptococcus/S. pyogenes)
  ▪ penicillin V or amoxicillin or erythromycin (if penicillin allergy) x 10 d
  ▪ can prevent rheumatic fever if given within 9 d of symptoms; does NOT alter risk of post-streptococcal glomerulonephritis
• supportive: hydration and acetaminophen for discomfort due to pain and/or fever
• follow-up: if uncomplicated course, no follow-up or post-antibiotic throat cultures needed
• prophylaxis: consider tonsillectomy for proven, recurrent streptococcal tonsillitis

Complications
• preventable with antibiotics: AOM, sinusitis, cervical adenitis, mastoiditis, retropharyngeal/peritonsillar abscess, sepsis
• immune-mediated complications: scarlet fever, acute rheumatic fever, post-streptococcal glomerulonephritis, reactive arthritis, pediatric autoimmune neuropsychiatric disorder associated with group A Streptococci (PANDAS)

SCARLET FEVER
• diffuse erythematous eruption
• delayed-type hypersensitivity reaction to pyrogenic exotoxin produced by Group A Streptococcus
• acute onset of fever, sore throat, strawberry tongue
• 24-48 h after pharyngitis, rash begins in the groin, axillae, neck, antecubital fossa; Pastia's lines may be present
• within 24 h, sandpaper rash becomes generalized with perioral sparing, non-pruritic, non-painful, blanchable
• rash fades after 3-4 d, may be followed by desquamation
• treatment is penicillin, amoxicillin, or erythromycin x 10 d

RHEUMATIC FEVER
• inflammatory disease due to antibody cross-reactivity following GAS infection
• affects ~1:10,000 children in developed world; much more prevalent in developing nations; peak incidence at 5-15 yr of age
• mainly a clinical diagnosis based on Jones Criteria (revised)
  ▪ requires 2 major OR 1 major and 2 minor (see sidebar) PLUS evidence of preceding strep infection [history of scarlet fever, group A streptococcal pharyngitis culture, positive rapid Ag detection test, anti-streptolysin O titers (ASOT)]
• treatment
  ▪ penicillin or erythromycin for acute course x 10 d
  ▪ prednisone if severe carditis
• secondary prophylaxis with daily penicillin or erythromycin
• complications:
  ▪ acute: myocarditis, conduction system aberrations (sinus tachycardia, atrial fibrillation), valvulitis (acute MR), pericarditis
  ▪ chronic: valvular heart disease (mitral and/or aortic insufficiency/stenosis), infectious endocarditis ± thromboembolic phenomenon
  ▪ onset of symptoms usually after 10-20 yr latency from acute carditis of rheumatic fever
POST-STREPTOCOCCAL GLOMERULONEPHRITIS
• glomerular immune complex disease following primary GAS infection of pharynx or skin
• most common in children aged 4-8 yr old; M>F
• antigen-antibody mediated complement activation with diffuse, proliferative glomerulonephritis
• occurs 1-3 wk following initial GAS infection (skin or throat)
• clinical presentation varies from asymptomatic, microscopic and macroscopic (cola coloured urine) hematuria to all features of nephritic syndrome (see P82)
• diagnosis is confirmed with elevated serum antibody titres against streptococcal antigens (ASOT, anti-DNAseB), low serum complement (C3)
• management:
  ▪ symptomatic: fluid and sodium restrictions; loop diuretics for hypertension and edema
  ▪ in severe cases, may require dialysis if renal function significantly impaired
  ▪ treat with penicillin or erythromycin if evidence of persistent GAS infection
• 95% of children recover completely within 1-2 wk; 5-10% have persistent hematuria

Meningitis

Definition
• inflammation of the meninges surrounding the brain and spinal cord

Epidemiology
• peak age: 6-12 mo; 90% of cases occur in children <5 yr old

Etiology
• viral: enteroviruses, herpes simplex virus (HSV)
• bacterial: age-related variation in specific pathogens (see Table 25)
• fungal and parasitic meningitis also possible
• most often due to hematogenous spread or direct extension from a contiguous site

Risk Factors
• unvaccinated
• immunocompromised: asplenia, diabetes mellitus, HIV, prematurity
• recent or current infections: AOM, sinusitis, orbital cellulitis,
• neuroanatomical: congenital defects, dermal sinus, neurosurgery, cochlear implants, recent head trauma
• exposures: day care centres, household contact, recent travel

History
• signs and symptoms variable and dependent on age, duration of illness and host response to infection
• infants: fever, lethargy, irritability, poor feeding, vomiting, diarrhea, respiratory distress, seizures
• children: fever, headache, photophobia, N/V, confusion, back/neck pain/stiffness, lethargy, irritability

Physical
• infants: toxic, hypothermia, bulging anterior fontanelle, respiratory distress, apnea, petechial/ purpuric rash, jaundice, omphalitis
• children: toxic, ↓ LOC, nuchal rigidity, Kernig's and Bruzinski's signs, focal neurologic findings, petechial/purpuric rash

Investigations
• blood work: CBC, electrolytes, Cr, BUN, glucose, culture with sensitivity
• lumbar puncture required for definitive diagnosis
  ▪ Gram stain, bacterial culture and sensitivity, WBC count and differential, RBC count, glucose, protein concentration (Table 24)
  ▪ acid-fast stain if suspect TB
  ▪ latex agglutination tests or PCR for specific bacteria if available (helpful if already treated with antibiotics)
  ▪ CSF cloudy in bacterial meningitis
  ▪ urinalysis and urine C&S in infants, Gram stain and culture of petechial/purpuric lesions

Signs of Meningismus
BONK on the head
Brudzinski’s sign
Opisthotonos*
Nuchal rigidity
Kernig’s sign

*Opisthotonos: rigid spasm of the body, with the back fully arched and the heels and head bent back
Table 24. CSF Findings of Meningitis

<table>
<thead>
<tr>
<th>Component</th>
<th>Normal Child</th>
<th>Normal Newborn</th>
<th>Bacterial Meningitis</th>
<th>Viral Meningitis</th>
<th>Herpes Meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (µL)</td>
<td>0-6</td>
<td>0-30</td>
<td>&gt;1000</td>
<td>100-500*</td>
<td>10-1000</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>0</td>
<td>2-3</td>
<td>&gt;50</td>
<td>&lt;40</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>40-80</td>
<td>32-121</td>
<td>&lt;30</td>
<td>&gt;30</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Protein (mg/dL)</td>
<td>20-30</td>
<td>19-149</td>
<td>&gt;100</td>
<td>50-100</td>
<td>&gt;75</td>
</tr>
<tr>
<td>RBC (µL)</td>
<td>0-2</td>
<td>0-2</td>
<td>0-10</td>
<td>0-2</td>
<td>10-50</td>
</tr>
</tbody>
</table>

*lymphocytes predominate  Modified from Peds in Review 1993;14:11-18 and Ped Inf Dis J 1996;15:298-303

Management

- **supportive care**
  - preservation of adequate cerebral perfusion by maintaining normal BP and managing ↑ ICP
  - close monitoring of fluids, electrolytes, glucose, acid-base disturbances, coagulopathies

- **bacterial meningitis**
  - if suspected or cannot be excluded, commence empiric antibiotic therapy while awaiting cultures or if LP contraindicated or delayed
  - adjuvant dexamethasone BEFORE antibiotic for Hib meningitis; consider for those >6 wk with pneumococcal meningitis
  - isolation with appropriate infection control procedures until 24 h after culture-sensitive antibiotic therapy
  - fluid restrict if any concern for SIADH
  - hearing test
  - report to public health; prophylactic antibiotics for close contacts of Hib and *N. meningitidis* meningitis

Table 25. Antibiotic Management of Bacterial Meningitis

<table>
<thead>
<tr>
<th>Age</th>
<th>Main pathogens</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 28 d</td>
<td>GBS, <em>E. coli</em>, <em>Listeria</em></td>
<td>Ampicillin + cefotaxime</td>
</tr>
<tr>
<td></td>
<td>Other: Gram-negative bacilli</td>
<td></td>
</tr>
<tr>
<td>28 to 90 d</td>
<td>Overlap of neonatal pathogens and those seen in older</td>
<td>Ampicillin + cefotaxime ± vancomycin</td>
</tr>
<tr>
<td></td>
<td>children</td>
<td></td>
</tr>
<tr>
<td>&gt;90 d</td>
<td><em>S. pneumococcus</em>, <em>N. meningitidis</em></td>
<td>Ceftriaxone ± vancomycin</td>
</tr>
</tbody>
</table>

- **viral meningitis**
  - mainly supportive (except for HSV)
  - acyclovir for HSV meningitis
  - report to public health

- **prophylaxis**: appropriate vaccinations significantly decrease incidence of bacterial meningitis (see Routine Immunization, P3)

Complications

- **mortality**: neonate 15-20%, children 4-8%; pneumococcus > meningococcus > HiB
- **acute**: SIADH, subdural effusion/empyema, brain abscess, disseminated infection (osteomyelitis, septic arthritis, abscess), shock/DIC
- **chronic**: hearing loss, neuromotor/cognitive delay, learning disabilities, neurological deficit, seizure disorder, hydrocephalus

Mumps

Definition

- acute, self-limited viral infection that is most commonly characterized by adenitis, and swelling of the parotid glands

Epidemiology

- incidence in Ontario has declined since introduction of two-dose MMR vaccination schedule
- average of 25 reported cases per year
- majority of reported cases in children between 5-10 yr of age

Etiology

- Mumps virus (RNA virus of the genus *Rubulavirus* in the *Paramyxoviridae* family)
- transmission via respiratory droplets, direct contact, fomites
- incubation period: 14-25 d
- infectivity period: 7 d pre-parotitis-5 d post-parotitis
- upper respiratory tract → lymph nodes → salivary glands, gonads, pancreas, meninges, kidney, heart, thyroid
History
• non-specific prodome of fever, headache, malaise, myalgias (especially neck pain)
• usually followed within 48 h by parotid swelling secondary to parotitis (bilateral, preauricular, ear pushed up and out)
• parotid gland is tender and pain worsened with spicy or sour foods
• one third of infections do not cause clinically apparent salivary gland swelling and may simply present as an URTI

Investigations
• clinical diagnosis, but may be confirmed with IgM positive serology within 4 wk of acute infection
  ▪ may also use PCR or viral cultures from oral secretions, urine, blood, and CSF
  ▪ blood work: CBC (leukopenia with relative lymphocytosis), serum amylase (elevated)

Management
• mainly supportive: analgesics, antipyretics, warm or cold packs to parotid may be soothing
• admit to hospital if serious complications (meningitis, pancreatitis)
• droplet precautions recommended until 5 d after onset of parotid swelling
• prophylaxis: routine vaccination (see Routine Immunization, P3)

Complications
• common: aseptic meningitis, orchitis/oophoritis
• less common: encephalitis, pancreatitis, thyroiditis, myocarditis, arthritis, glomerulonephritis, ocular complications, hearing impairment

Pertussis

Definition
• prolonged respiratory illness characterized by paroxysmal coughing and inspiratory "whoop"

Epidemiology
• ~10 million children <1 yr old affected worldwide, causes up to 400,000 deaths per year
• greatest incidence among children <1 yr (not fully immunized) and adolescents (waning immunity)

Etiology
• Bordetella pertussis: Gram negative pleomorphic rod
• highly contagious; transmitted via respiratory droplets released during intense coughing
• incubation period: 6-20 d; most contagious during catarrhal phase but may remain contagious for weeks after

History
• prodromal catarrhal stage
  ▪ lasts 1-7 d; URTI symptoms (coryza, mild cough, sneezing) with NO or LOW-GRADE fever
• paroxysmal stage
  ▪ lasts 4-6 wk; characterized by paroxysms of cough ("100 day cough"), sometimes followed by inspiratory whoop ("whooping cough")
  ▪ infants <6 mo may present with post-tussive apnea, whoop is often absent
  ▪ onset of attacks precipitated by yawning, sneezing, eating, physical exertion
  ▪ ± post-tussive emesis, may become cyanotic before whoop
• convalescent stage
  ▪ lasts 1-2 wk; characterized by occasional paroxysms of cough, but decreased frequency and severity
  ▪ non-infectious but cough may last up to 6 mo

Investigations
• nasopharyngeal (NP) specimen using aspirate or NP swab
  ▪ gold standard: culture using special media (Regan-Lowe agar)
  ▪ PCR to detect pertussis antigens
• blood work: CBC (lymphocytosis) and serology (antibodies against B. pertussis)

Management
• admit if paroxysms of cough are associated with cyanosis and/or apnea and give O₂
• supportive care
• antimicrobial therapy indicated if B. pertussis isolated, or symptoms present for <21 d
  ▪ use macrolide antibiotics (azithromycin, erythromycin or clarithromycin)
• droplet isolation until 5 d of treatment
  ▪ report to public health
• prophylaxis
  - macrolide antibiotics for all household contacts
  - prevention with vaccination in infants and children (Pentacel®), and booster in adolescents (Adacel®) (see Routine Immunization, P3)

Complications
• pressure related from paroxysms: subconjunctival hemorrhage, rectal prolapse, hernias, epistaxis
• respiratory: sinusitis, pneumonia, aspiration, atelectasis, pneumomediastinum, pneumothorax, alveolar rupture
• neurological: seizures (~3%), encephalopathy, intracranial hemorrhage
• mortality: ~0.3%; highest risk in infants <6 mo old

Pneumonia
• see P93

Periorbital (Preseptal) and Orbital Cellulitis
• see Ophthalmology, OP10
  - preseptal cellulitis ~3 times more common than orbital cellulitis
  - causative pathogens include: S. aureus, S. pyogenes, S. pneumonia, M. catarrhalis, H. influenzae (less common now due to vaccination)
  - key to management is distinguishing between preseptal and orbital cellulitis (which is an OCULAR and MEDICAL EMERGENCY)

Sexually Transmitted Infection
• see Family Medicine, FM46 and Gynecology, GY26

Sinusitis
• see Family Medicine, FM47
  - complication of ≤10% of URTIs in children
  - clinical diagnosis
  - diagnostic imaging is NOT required to confirm diagnosis in children
    - routine CT not recommended, but consider if suspect complications of sinusitis, persistent/recurrent disease, need for surgery
  - antibiotic therapy for all children (although nearly half resolve spontaneously within 4 wk)
  - complications: preseptal/orbital (cellulitis, orbital abscess, osteomyelitis, etc.), intracranial (meningitis, abscess, etc.), Pott's Puffy tumour

Urinary Tract Infection (UTI)

Definition
• infection of the urinary bladder (cystitis) and/or kidneys (pyelonephritis)

Epidemiology
• overall prevalence in infants and young children presenting with fever is 7%
  - <4-6 wk old: more common in boys
  - >1 yr old: females have two to four fold higher prevalence

Etiology
• majority (>95%) have a monomicrobial cause with E. coli identified as the causative agent most of the time (~70%)
• Gram-negative bacilli: E. coli, Klebsiella, Proteus, Enterobacter, Pseudomonas
• Gram-positive cocci: S. saprophyticus, Enterococcus

Risk Factors
• non-modifiable: female gender, Caucasian, previous UTIs, family history
• modifiable: urinary tract abnormalities (vesicoureteral reflux, neurogenic bladder, obstructive uropathy, posterior urethral valve), dysfunctional voiding, repeated bladder catheterization, uncircumcised males, labial adhesions, sexually active, constipation, toilet training
History

- infants and young child: often just fever or non-specific symptoms (poor feeding, irritability, FTT, jaundice if <28 d old, vomiting)
- older child: fever, urinary symptoms (dysuria, urgency, frequency, incontinence, hematuria), abdominal and/or flank pain

Physical

- infants and young child: toxic vs non-toxic, febrile, FTT, jaundice; look for external genitalia abnormalities (phimosis, labial adhesions) and lower back signs of occult myelodysplasia (e.g. hair tufts), which may be associated with neurogenic bladder
- older child: febrile, suprapubic and/or CVA tenderness, abdominal mass (enlarged bladder or kidney); may present with short stature, FTT or hypertension secondary to renal scarring from previously unrecognized or recurrent UTIs

Investigations

- sterile urine specimen
  - clean catch, catheterization or suprapubic aspiration
  - urinalysis (leukocyteesterase, nitrites, erythrocytes), microscopy (bacteria and leukocytes), culture and sensitivity
- diagnosis established if urinalysis suggests infection AND if ≥50,000 colony-forming units per mL of a uropathogen cultured

Management

- admit if: <2 mo old, urosepsis, persistent vomiting, inability to tolerate oral medication, moderate-severe dehydration, immunocompromised, complex urologic pathology, inadequate follow-up, failure to respond to outpatient therapy
- supportive care: maintenance of hydration and adequate pain control
- antibiotics
  - base on local antimicrobial susceptibility patterns
  - commence broad empiric therapy until results of urine culture and sensitivity known, and then tailor as appropriate
- neonates: IV ampicillin and gentamicin
- infants and older children: oral cephalexin if outpatient; IV ampicillin and gentamicin if inpatient
- duration 7-14 d
- imaging
  - renal and bladder U/S for all febrile infants with UTIs looking for anatomical abnormalities, hydronephrosis, abscess
  - voiding cystourethrogram (VCUG) not recommended after 1st febrile UTI unless U/S reveals hydronephrosis, obstructive uropathies or other signs suggestive of high-grade vesicoureteral reflux (VUR)
- follow-up: outpatients to return in 24-48 h if no clinical response and seek prompt medical evaluation for future febrile illnesses
- prophylaxis: generally not recommended unless higher grades of VUR

Complications

- long term morbidity: focal renal scarring develops in 8% of patients; long term significance unknown

Neonatology

Gestational Age (GA) and Size

Definitions

- classification by gestational age (GA)
  - preterm: <37 wk
  - term: 37-42 wk
  - post-term: >42 wk
- classification by birth weight
  - small for gestational age (SGA): 2 SD < mean weight for GA or <10th percentile
  - appropriate for gestational age (AGA): within 2 SD of mean weight for GA
  - large for gestational age (LGA): 2 SD > mean weight for GA or >90th percentile
### Table 26. Abnormalities of Gestational Age and Size

<table>
<thead>
<tr>
<th>Features</th>
<th>Causes</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-term Infants</strong></td>
<td>College: cause unknown</td>
<td>Respiratory distress syndrome, apnea of prematurity, chronic lung disease, bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>&lt;37 wk</td>
<td>Maternal disease: hypertension, diabetes, cardiac and renal disorders</td>
<td>Feeding difficulties, necrotizing enterocolitis (NEC)</td>
</tr>
<tr>
<td></td>
<td>Fetal conditions: multiple pregnancy, congenital abnormalities</td>
<td>Hypocalcaemia, hypoglycaemia, hypothermia</td>
</tr>
<tr>
<td></td>
<td>Pregnancy issues: placental insufficiency, placenta previa, uterine malformations, previous preterm birth, infection</td>
<td>Anaemia, jaundice</td>
</tr>
<tr>
<td></td>
<td>Behavioural and psychological contributors: smoking, EtOH, drug use, psychosocial stressors</td>
<td>Retinopathy of prematurity</td>
</tr>
<tr>
<td></td>
<td>Sociodemographic factors: age, socioeconomic conditions</td>
<td>Intracranial/intraventricular hemorrhage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patent ductus arteriosus (PDA)</td>
</tr>
<tr>
<td><strong>Post-term Infants</strong></td>
<td>College: unknown</td>
<td>Increased risk of stillbirth or neonatal death</td>
</tr>
<tr>
<td>&gt;42 wk</td>
<td>Increased in first pregnancies</td>
<td>Fetal &quot;postmaturity syndrome&quot;: impaired growth due to placental dysfunction</td>
</tr>
<tr>
<td></td>
<td>Previous post-term birth</td>
<td>Meconium aspiration</td>
</tr>
<tr>
<td></td>
<td>Genetic factors</td>
<td></td>
</tr>
<tr>
<td><strong>SGA Infants</strong></td>
<td>Extrinsic causes: placental insufficiency, poor nutrition, hypertension, multiple pregnancies, drugs, EtOH, smoking</td>
<td>Perinatal hypoxia</td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td></td>
<td>Hypoglycemia, hypocalcaemia, hypothermia</td>
</tr>
<tr>
<td>Asymmetric (head-sparing):</td>
<td></td>
<td>Hyperviscosity (polycythemia), jaundice, hypomobility</td>
</tr>
<tr>
<td>late onset, growth arrest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symmetric: early onset,</td>
<td>Intrinsic causes: maternal infections (TORCH), congenital abnormalities, syndromal, idiopathic</td>
<td>Patien ductus arteriosus (PDA)</td>
</tr>
<tr>
<td>lower growth</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LGA Infants</strong></td>
<td>Maternal diabetes</td>
<td>Birth trauma, perinatal depression</td>
</tr>
<tr>
<td>&gt;90th percentile</td>
<td>Racial or familial factors</td>
<td>(meconium aspiration, respiratory distress syndrome (infants of diabetic mothers), transient tachypnea of newborn, jaundice, polycythaemia, hypoglycaemia, hypocalcaemia</td>
</tr>
<tr>
<td></td>
<td>Increasing parity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Previous LGA infant, high BMI, large pregnancy weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Certain syndromes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Routine Neonatal Care

1. erythromycin ointment: applied to both eyes for prophylaxis of ophthalmaeonatorum
2. vitamin K IM: prophylaxis against hemorrhagic disease of newborn
3. screening tests
   - in Ontario, newborn screening tests for
     - hearing loss
     - endocrine disorders (congenital adrenal hyperplasia, congenital hypothyroidism)
     - cystic fibrosis
     - hemoglobinopathies (HbSS, HbSc, etc.)
     - inborn errors of metabolism including galactosemia, biotinidase deficiency, fatty acid oxidation defects
4. if mother Rh negative: send cord blood for blood group and direct antiglobulin test
5. if mother hepatitis B surface antigen positive: HBcAg and start hepatitis B vaccine series

### Neonatal Resuscitation

- assess Apgar at 1 and 5 min
- if <7 at 5 min then reassess q5min, until >7
- do not wait to assign Apgar score before initiating resuscitation

### Table 27. Apgar Score

<table>
<thead>
<tr>
<th>Sign</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>Absent</td>
<td>&lt;100/min</td>
<td>&gt;100/min</td>
</tr>
<tr>
<td>Respiratory Effort</td>
<td>Absent</td>
<td>Slow, irregular</td>
<td>Good, crying</td>
</tr>
<tr>
<td>Irritability</td>
<td>No response</td>
<td>Grimace</td>
<td>Cough/cry</td>
</tr>
<tr>
<td>Tone</td>
<td>Limp</td>
<td>Some flexion of extremities</td>
<td>Active motion</td>
</tr>
<tr>
<td>Colour</td>
<td>Blue, pale</td>
<td>Body pink, extremities blue (acrocyanosis)</td>
<td>Completely pink</td>
</tr>
</tbody>
</table>
Initial Resuscitation

- anticipation: know maternal history, history of pregnancy, labour, and delivery
- steps to take for all infants (before ABCs)
  - warm (radiant heater, warm towels) and dry the newborn (remove wet towels)
  - position and clear airway ("sniffing" position)
  - stimulate infant: rub lower back gently or flick soles of feet EXCEPT if meconium present (in which case tracheal suction first)
  - assess breathing and heart rate

Airway

- if meconium is present and
  - baby is vigorous (strong respiratory effort, good muscle tone, HR >100): no further reuscitative interventions required
  - baby is not vigorous: intubate and suction trachea while monitoring vital signs. If prolonged or unsuccessful intubation, attempt bag mask ventilation
- if no meconium and suction required, suction mouth first and then nose

Breathing

- if HR <100 or apnoeic, apply positive pressure ventilation (PPV)
  - PPV at rate of 40-60/min with enough pressure to see visible chest expansion and note increase in HR
- if PPV not effective (no increase in HR, no chest rise), incorporate MR SOPA corrective actions

Circulation

- if HR <60 after 30 s of effective ventilation, start chest compressions ("60 or less, compress")
  - should provide 100% oxygen as soon as chest compressions are required
- chest compressions at lower 1/3 of the sternum and 1/3 of the AP depth at a rate of 120 events per min (3 compressions:1 ventilation = 90 compressions/min:30 breaths/min)

Table 28. Interventions Used in Neonatal Resuscitation

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine (adrenalin)</td>
<td>0.1-0.3 mL/kg/dose of 1:10,000</td>
<td>HR &lt;60 and not rising</td>
<td>Side effects: tachycardia, hypertension, cardiac arrhythmias</td>
</tr>
<tr>
<td></td>
<td>(0.01-0.03 mg/kg) IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.05-0.1 mg/kg (0.5-1 mL/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1:10,000) endotracheally can be</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>considered while awaiting IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>access (IV preferred)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can be repeated q3-5 min prn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naloxone (Narcan®)</td>
<td>0.1 mg/kg IV/M</td>
<td>Not recommended as part of</td>
<td>Do not use for chronic opiate exposure – may cause withdrawal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>initial resuscitation. HR</td>
<td>symptoms including hypertension, irritability, seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and oxygenation should be</td>
<td>Action of opioid outlasts action of naloxone therefore close monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>restored by supporting</td>
<td>required after administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ventilation</td>
<td></td>
</tr>
<tr>
<td>Fluid Bolus</td>
<td>10 mL/kg</td>
<td>Evidence of hypovolemia</td>
<td></td>
</tr>
<tr>
<td>(NS, whole blood,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ringer’s lactate)</td>
<td>May need to be repeated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not to give too rapidly as large volume rapid infusions can be associated with IVH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Approach to the Depressed Newborn

- a depressed newborn lacks one or more of the following characteristics of a normal newborn
  - pulse >100 bpm
  - cries when stimulated
  - actively moves all extremities
  - has a good strong cry
- approximately 10% of newborn babies require assistance with breathing after delivery

Table 29. Etiology of Respiratory Depression in the Newborn

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Problems</td>
<td>Respiratory distress syndrome/Hyaline membrane disease</td>
</tr>
<tr>
<td></td>
<td>Pulmonary hypoplasia</td>
</tr>
<tr>
<td></td>
<td>CNS depression</td>
</tr>
<tr>
<td></td>
<td>Meconium aspiration</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax</td>
</tr>
<tr>
<td></td>
<td>Pleural effusions</td>
</tr>
<tr>
<td></td>
<td>Congenital malformations</td>
</tr>
</tbody>
</table>
Table 29. Etiology of Respiratory Depression in the Newborn (continued)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia (severe)</td>
<td>Enphythroblastosis fetalis</td>
</tr>
<tr>
<td></td>
<td>Secondary hydrops fetalis</td>
</tr>
<tr>
<td>Maternal Causes</td>
<td>Drugs/anesthesia (opiates, mag sulphate)</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Maternal myasthenia gravis</td>
</tr>
<tr>
<td>Congenital Malformations/Birth Injury</td>
<td>Nuchal cord, perinatal depression</td>
</tr>
<tr>
<td></td>
<td>Bilateral phrenic nerve injury</td>
</tr>
<tr>
<td></td>
<td>Potter’s sequence</td>
</tr>
<tr>
<td>Shock</td>
<td>Antepartum hemorrhage</td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td>Transposition of the great arteries with intact ventricular septum</td>
</tr>
<tr>
<td>Other</td>
<td>Hypothermia</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
</tr>
</tbody>
</table>

Diagnosis
- vital signs
- detailed maternal history
  - include prenatal care, illnesses, use of drugs, labour, previous high risk pregnancies, infections during pregnancy, current infections, duration of ruptured membranes, blood type and Rh status, amniotic fluid status, gestational age, meconium, Apgar scores
- clinical findings (observe for signs of respiratory distress: cyanosis, tachypnea, retractions, grunting, temperature instability)
- laboratory results (CBC, ABG, blood type, glucose)
- transillumination
- CXR

Management
- ABCs
- intubation and suction if meconium present
- apply tactile stimulation if no meconium
- provide PPV if apneic or HR <100 bpm
- monitor oxygen saturation and heart rate (if HR <60 bpm, start chest compressions)
- provide ventilatory support and treat the underlying cause

Common Conditions of Neonates

Apnea

Definition
- “periodic breathing”: normal respiratory pattern seen in newborns in which periods of rapid respiration are alternated with pauses lasting 5-10 s
- “apnea”: absence of respiratory gas flow for >15 s (or less if associated with bradycardia or desaturation) – 3 types:
  - central: no chest wall movement, no signs of obstruction
  - obstructive: chest wall movement continues against obstructed upper airway, no airflow
  - mixed: combination of central and obstructive apnea

Differential Diagnosis
- in term infants, apnea requires full work-up as it can be associated with sepsis
- other causes:
  - CNS
    - apnea of prematurity (<34 wk): combination of CNS immaturity and obstructive apnea; resolves by 36 wk GA; diagnosis of exclusion
    - seizures
    - intracranial hemorrhage (ICH)
    - hypoxic injury
  - infectious: sepsis, meningitis, necrotizing enterocolitis (NEC)
  - GI: gastroesophageal reflux disease (GERD), aspiration with feeding
  - metabolic: hypoglycemia, hyponatremia, hypocalcemia, IEM
  - cardiovascular: anemia, hypovolemia, PDA, heart failure
  - drugs: morphine
Management
• O2, ventilatory support, maintain normal blood gases
• tactile stimulation
• correct underlying cause
• medications: methylxanthines (caffeine) stimulate the CNS and diaphragm and are used for apnea of prematurity (not in term infants)

**Bleeding Disorders in Neonates**

**Clinical Presentation**
• oozing from the umbilical stump, excessive bleeding from peripheral venipuncture/heel stick sites/IV sites, large caput succedaneum, cephalohematomas (in absence of significant birth trauma), subgaleal haemorrhage and prolonged bleeding following circumcision

**Approach to Bleeding Disorders in Neonates**
• 4 major categories

1. increased platelet destruction:
   • maternal ITP, SLE
   • neonatal alloimmune thrombocytopenia (NAIT)
   • infection
   • DIC
   • drugs
   • extensive localized thrombosis

2. decreased platelet production/function:
   • bone marrow replacement
   • pancytopenia
   • Fanconi anemia
   • Trisomy 13 and 18

3. metabolic:
   • congenital thyrotoxicosis
   • inborn error of metabolism

4. coagulation factor deficiencies (see Hematology, H29):
   • hemophilia A
   • hemophilia B
   • hemorrhagic disease of the newborn

**NEONATAL ALLOIMMUNE THROMBOCYTOPENIA (NAIT)**

**Epidemiology**
• 1 per 4000-5000 live births

**Pathophysiology**
• platelet equivalent of Rh disease of the newborn
• occurs when mother is negative for human platelet antigen (HPA) and fetus is positive
• development of maternal IgG antibodies against HPA antigens on fetal platelets

**Clinical Presentation**
• petechiae, purpura, thrombocytopenia in otherwise healthy neonate
• severe NAIT can lead to intracranial bleeding

**Diagnosis**
• maternal and paternal platelet typing and identification of platelet alloantibodies

**Treatment**
• IVIG to mother prenatally starts in second trimester ± steroids ± fetal platelet transfusions
• treat neonate with IVIG
• if transfusion required should be with washed maternal platelets or donor HPA negative platelets

**AUTOIMMUNE THROMBOCYTOPENIA**

**Pathophysiology**
• caused by antiplatelet antibodies from maternal ITP or SLE
• passive transfer of antibodies across placenta

**Clinical Presentation**
• similar presentation to NAIT, but thrombocytopenia usually less severe

**Treatment**
• steroids to mother for 10-14 d prior to delivery or IVIG to mother before delivery
• IVIG infant after delivery (usually if platelets <60,000)
• transfusion of infant with maternal/donor platelets only in severe cases, as antibodies will destroy transfused platelets
HEMORRHAGIC DISEASE OF THE NEWBORN
- caused by vitamin K deficiency
- factors II, VII, IX, X are vitamin K-dependent, therefore both PT and PTT are abnormal

Etiology and Clinical Presentation
- neonates at risk of vitamin K deficiency if:
  - vitamin K poorly transferred across the placenta
  - maternal use of anticonvulsants
  - insufficient bacterial colonization of colon at birth to synthesize vitamin K
  - dietary intake of vitamin K inadequate in breastfed infants

Prevention
- vitamin K IM administration at birth to all newborns

Bronchopulmonary Dysplasia (BPD)

Definition
- also known as chronic lung disease (CLD)
- clinically defined as O\textsubscript{2} requirement for >28 d plus persistent need for oxygen and/or ventilatory support at 36 wk corrected GA
- damage to developing lungs with prolonged intubation/ventilation

Investigations
- CXR findings may demonstrate decreased lung volumes, areas of atelectasis and hyperinflation

Treatment
- no good treatments
- gradual wean from ventilator, optimize nutrition
- dexamethasone may help decrease inflammation and encourage weaning, but use of dexamethasone is associated with increased risk of adverse neurodevelopmental outcomes

Prognosis
- chronic respiratory failure may lead to pulmonary hypertension, poor growth, and right-sided heart failure
- patients with BPD may continue to have significant impairment and deterioration in lung function late into adolescence
- some lung abnormalities may persist into adulthood including airway obstruction, airway hyper-reactivity, and emphysema
- associated with increased risk of adverse neurodevelopmental outcomes

Cyanosis

Figure 12. Approach to neonatal cyanosis
Management

- **ABGs**
  - elevated CO₂ suggests respiratory cause
  - hyperoxia test (to distinguish between cardiac and respiratory causes of cyanosis): get baseline PaO₂ in room air, then PaO₂ on 100% O₂ for 10-15 min
    - PaO₂ <150 mmHg: suggests cyanotic congenital heart disease or possible persistent newborn pulmonary hypertension (PPHN) (see Pediatric Cardiology, P16)
    - PaO₂ >150 mmHg: suggests cyanosis likely due to respiratory or non-cardiac cause
- **CXR**: look for respiratory abnormalities (respiratory tract malformations, evidence of shunting, pulmonary infiltrates) and cardiac abnormalities (cardiomegaly, abnormalities of the great vessels)

### Diaphragmatic Hernia

**Definition**
- developmental defect of the diaphragm with herniation of abdominal organs into thorax
- associated with pulmonary hypoplasia and PPHN

**Clinical Presentation**
- respiratory distress, cyanosis
- scaphoid abdomen and barrel-shaped chest
- affected side dull to percussion and breath sounds absent, may hear bowel sounds instead
- heart sounds shifted to contralateral side
- asymmetric chest movements, trachea deviated away from affected side
- may present outside of neonatal period
- often associated with other anomalies (cardiovascular, CNS, chromosomal abnormalities)
- **CXR**: bowel loops in thorax (usually left side), displaced mediastinum

**Treatment**
- immediate intubation required at birth: DO NOT bag mask ventilate because air will enter stomach and further compress lungs
- place large bore orogastric tube to decompress bowel
- initial stabilization and management of pulmonary hypoplasia and PPHN, hemodynamic support and surgery when stable

### Hypoglycemia

**Definition**
- glucose <2.6 mmol/L (40 mg/dL)

**Etiology**
- decreased carbohydrate stores (premature, IUGR)
- infant of a diabetic mother (IDM): maternal hyperglycemia → fetal hyperglycemia and hyperinsulinism → hypoglycemia in the newborn infant because of high insulin levels
- sepsis
- hyperinsulinism due to islet cell hyperplasia (e.g. Beckwith-Wiedemann syndrome)
- panhypopituitarism
- inborn errors of metabolism: fatty acid oxidation defects, galactosemia

**Clinical Findings**
- signs often non-specific and subtle: lethargy, poor feeding, irritability, tremors, apnea, cyanosis, seizures

**Management**
- identify and monitor infants at risk (pre-feed blood glucose checks)
- begin oral feeds as soon as possible after birth and ensure regular feeds
- if significant and/or symptomatic hypoglycemia, provide glucose IV and titrate according to blood sugar levels
- if persistent hypoglycemia or no predisposing cause for hypoglycemia, send “critical bloodwork” during an episode of hypoglycemia:
  - insulin
  - cortisol
  - growth hormone (GH)
  - β-hydroxybutyrate
  - lactate
  - ammonia
  - free fatty acids (FFAs)
  - ABG
- hyperinsulinism managed with glucagon and/or diazoxide, consultation with pediatric endocrinologist

---

**Carboxyhemoglobinemia** (secondary to carbon monoxide poisoning) results in impaired binding of oxygen to hemoglobin but does not discolour the blood. Therefore it may not register on pulse-oximetry and cyanosis may not be evident clinically.

**Methemoglobinemia** pulse oximetry typically reads higher than the true level of oxyhemoglobin. Methemoglobin alters the absorption of red light at the two wavelengths that pulse oximetry uses to predict oxygen saturation.
**Intraventricular Hemorrhage (IVH)**

**Definition**
- hemorrhage originating in the periventricular subependymal germinal matrix (GM)

**Epidemiology**
- incidence and severity inversely proportional to gestational age
- 50% of IVH occurs within 8 h of birth; 90% occurs by day 3

**Risk Factors**
- prematurity (<32 wk), BW <1500 g, need for vigorous resuscitation at birth, pneumothorax, ventilated preterm infants, hemodynamic instability, RDS, coagulopathy

**Clinical Presentation**
- many infants with IVH are asymptomatic
- subtle signs: apnea, bradycardia, changes in tone or activity, altered level of consciousness
- catastrophic presentation: bulging fontanelle, sudden drop in hematocrit, acidosis, seizures, hypotension

**Classification**
- Papile classification
- parenchymal hemorrhage may also occur in the absence of intraventricular hemorrhage
- routine head ultrasound screening of all preterm infants <32 wk or <1500 g gestation throughout NICU stay

**Management of Acute Hemorrhage**
- supportive care to maintain blood volume and acid-base status
- avoid fluctuations in blood pressure and cerebral blood flow
- follow-up with serial imaging

**Prognosis**
- outcome depends on grade of IVH
- short-term sequelae for severe IVH: mortality, extension of bleed, posthemorrhagic hydrocephalus (PHH), posthemorrhagic infarction, cyst formation
- possible long-term major neurological sequelae: cerebral palsy, cognitive deficits, motor deficits, visual and hearing impairment
- grades I and II hemorrhages have a relatively favourable prognosis
- greatest morbidity and mortality is seen with Grade IV hemorrhage and PHH requiring ventriculoperitoneal shunt placement

---

**Jaundice**

**Clinical Presentation**
- jaundice is visible at serum bilirubin levels of 85-120 µmol/L
- look at sclera, tip of nose in natural light
- jaundice more severe/prolonged (due to increased retention of bilirubin in the circulation) with:
  - prematurity, acidosis, hypoalbuminemia, dehydration

---

![Figure 13. Approach to neonatal hyperbilirubinemia](image-url)
**PHYSIOLOGIC JAUNDICE**

**Epidemiology**
- term infants: onset 2-3 d of life, resolution by 7 d of life
- premature infants: higher peak and longer duration

**Pathophysiology**
- increased hematocrit and decreased RBC lifespan
- immature glucuronyl transferase enzyme system (slow conjugation of bilirubin)
- increased enterohepatic circulation

**Table 30. Risk Factors for Jaundice**

<table>
<thead>
<tr>
<th>Maternal Factors</th>
<th>Perinatal Factors</th>
<th>Neonatal Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic group (e.g. Asian, native American)</td>
<td>Birth trauma (cephalohematoma, ecchymoses)</td>
<td>Difficulty establishing breastfeeding</td>
</tr>
<tr>
<td>Complications during pregnancy (infant of diabetic mother, Rh or ABO incompatibility)</td>
<td>Prematurity</td>
<td>Infection</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td></td>
<td>Genetic factors</td>
</tr>
</tbody>
</table>

**Table 31. Causes of Neonatal Jaundice by Age**

<table>
<thead>
<tr>
<th>&lt;24 h</th>
<th>24-72 h</th>
<th>72-96 h</th>
<th>Prolonged (&gt;1 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALWAYS PATHOLOGIC</td>
<td>Physiologic, polycythemia</td>
<td>Physiologic ± breastfeeding Sepsis</td>
<td>Breast milk jaundice</td>
</tr>
<tr>
<td>Hemolytic</td>
<td>Dehydration (breastfeeding jaundice)</td>
<td></td>
<td>Prolonged physiologic jaundice in preterm</td>
</tr>
<tr>
<td>Rh or ABO incompatibility</td>
<td>Hemolysis</td>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Sepsis, e.g. GBS</td>
<td>G6PD deficiency</td>
<td></td>
<td>Neonatal hepatitis</td>
</tr>
<tr>
<td>Congenital infection (TORCH)</td>
<td>Pyruvate kinase deficiency</td>
<td></td>
<td>Conjugation dysfunction</td>
</tr>
<tr>
<td>Severe bruising/hemorrhage</td>
<td>Spherocytosis</td>
<td>e.g. Gilbert syndrome, Crigler-Najjar syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brusing, hemorhage, hematoma</td>
<td>Inborn errors of metabolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polycythemia</td>
<td>e.g. galactosemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sepsis/congenital infection</td>
<td>Biliary tract obstruction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>e.g. biliary atresia</td>
<td></td>
</tr>
</tbody>
</table>

**Breastfeeding Jaundice**
- common; due to a lack of milk production → dehydration → exaggerated physiologic jaundice

**Breast Milk Jaundice**
- 1 per 200 breastfed infants
- glucuronyl transferase inhibitor found in breast milk
- onset 7 d of life, peak at 2-3 wk of life, usually resolved by 6 wk

**PATHOLOGIC JAUNDICE**
- must be investigated if:
  - jaundice at <24 h of age
  - serum unconjugated bilirubin rises rapidly or is excessive for patient's age and weight
  - conjugated hyperbilirubinemia
  - persistent jaundice lasting beyond 1-2 wk of age
- investigations
  - unconjugated hyperbilirubinemia:
    - hemolytic work-up: CBC, reticulocyte count, blood group (mother and infant), peripheral blood smear, Coombs test, bilirubin (conjugated, unconjugated)
    - if baby is unwell or has fever: septic work-up (CBC and differential, blood and urine cultures ± LP, CXR)
    - other: G6PD screen (in males), TSH
  - conjugated hyperbilirubinemia: consider liver enzymes (AST, ALT), coagulation studies (PT, PTT), serum albumin, ammonia, TSH, TORCH screen, septic work-up, galactosemia screen (erythrocyte galactose-1-phosphate uridyltransferase levels), metabolic screen, abdominal U/S, HIDA scan, sweat chloride

**TREATMENT OF UNCONJUGATED HYPERBILIRUBINEMIA**
- to prevent kernicterus (see P75)
- breastfeeding does not need to be discontinued, ensure adequate feeds and hydration
- lactation consultant support, mother to pump after feeds
- treat underlying causes (e.g. sepsis)
- phototherapy
  - insoluble unconjugated bilirubin is converted to excretable form via photoisomerization
  - serum bilirubin should be monitored during and immediately after therapy (risk of rebound because photoisomerization reversible when phototherapy discontinued)
contraindicated in conjugated hyperbilirubinemia: results in “bronzed” baby
side effects: skin rash, diarrhea, eye damage
use published guidelines for initiation of phototherapy
exchange transfusion
indications: high bilirubin levels as per published graphs based on age, weeks gestation
most commonly performed for hemolytic disease and G6PD deficiency

KERNICTERUS

Etiology
- unconjugated bilirubin concentrations exceed albumin binding capacity and bilirubin is deposited in the brain resulting in permanent damage (typically basal ganglia or brainstem)
- incidence increases as serum bilirubin levels increase above 340 µmol/L (19.8 mg/dL)
- can occur at lower levels in presence of sepsis, meningitis, hemolysis, hypoxia, acidosis, hypothermia, hypoglycemia and prematurity

Clinical Presentation
- up to 15% of infants have no obvious neurologic symptoms
- early stage: lethargy, hypotonia, poor feeding, emesis
- mid stage: hypertonia, high pitched cry, opisthotonic posturing (back arching), bulging fontanelle, seizures, pulmonary hemorrhage
- late stage (first year and beyond)
  - hypotonia, delayed motor skills, extrapyramidal abnormalities (choreoathetoid cerebral palsy), gaze palsy, mitral regurgitation, sensorineural hearing loss

Prevention
- exchange transfusion

Complications
- sensorineural deafness, choreoathetoid cerebral palsy (CP), gaze palsy, mental retardation

BILIARY ATRESIA

Definition
- atresia of the extrahepatic bile ducts which leads to cholestasis and increased conjugated bilirubin after the first week of life

Epidemiology
- incidence: 1:10,000-15,000 live births

Clinical Presentation
- dark urine, pale stool, jaundice (persisting for >2 wk), abdominal distension, hepatomegaly

Diagnosis
- conjugated hyperbilirubinemia, abdominal ultrasound
- HIDA scan
- liver biopsy

Treatment
- surgical drainage procedure
- hepatopportoenterostomy (Kasai procedure; most successful if <8 wk of age)
- usually requires liver transplantation
- vitamins A, D, E, and K; diet should be enriched with medium-chain triglycerides to ensure adequate fat ingestion

Necrotizing Enterocolitis (NEC)

Definition
- intestinal inflammation associated with focal or diffuse ulceration and necrosis
- primarily affecting terminal ileum and colon

Epidemiology
- affects 1-5% of preterm newborns admitted to NICU

Pathophysiology
- postulated mechanism of bowel ischemia: mucosal damage and enteral feeding → bacterial growth → bowel necrosis/gangrene/perforation
Risk Factors
- prematurity (immature defenses)
- asphyxia, shock (poor bowel perfusion)
- hyperosmolar feeds
- enteral feeding with formula (breast milk can be protective)
- sepsis

Clinical Presentation
- distended abdomen
- increased amount of gastric aspirate/vomit with bile staining
- frank or occult blood in stool
- feeding intolerance
- diminished bowel sounds
- signs of bowel perforation (sepsis, shock, peritonitis, DIC)

Investigations
- AXR: pneumonitis intestinalis (intramural air is a hallmark of NEC), free air, fixed loops, ileus, thickened bowel wall, portal venous gas
- CBC, ABG, lactate, blood culture, electrolytes
- high or low WBC, low platelets, hyponatremia, acidosis, hypoxia, hypercapnea

Treatment
- NPO (7-10 d), vigorous IV fluid resuscitation, decompression with NG tube, supportive therapy
- TPN
- antibiotics (usually ampicillin, gentamicin ± metronidazole if risk of perforation x 7-10 d)
- serial AXRs detect early perforation
- peritoneal drain/surgery if perforation
- surgical resection of necrotic bowel and surgery for complications (e.g. perforation, strictures)

Persistent Pulmonary Hypertension of the Newborn (PPHN)

Epidemiology
- incidence 1.9 per 1000 live births

Clinical Presentation
- usually presents within 12 h of birth with severe hypoxemia/cyanosis; may have only mild respiratory distress

Pathophysiology
- persistence of fetal circulation as a result of persistent elevation of pulmonary vascular resistance
- R → L shunt through PDA, foramen ovale → decreased pulmonary blood flow and hypoxemia → further pulmonary vasoconstriction

Risk Factors
- secondary PPHN: asphyxia, meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), sepsis, pneumonia, structural abnormalities (e.g. diaphragmatic hernia, pulmonary hypoplasia)
- primary PPHN occurs in absence of risk factors

Investigations
- measure pre- and post-ductal oxygen levels
- ECHO reveals increased pulmonary arterial pressure and a R → L shunt across PDA and PFO; also used to rule out other cardiac defects

Treatment
- maintain good oxygenation (SaO₂ >95%) in at-risk infants
- O₂ given early and tapered slowly, minimize stress and metabolic demands, maintain normal blood gases, circulatory support
- mechanical ventilation, high frequency oscillation (HFO)
- nitric oxide
- extracorporeal membrane oxygenation (ECMO) used in some centres when other therapy fails

Respiratory Distress in the Newborn

Clinical Presentation
- tachypnea: RR >60/min; tachycardia: HR >160/min
- grunting, subcostal/intercostal indrawing, nasal flaring
- dusky appearance, central cyanosis
- decreased air entry, crackles on auscultation
Differential Diagnosis of Respiratory Distress
- pulmonary
  - respiratory distress syndrome (RDS)
  - transient tachypnea of the newborn (TTN)
  - meconium aspiration syndrome (MAS)
  - pleural effusions, pneumothorax
  - congenital lung malformations
- infectious
  - sepsis, pneumonia
- cardiac
  - congenital heart disease (cyanotic, acyanotic)
  - persistent pulmonary hypertension of the newborn (PPHN)
- hematologic
  - blood loss, polycythemia
- anatomic
  - tracheoesophageal fistula
  - congenital diaphragmatic hernia
  - upper airway obstruction (see Otolaryngology, OT44)
    - choanal atresia
    - Pierre-Robin sequence (retrognathia ± micrognathia, cleft palate, glossoptosis)
    - laryngeal (malacia)
    - tracheal (malacia, vascular ring)
    - mucous plug
    - cleft palate
- metabolic
  - hypoglycemia
  - inborn errors of metabolism (amino acidemia, organic acidemia, urea cycle disturbance, galactosemia, 1st lactic acidosis)
- neurologic
  - CNS damage (trauma, hemorrhage)
  - drug withdrawal syndromes

Investigations
- CXR, ABG
- CBC, blood cultures, blood glucose
- ECHO, ECG if indicated

Table 32. Distinguishing Features of RDS, TTN, MAS

<table>
<thead>
<tr>
<th></th>
<th>RDS (&quot;Hyaline Membrane Disease&quot;)</th>
<th>TTN (&quot;Wet Lung Syndrome&quot;)</th>
<th>MAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Surfactant deficiency → poor lung compliance due to high alveolar surface tension → atelectasis → ↓ surface area for gas exchange → hypoxia + acidosis → respiratory distress</td>
<td>Delayed resorption of fetal lung fluid → accumulation of fluid in peribronchial lymphatics and vascular spaces → tachypnoea</td>
<td>Meconium is sterile but causes airway obstruction, chemical inflammation, and surfactant inactivation</td>
</tr>
<tr>
<td><strong>Gestational age</strong></td>
<td>Preterm</td>
<td>More commonly term and late preterm</td>
<td>Term and post-term</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td>Maternal diabetes</td>
<td>Maternal diabetes</td>
<td>Meconium-stained amniotic fluid</td>
</tr>
<tr>
<td></td>
<td>Preterm delivery</td>
<td>Maternal asthma</td>
<td>Post-term delivery</td>
</tr>
<tr>
<td></td>
<td>Male sex</td>
<td>Male sex</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low birth weight</td>
<td>Macrosomia (&gt;4500 g)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acidosis, sepsis</td>
<td>Elective caesareaen section or short labour</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypothermia</td>
<td>Late preterm delivery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Second born twin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Presentation</strong></td>
<td>Onset within first few hours of life, worsens over next 24-72 h</td>
<td>Tachypnoea within the first few hours of life ± retractions, grunting, nasal flaring</td>
<td>Respiratory distress within hours of birth</td>
</tr>
<tr>
<td></td>
<td>Respiratory distress (tachypnoea, tachycardia, grunting, intercostal indrawing, nasal flaring, cyanosis, lung crackles)</td>
<td>Often NO hypoxia or cyanosis</td>
<td>Small airway obstruction, chemical pneumonitis → tachypnoea, barrel chest with audible crackles</td>
</tr>
<tr>
<td></td>
<td>Hypoxia</td>
<td></td>
<td>Hypoxia</td>
</tr>
<tr>
<td></td>
<td>Cyanosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CXR Findings</strong></td>
<td>Homogenous infiltrates</td>
<td>Penhilar infiltrates</td>
<td>Hyperinflation</td>
</tr>
<tr>
<td></td>
<td>Air bronchograms</td>
<td>&quot;wet silhouette&quot;; fluid in fissures</td>
<td>Patchy atelectasis</td>
</tr>
<tr>
<td></td>
<td>Decreased lung volumes</td>
<td></td>
<td>Patchy and coarse infiltrates</td>
</tr>
<tr>
<td></td>
<td>May resemble pneumonia (GBS)</td>
<td></td>
<td>10-20% have pneumothorax</td>
</tr>
<tr>
<td></td>
<td>If severe, &quot;white-out&quot; with no differentiation of cardiac border</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 32. Distinguishing Features of RDS, TTN, MAS (continued)

<table>
<thead>
<tr>
<th></th>
<th>RDS (&quot;Hyaline Membrane Disease&quot;)</th>
<th>TTN (&quot;Wet Lung Syndrome&quot;)</th>
<th>MAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention</td>
<td>Prenatal corticosteroids (e.g. Celestone® 12 mg q24h x 2 doses) if risk of preterm delivery &lt;34 wk</td>
<td>Where possible, avoidance of elective caesarean delivery, particularly before 38 wk gestation</td>
<td>If infant is depressed at birth, intubate and suction below vocal cords</td>
</tr>
<tr>
<td></td>
<td>Monitor lecithin:sphingomyelin (L/S) ratio with amniocentesis, L/S &gt;2:1 indicates lung maturity</td>
<td></td>
<td>Avoidance of factor associated with in utero passage of meconium, e.g. post term delivery</td>
</tr>
<tr>
<td>Treatment</td>
<td>Resuscitation</td>
<td>Supportive</td>
<td>Resuscitation</td>
</tr>
<tr>
<td></td>
<td>Oxygen</td>
<td>Oxygen if hypoxic ventilator support (e.g. CPAP)</td>
<td>Oxygen</td>
</tr>
<tr>
<td></td>
<td>Ventilation</td>
<td>IV fluids andavage feeds</td>
<td>Ventilatory support</td>
</tr>
<tr>
<td></td>
<td>Surfactant (decreases alveolar surface tension, improves lung compliance and maintains functional residual capacity)</td>
<td></td>
<td>Surfactant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhaled nitric oxide, extracorporeal membrane oxygenation at some centres for PPHN</td>
</tr>
<tr>
<td>Complications</td>
<td>In severe prematurity and/or prolonged ventilation, increased risk of bronchopulmonary dysplasia (BPD)</td>
<td>Hypoxaemia</td>
<td>Hypoxaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypercapnnea</td>
<td>Hypercapnnea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acidosis</td>
<td>Acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPHN</td>
<td>PPHN</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pneumothorax</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pneumomediastinum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemical pneumonitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Secondary surfactant inhibition</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Dependent on gestation at birth and severity of underlying lung disease; long term risks of CLD</td>
<td>Recovery usually expected in 2-5 d</td>
<td>Dependent on severity, mortality up to 20%</td>
</tr>
</tbody>
</table>

PNEUMONIA

- see Pediatric Respirology, P93
- consider in infants with prolonged or premature rupture of membranes (PROM), maternal fever, or if mother is GBS positive
- suspect if infant exhibits respiratory distress, temperature instability, or WBC is low, elevated or left-shifted
- symptoms may be non-specific
- CXR: hazy lung and/or distinct infiltrates (may be difficult to differentiate from RDS)

Retinopathy of Prematurity (ROP)

- see Ophthalmology, OP41

Common Neonatal Skin Conditions

Table 33. Common Neonatal Skin Conditions

<table>
<thead>
<tr>
<th>Neonatal Skin Conditions</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor Response</td>
<td>Transient mottling when exposed to cold; usually normal, particularly if premature</td>
</tr>
<tr>
<td>(Cutis Marmorata, Acrocyanosis)</td>
<td></td>
</tr>
<tr>
<td>Vernix Caseosa</td>
<td>Soft, creamy, white layer covering baby at birth</td>
</tr>
<tr>
<td>Slate-Grey Nevus of Childhood</td>
<td>Blushy grey macules over lower back and buttocks (may look like bruises); common in dark skinned infants</td>
</tr>
<tr>
<td>(&quot;Mongolian spots&quot;)</td>
<td></td>
</tr>
<tr>
<td>Capillary Hemangioma</td>
<td>Raised red lesion, which increases in size after birth and involutes; 50% resolved by 5 yr, 90% by 9 yr</td>
</tr>
<tr>
<td>Erythema Toxicum</td>
<td>Yellow-white papules surrounded by erythema; common rash, resolves by 2 wk</td>
</tr>
<tr>
<td>Milia</td>
<td>Lesions 1-2 mm firm white pearly papules on nasal bridge, cheeks, and palate; self-resolving</td>
</tr>
<tr>
<td>Pustular Melanosis</td>
<td>Brown macular base with pustules, seen more commonly in African American infants; may be present at birth</td>
</tr>
<tr>
<td>Angiomatous Lesions (Salmon Patch)</td>
<td>Transitory macular capillary hemangiom of the eyelids and neck (&quot;Angel Kiss&quot; and &quot;Stork Bite&quot;); usually disappears with age</td>
</tr>
<tr>
<td>Neonatal Acne</td>
<td>Inflammatory papules and pustules mainly on face; self-resolving</td>
</tr>
</tbody>
</table>
Sepsis in the Neonate

Table 34. Sepsis Considerations in the Neonate

<table>
<thead>
<tr>
<th>Early Onset (72 h)</th>
<th>Late Onset (&gt;72 h – 28 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertical transmission, 95% present within 24 h after birth</td>
<td>Acquired after birth</td>
</tr>
<tr>
<td>Risk factors:</td>
<td>Most common in preterm infants in NICU (most commonly due to coagulase negative staphycococci)</td>
</tr>
<tr>
<td>Maternal infection: UTI, GBS positive, previous child with GBS sepsis or meningitis</td>
<td>Other pathogens implicated include GBS, anaerobes, E. Coli, Klebsiella, sepsis and meningitis more common than early onset</td>
</tr>
<tr>
<td>Maternal fever/leukocytosis/chorioamnionitis</td>
<td>Pathogens: GBS, E. coli, Listeria most common</td>
</tr>
<tr>
<td>Prolonged rupture of membranes (&gt;18 h)</td>
<td>Pneumonia more common with early onset sepsis</td>
</tr>
<tr>
<td>Preterm labour</td>
<td>Pathogens: GBS, E. coli, Listeria most common</td>
</tr>
</tbody>
</table>

Signs of Sepsis
- no reliable absolute indicator of occult bacteremia in infants <3 mo, most specific result has been WBC <5
- temperature instability (hypo/hyperthermia)
- respiratory distress, cyanosis, apnea
- tachycardia/bradycardia
- lethargy, irritability
- poor feeding, vomiting, abdominal distension, diarrhea
- hypotonia, seizures, lethargy
- jaundice, hepatomegaly, petechiae, purpura

Nephrology

Approach to Infant/Child with Dehydration

Etiology
- decreased intake: poor oral intake during acute illness, breastfeeding difficulties, eating disorders
- increased losses, common sites include:
  - GI: diarrhea, vomiting, bleeding
  - skin/mucous membranes: fever, burns, hemorrhage, stomatitis
  - urinary: osmolar diuresis (e.g. hyperglycemia, DKA), diuretic therapy, diabetes insipidus, post-obstructive/post ATN recovery diuresis
  - respiratory: tachypnea, bronchitis, pneumonia

Management
- if suspect dehydration based on history (acute illness, number of wet diapers, lethargy, changes in mental status, thirst, etc.), you must:

1) Determine degree of extracellular volume contraction

Table 35. Assessment of Degree of Extracellular Volume Contraction based on Physical Examination

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 yr</td>
<td>5%</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>&gt;2 yr</td>
<td>3%</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>Pulse (HR)</td>
<td>Normal, full</td>
<td>Rapid</td>
<td>Rapid, weak</td>
</tr>
<tr>
<td>Blood Pressure (BP)</td>
<td>Normal</td>
<td>Normal-low</td>
<td>Shock – decreased BP (very late finding in pediatrics and very dangerous)</td>
</tr>
<tr>
<td>Urine Output (UO)</td>
<td>Decreased</td>
<td>Markedly decreased</td>
<td>Anuria</td>
</tr>
<tr>
<td>Oral Mucosa</td>
<td>Slightly dry</td>
<td>Dry</td>
<td>Parched</td>
</tr>
<tr>
<td>Anterior Fontanelle</td>
<td>Normal</td>
<td>Sunken</td>
<td>Markedly sunken</td>
</tr>
<tr>
<td>Eyes</td>
<td>Normal</td>
<td>Sunken</td>
<td>Markedly sunken</td>
</tr>
<tr>
<td>Skin Turgor</td>
<td>Normal</td>
<td>Decreased</td>
<td>Tenting</td>
</tr>
<tr>
<td>Capillary Refill</td>
<td>Normal (&lt;3 s)</td>
<td>Normal to increased</td>
<td>Increased (&gt;3 s)</td>
</tr>
</tbody>
</table>

* Note that percentages refer to percent loss of pre-illness body weight

Assessment of Severity of Dehydration

<table>
<thead>
<tr>
<th></th>
<th>ICF</th>
<th>ECF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>10</td>
<td>140</td>
</tr>
<tr>
<td>Potassium</td>
<td>150</td>
<td>4</td>
</tr>
</tbody>
</table>

Figure 14. Body fluid compartments

Chronic Perinatal Infections

C H E A P T O R C H E S
Chicken pox/shingles
Hepatitis B
Ebstein-Barr virus
AIDS (HIV)
Parvovirus B19 (erythema infectiosum)
Toxoplasmosis
Other
Rubella virus
Cytomegalovirus/Coxsackievirus
Herpes simplex virus
Every STI
Syphilis

See Obstetrics, OB20

Electrolyte Concentrations of Na⁺ and K⁺ (in mEq/L)

<table>
<thead>
<tr>
<th></th>
<th>ICF</th>
<th>ECF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>10</td>
<td>140</td>
</tr>
<tr>
<td>Potassium</td>
<td>150</td>
<td>4</td>
</tr>
</tbody>
</table>

Assessment of Severity of Dehydration

C BASE H₂O
Capillary refill
BP
Anterior fontanelle
Skin turgor
Eyes sunken
HR
Oral mucosa
Output of urine
2) Determine the likely electrolyte disturbance
• dependent on etiology of dehydration and type of fluid loss (isotonic vs. hypertonic vs. hypotonic) (See Table 36)

Table 36. Electrolyte content of various bodily fluids

<table>
<thead>
<tr>
<th>Bodily Fluid</th>
<th>Na⁺ concentration (mmol/L)</th>
<th>K⁺ concentration (mmol/L)</th>
<th>Cl⁻ concentration (mmol/L)</th>
<th>HCO₃⁻ concentration (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva</td>
<td>30-80</td>
<td>20</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>Gastric juice</td>
<td>60-80</td>
<td>15</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatic juice</td>
<td>140</td>
<td>5-10</td>
<td>60-90</td>
<td>40-100</td>
</tr>
<tr>
<td>Bile</td>
<td>140</td>
<td>5-10</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>Small bowel</td>
<td>75</td>
<td>20</td>
<td>100</td>
<td>25-50</td>
</tr>
<tr>
<td>Large bowel</td>
<td>20-70</td>
<td>5-10</td>
<td>40-60</td>
<td>0</td>
</tr>
</tbody>
</table>

• initial investigations should include blood work for ALL patients looking at:
  ▪ electrolyte disturbances (Na⁺, K⁺, Cl⁻) + glucose
  ▪ acid-base disturbances (blood pH, pCO₂, HCO₃⁻)
  ▪ impaired renal function (creatinine, BUN)

3) Determine if the child requires oral or intravenous rehydration
• dehydrated child must receive adequate fluid management, including replacement of ongoing losses and providing maintenance fluids
• initial management using oral rehydration therapy (ORT) advantages: ↓ cost, no IV needed, ↓ incidence if iatrogenic hyper/hyponatremia, parental involvement
• indications for intravenous rehydration therapy:
  ▪ severe dehydration, which requires close monitoring and frequent assessment of electrolytes
  ▪ inability to tolerate ORT (e.g. vomiting, alteration in mental status, ileus, monosaccharide malabsorption, etc.)
  ▪ inability to provide ORT
  ▪ failure of ORT in providing adequate rehydration (e.g. persistent diarrhea or vomiting)

4) Return the child to a normal volume and electrolyte status by replacing current deficits and ongoing losses

Figure 15. Algorithm for deficit replacement and replacement of ongoing losses in the dehydrated child
5) Provide the appropriate fluid and electrolyte maintenance daily requirements (Tables 36 and 37)

Table 37. Maintenance Fluid Requirements

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>100:50:20 Rule (24-h maintenance fluids)</th>
<th>4:2:1 Rule (hourly rate of maintenance fluids)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-10 kg</td>
<td>100 cc/kg/d</td>
<td>4 cc/kg/h</td>
</tr>
<tr>
<td>11-20 kg</td>
<td>50 cc/kg/d</td>
<td>2 cc/kg/h</td>
</tr>
<tr>
<td>&gt;20 kg</td>
<td>20 cc/kg/d</td>
<td>1 cc/kg/h</td>
</tr>
</tbody>
</table>

- Types of fluids used:
  - normal saline (NS), Ringer's lactate (RL), half-normal saline (0.45% NaCl), 0.2% NS (for neonates only), D5W, and D10W (for neonates only), add potassium chloride (if hypokalemic)
- Common IV fluid combinations used in pediatrics:
  - first month of life: D5W/0.2 NS + 20 mEq KCl/L (only add KCl if voiding well)
  - children: D5W/NS + 20 mEq KCl/L or D5W/0.45 NS + 20 mEq KCl/L
  - NS: as bolus to restore circulation in dehydrated children (remains almost entirely distributed in intravascular space)
- Correction of Fluid and Electrolyte Deficits
  - if serum [Na+] <138-144 mmol/L, use NS or RL
  - if serum [Na+] 145-154 mmol/L, IV fluid sodium concentration should approximate 0.45 NS
  - if serum [Na+] >154 mmol/L, risk of cerebral edema with rapid rehydration of hypotonic solutions (i.e. NS) therefore replace fluid slowly with close monitoring.

6) Continue to monitor fluid and electrolyte status

- accurate monitoring of daily fluid intake (oral and IV) and ongoing losses (urine output, diarrhea, emesis, drains)
- if child receiving >50% of maintenance fluids through IV, serum electrolyte values should be monitored DAILY and adjusted accordingly
- avoid iatrogenic hyper/hyponatremia, keep the possibility of SIADH in mind

**Common Pediatric Renal Diseases**

Table 38. Common Manifestations of Renal Disease

<table>
<thead>
<tr>
<th>Neonate Common Causes</th>
<th>Neonate Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flank Mass</td>
<td>Hydronephrosis, polycystic disease (ARPKD or ADPKD), tumour</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Renal vein thrombosis, asphyxia, malformation, trauma</td>
</tr>
<tr>
<td>Anuria/Oliguria</td>
<td>Bilateral renal agenesis, obstruction, asphyxia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Child and Adolescent Common Causes</th>
<th>Child and Adolescent Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cola/Red-Coloured Urine</td>
<td>Acute glomerulonephritis (post-Strep GN, HSP, IgA nephropathy, etc.), hemoglobinuria (hemolytic), myoglobinuria (rhabdomyolysis)</td>
</tr>
<tr>
<td>Gross Hematuria</td>
<td>Urologic disease (nephrolithiasis, trauma, etc.), urinary tract infection (UTI), acute glomerulonephritis</td>
</tr>
<tr>
<td>Edema</td>
<td>Nephrotic syndrome, nephritis, acute/chronic renal failure, consider cardiac or liver disease</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Glomerulonephritis, renal failure, dysplasia (consider coarctation, drugs, endocrine causes)</td>
</tr>
<tr>
<td>Polyuria</td>
<td>DM, central and nephrogenic diabetes insipidus, renal Fanconi’s syndrome (genetic/metabolic/obstructed kidneys), hypercalciemia, pycnuric renal failure (renal dysplasia)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Orthostatic, nephrotic syndrome (minimal change disease, etc.), glomerulonephritis</td>
</tr>
<tr>
<td>Oliguria</td>
<td>Dehydration, acute tubular necrosis (ATN), interstitial nephritis, acute or chronic kidney disease (i.e. renal failure)</td>
</tr>
<tr>
<td>Urgency</td>
<td>UTI, vulvovaginitis</td>
</tr>
</tbody>
</table>

**Hemolytic Uremic Syndrome (HUS)**

Definition

- simultaneous occurrence of the triad of 1) non-immune microangiopathic hemolytic anemia, 2) thrombocytopenia and 3) acute renal injury

Epidemiology

- annual incidence of 1-2 per 100,000 in Canada
- most common cause of acute renal failure in children
Etiology
- diarrhea positive HUS: 90% of pediatric HUS from E. coli O157:H7 shiga toxin or verotoxin
- diarrhea negative HUS: other bacteria, viruses, familial, drugs

Pathophysiology
- toxin binds, invades and destroys colonic epithelial cells, causing bloody diarrhea
- toxin enters the systemic circulation, attaches and injures endothelial cells (especially in kidney) causing a release of endothelial products (e.g. von Willebrand factor, platelet aggregating factor)
- form platelet/fibrin thrombi in multiple organ systems (e.g. kidney, pancreas, brain, etc.) resulting in thrombocytopenia
- RBCs are forced through occluded vessels resulting in fragmented RBCs (schistocytes) that are removed by the reticuloendothelial system (hemolytic anemia)

History and Physical
- initial presentation of abdominal pain and diarrhea, followed by bloody diarrhea
- within 5–7 d begins to show signs of anemia, thrombocytopenia and renal insufficiency
- history: weakness, lethargy, oliguria
- physical exam: pallor, jaundice (hemolysis), edema, petechiae, hypertension

Investigations
- CBC (anemia, thrombocytopenia), blood smear (schistocytes), electrolytes, renal function, urinalysis (microscopic hematuria), stool cultures and verotoxin/shigella toxin assay

Management
- mainly supportive: nutrition, hydration, ventilation (if necessary), blood transfusion for symptomatic anemia
- monitor electrolytes and renal function: dialysis if electrolyte abnormality cannot be corrected, fluid overload, or uremia
- steroids are NOT helpful
- antibiotics are contraindicated because death of bacteria leads to increased toxin release and worse clinical course

Prognosis
- 5-10% mortality, 10-30% renal damage

Nephritic Syndrome

Definition
- acute or chronic syndrome affecting the kidney, characterized by glomerular injury and inflammation, and defined by hematuria (>5 RBCs per high-powered microscope field) and the presence of dysmorphic RBCs and RBC casts on urinalysis
- often accompanied by at least one of proteinuria (<50 mg/kg/d), edema, hypertension, azotemia, and oliguria

Epidemiology
- highest incidence in children aged 5-15 yr old

Etiology
- humoral immune response to a variety of etiologic agents → immunoglobin deposition → complement activation, leukocyte recruitment, release of growth factors/cytokines → glomerular inflammation and injury → porous podocytes → hematuria + RBC casts ± proteinuria
- hypertension secondary to fluid retention and increased renin secretion by ischemic kidneys
- primary (idiopathic) versus secondary (to a systemic disease), low complement levels versus normal complement levels (Table 39)

Table 39. Major Causes of Nephritic Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Decreased C3</th>
<th>Normal C3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td>Post-infectious GN (most common cause of acute</td>
<td>IgA Nephropathy</td>
</tr>
<tr>
<td></td>
<td>GN in pediatrics)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Membranoproliferative</td>
<td>Idiopathic rapidly progressive GN</td>
</tr>
<tr>
<td></td>
<td>• Type I (50-80%)</td>
<td>Anti-GBM disease</td>
</tr>
<tr>
<td></td>
<td>• Type II (&gt;80%)</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td>SLE</td>
<td>Henoch-Schönlein purpura (very common)</td>
</tr>
<tr>
<td></td>
<td>Bacterial endocarditis</td>
<td>Polytartentis nodosa</td>
</tr>
<tr>
<td></td>
<td>Abscess or shunt nephritis</td>
<td>Granulomatosis with polyangitis (GPA)</td>
</tr>
<tr>
<td></td>
<td>Cryoglobulinemia</td>
<td>Goodpasture’s syndrome</td>
</tr>
</tbody>
</table>
Risk Factors
- recent streptococcal pharyngitis or skin infection, systemic illnesses (see Etiology of Nephritic Syndrome, P82)

History and Physical
- often asymptomatic; some overlap in clinical findings for nephritic and nephrotic syndrome
- gross hematuria, mild-moderate edema, oliguria
- signs and symptoms suggestive of underlying systemic causes (e.g. fever, arthralgias, rash, dyspnea, pulmonary hemorrhage)

Investigations
- urine
  - dipstick (hematuria, 0 to 2+ proteinuria) and microscopy (>5 RBCs per high-powered microscope field, acanthocytes, RBC casts)
  - first morning urine protein/creatinine ratio (<200 mg/mmol)
- blood work
  - impaired renal function (↑ Cr and BUN) resulting in ↓ pH and electrolyte abnormalities (hyperkalemia, hyperphosphatemia, hypocalcemia)
  - mild anemia on CBC (secondary to hematuria)
  - hypoalbuminemia (secondary to proteinuria)
  - appropriate investigations to determine etiology: C3/C4 levels, serologic testing for recent streptococcal infection (ASOT, anti-hyaluronidase, anti-streptokinase, anti-NAD, anti-DNase B), ANA, anti-DNA antibodies, ANCA, serum IgA levels, anti-GBM antibodies
- renal biopsy
  - should be considered only in presence of: acute renal failure, no evidence of streptococcal infection, normal C3/C4

Management
- treat underlying cause
- symptomatic
  - renal insufficiency: supportive (dialysis if necessary), proper hydration
  - hypertension: salt and fluid restriction (but not at expense of renal function), ACE inhibitors or ARBs for chronic persistent HTN (not acute cases since ACE inhibitors or ARBs may decrease GFR further)
  - edema: salt and fluid restriction, possibly diuretics (avoid if significant intravascular depletion)
  - corticosteroids if indicated: IgA nephropathy, lupus nephritis, etc.

Prognosis
- dependent on underlying etiology
- complications include hypertension, heart failure, pulmonary edema, chronic kidney injury (requiring renal transplant)

Nephrotic Syndrome

Definition
- clinical syndrome affecting the kidney, characterized by significant proteinuria, peripheral edema, hypoalbuminemia, and hyperlipidemia

Epidemiology
- highest incidence in children of 2 to 6 yr old, M>F

Etiology
- primary nephrotic syndrome; nephrotic syndrome (NS) in the absence of systemic disease (most common cause in pediatrics)
  - glomerular inflammation ABSENT on renal biopsy: minimal change disease (>90% of all NS), focal segmental glomerular sclerosis (FSGS)
  - glomerular inflammation PRESENT on renal biopsy: membranoproliferative glomerulonephritis, IgA nephropathy, other minor causes
- secondary nephrotic syndrome: NS associated with systemic disease or due to another process causing glomerular injury (very rare in pediatrics)
  - autoimmune: SLE, diabetes mellitus, rheumatoid arthritis, etc.
  - genetic: sickle cell disease, Alport syndrome, etc.
  - infections: HBV/HCV, post-streptococcal, infective endocarditis, HUS, HIV, etc.
  - malignancies: leukemia, lymphoma, etc.
  - medications: captopril, penicillamine, NSAIDs, anticonvulsants, etc.
  - vasculitides: Henoch-Schönlein, GPA, etc.
- congenital nephrotic syndrome: congenital nephropathy of the Finnish type, Denys-Drash syndrome, etc.
**Risk Factors**
- family history, certain systemic illnesses and medications (as per Etiology, P83)

**History and Physical**
- non-specific (e.g. irritability, malaise, fatigue, anorexia, diarrhea)
- edema
  - often first sign; detectable when fluid retention exceeds 3 to 5 percent of body weight
  - starts periorbital and often pretibial → edematous areas are white, soft, and pitting
  - gravity dependent: periorbital edema ↓ and pretibial edema ↑ over the day
  - anasarca may develop (i.e. marked periorbital and peripheral edema, ascites, pleural effusions, scrotal/labial edema)
- decrease in effective circulating volume (e.g. tachycardia, hypertension, oliguria, etc.)
- foamy urine is a possible sign of proteinuria

**Investigations**
- urine
  - urine dipstick (3 to 4+ proteinuria, microscopic hematuria) and microscopy (oval fat bodies, hyaline casts)
  - first morning urine protein/creatinine ratio (>200 mg/mmol)
- blood work
  - diagnostic: hypoalbuminemia (<25 g/L), hyperlipidemia/hypercholesterolemia (total cholesterol >5 mmol/L)
  - secondary: electrolytes (hypocalcemia, hyperkalemia, hyponatremia), renal function (↑ BUN and Cr), coagulation profile (↑ PTT)
  - appropriate investigations to rule out secondary causes of NS: CBC, blood smear, C3/C4, ANA, HBV/HCV titers, ASOT, HIV serology, etc.
- consider renal biopsy if:
  - HTN (↑ risk of FSGS), gross hematuria, renal function, low serum C3/C4
  - no response to steroids after 4 wk of therapy
  - frequent relapses (>2 relapses in 6 mo)
  - presentation before first year of life (high likelihood of congenital nephrotic syndrome)
  - presentation ≥12 yr (rule out more serious renal pathology than minimal change disease)

**Management**
- minimal change disease: oral prednisone 2 mg/kg/d (or equivalent) for up to 12 wk → varicella status should be known before starting
- consider cytotoxic agents, immunomodulators or high-dose pulse corticosteroid if steroid resistant
- symptomatic
  - edema: salt and fluid restriction, possibly diuretic (avoid if significant intravascular depletion); furosemide + albumin for anasarca
  - hyperlipidemia: generally resolves with remission; limit dietary fat intake; consider statin therapy if persistently nephrotic
  - hypoalbuminemia: IV albumin and lasix not routinely given; consider if refractory edema
  - abnormal BP: control BP; fluid resuscitation if severe intravascular depletion; ACE inhibitors or ARBs for persistent HTN
- diet: NAS (no added salt) diet; monitor caloric intake and supplement with Ca²⁺ and Vit D if on corticosteroids
- daily weights and blood pressure to assess therapeutic progress
- secondary infections:
  - treat with appropriate antimicrobials; antibiotic prophylaxis not recommended
  - pneumococcal vaccine at diagnosis and varicella vaccine after remission; varicella Ig + acyclovir if exposed while on corticosteroids
- secondary hypercoagulability: mobilize, avoid hemoconcentration due to hypovolemia, prompt sepsis treatment; heparin if thrombi occur

**Prognosis**
- generally good: 80% of children responsive to corticosteroids
- up to 2/3 experience relapse, often multiple times; sustained remission with normal kidney function usually by adolescence
- complications: ↑ risk of infections (spontaneous peritonitis, cellulitis, sepsis); hypercoagulability due to decreased intravascular volume and antithrombin III depletion (pulmonary embolism, renal vein thrombosis; intravascular depletion-hypotension, shock, renal failure; side effects of drugs)
Hypertension in Childhood

Definition
- hypertension: systolic and/or diastolic blood pressure (BP) that is ≥95th percentile for sex, age and height (Table 40) on ≥3 occasions
- prehypertension: systolic and/or diastolic BP ≥90th percentile but <95th percentile OR BP ≥120/80 irrespective of age, gender and height

Table 40. 95th Percentile Blood Pressures (mmHg)

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Female 50th Percentile for Height</th>
<th>75th Percentile for Height</th>
<th>Male 50th Percentile for Height</th>
<th>75th Percentile for Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>104/58</td>
<td>105/59</td>
<td>102/57</td>
<td>104/58</td>
</tr>
<tr>
<td>6</td>
<td>111/73</td>
<td>112/73</td>
<td>114/74</td>
<td>115/75</td>
</tr>
<tr>
<td>12</td>
<td>123/80</td>
<td>124/81</td>
<td>123/81</td>
<td>125/82</td>
</tr>
<tr>
<td>17</td>
<td>129/84</td>
<td>130/85</td>
<td>136/87</td>
<td>138/88</td>
</tr>
</tbody>
</table>

Adapted from Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents working group report from the National High Blood Pressure Education Program

Epidemiology
- increasing prevalence of both hypertension and prehypertension over the last 25+ yr
- prevalence: 3-5% for hypertension, 7-10% for prehypertension; M>F

Etiology
- primary HTN
  - diagnosis of exclusion
  - most common in older children (≥10 yr), especially if positive family history, overweight and only mild hypertension
  - responsible for ~90% of cases of HTN in adolescents, rarely in young children
- secondary HTN
  - identifiable cause of HTN
  - responsible for majority of childhood hypertension
  - most likely etiology dependent on age (see Table 41), renal parenchymal disease most common cause (60 to 70% of cases)
  - always consider white coat HTN for all ages

Table 41. Etiology of Secondary Hypertension by Age Group

<table>
<thead>
<tr>
<th>System</th>
<th>Neonates</th>
<th>1 month to 6 years</th>
<th>7-12 years</th>
<th>&gt;13 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine/Metabolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Congenital renal disease</td>
<td>Renal parenchymal disease</td>
<td>Renal parenchymal disease</td>
<td>Renal parenchymal disease</td>
</tr>
<tr>
<td>Vascular</td>
<td>Coarctation of the aorta</td>
<td>Coarctation of the aorta</td>
<td>Renovascular abnormalities</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Corticosteroids</td>
<td>Corticosteroids</td>
<td>Corticosteroids</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Other</td>
<td>Iatrogenic</td>
<td>Iatrogenic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: endocrinopathies may include hyperthyroid, hyperparathyroid, Cushing’s syndrome, primary hyperaldosteronism/Conn’s syndrome, pheochromocytoma

Risk Factors
- primary HTN: male gender, positive family history, metabolic syndrome, OSA, African-American, prematurity/low-birth weight
- secondary HTN: history of renal disease, abdominal trauma, family history of autoimmune diseases, umbilical artery catheterization

History
- often asymptomatic, but can include FTT, fatigue, epistaxis
- symptoms of hypertensive emergency
  - neurologic: headache, seizures, focal complaints, change in mental status, visual disturbances
  - cardiovascular: symptoms of MI or heart failure (chest pain, palpitations, cough, shortness of breath)
- symptoms of secondary HTN: guided by etiology above; ask about medications and recreational drugs (current and past)
Physical
- BP measurement (make sure correct cuff size is used), plot on growth chart, BMI
- look for signs of hypertensive emergency (e.g. full neurologic exam, ophthalmoscopy, precordial exam, peripheral pulses, perfusion status)
- look for signs of secondary HTN

Investigations
- laboratory:
  - urine dipstick for hematuria and/or proteinuria (renal disease), urine catecholamines (pheochromocytoma, neuroblastoma)
  - blood work: renal function tests (electrolytes, Cr, BUN), consider renin and aldosterone levels (RAS, Conn’s syndrome, Wilms’ tumour)
  - other specific hormones if indicated on history and physical
- imaging: echocardiography (coarctation, heart function), abdominal U/S (RAS, abdominal mass), renal radionucleide imaging (renal scarring)
- other: ocular exam

Management
- treat underlying cause
- non-pharmacologic: modify concurrent cardiovascular risk factors (rate reduction, exercise, salt restriction, smoking cessation, etc.)
- pharmacologic: gradual lowering of BP using thiazide diuretics; no antihypertensives have been formally studied in children; if hypertensive emergencies: hydralazine, labetalol, sodium nitroprusside
- management of end organ damage (e.g. retinopathy, LVH)
- consider referral to specialist

Prognosis
- end-organ damage (similar to adults) including: left ventricular hypertrophy, CHF, cerebrovascular insults, renal disease, retinopathy

Neurology

Seizure Disorders
- see Neurology, N14

Differential Diagnosis of Seizures in Children
- benign febrile seizure
- CNS
  - infection, tumour, hypoxic ischemic encephalopathy
  - trauma, hemorrhage
- metabolic causes (e.g. hypoglycemia, hypocalcemia, hyponatremia)
- idiopathic epilepsy and epileptic syndromes
- others:
  - neurocutaneous syndromes
  - arteriovenous malformation
  - drug ingestions/withdrawal
  - seizure mimics

Investigations
- lab tests: CBC, electrolytes, calcium, magnesium, glucose
- toxicology screen if indicated
- EEG, CT/MRI if indicated, e.g. focal neurological deficit or has not returned to baseline after several hours after seizure
- LP, if first-time non-febrile seizure but not indicated for determining recurrence risk of benign febrile seizures or to determine seizure type or epileptic syndrome

CHILDHOOD EPILEPTIC SYNDROMES

Infantile Spasms
- brief, repeated symmetric contractions of neck, trunk, extremities (flexion and extension) lasting 10-30 s
- occur in clusters; often associated with developmental delay; onset 4-8 mo
- 20% unknown etiology (usually good response to treatment); 80% due to metabolic or developmental abnormalities, encephalopathies, or are associated with neurocutaneous syndromes (usually poor response to treatment)
can develop into West syndrome (infantile spasms, psychomotor developmental arrest, and hyperactivity) or Lennox Gastaut (see below)

- typical EEG: hypsarrhythmia (high voltage slow waves, spikes and polyspikes, background disorganization)
- management: ACTH, vigabatrin, benzodiazepines

Lennox-Gastaut

- characterized by triad of 1) multiple seizure types, 2) diffuse cognitive dysfunction and 3) slow generalized spike and slow wave EEG
- onset commonly 3-5 yr of age
- seen with underlying encephalopathy and brain malformations
- management: valproic acid, benzodiazepines and ketogenic diet; however, response often poor

Juvenile Myoclonic Epilepsy (Janz Syndrome)

- myoclonus particularly in morning; frequently presents as generalized tonic-clonic seizures
- adolescent onset (12-16 yr of age); autosomal dominant with variable penetrance
- typical EEG: 3.5-6 Hz irregular spike and wave, increased with photic stimulation
- management: lifelong treatment (valproic acid); excellent prognosis

Childhood Absence Epilepsy

- multiple daily absence seizures lasting <30 s without post-ictal state that may resolve spontaneously or become generalized in adolescence
- peak age of onset 6-7, F>M, strong genetic predisposition
- typical EEG: 3/s spike and wave
- management: valproic acid or ethosuximide

Benign Focal Epilepsy of Childhood with Rolandic/Centrotemporal Spikes

- focal motor seizures involving tongue, mouth, face, upper extremity usually occurring in sleep-wake transition states; remains conscious, but aphasic post-ictally
- onset peaks at 5-10 yr of age, 16% of all non-febrile seizures; remits spontaneously in adolescence without sequelae
- typical EEG: repetitive spikes in centrotemporal area with normal background
- management: frequent seizures controlled by carbamazepine, no medication if infrequent seizures

General Approach to Treatment

- medication
  - initiate: treatment with drug appropriate to seizure type; often initiate anticonvulsants if >2 unprovoked afebrile seizures within 6-12 mo
  - optimize: start with one drug and increase dosage until seizures controlled
  - if no effect, switch over to another before adding a second antiepileptic
  - continue anticonvulsant treatment until patient free of seizures for >2 yr, then wean medications over 4-6 mo
- ketogenic diet (high fat diet): used in patients who do not respond to polytherapy or who do not wish to take medication (valproic acid contraindicated in conjunction with ketogenic diet because may increase hepatotoxicity)
- education for patient and parents including education and precautions in daily life (e.g. buddy system, showers instead of baths)
- legal obligation to report to Ministry of Transportation if patient wishes to drive

Generalized and Partial Seizures

- see Neurology, N14

Febrile Seizures

Epidemiology

- most common cause of seizure in children (3-5% of children)
- M>F; age 6 mo-6 yr

Clinical Presentation

- short (~1 min, always <5 min) generalized tonic-clonic seizure with short post-ictal state
- often with associated illness or fever and family history
- no evidence of CNS infection/inflammation before or after seizure; no history of non-febrile seizures

Ketogenic Diet and other Dietary Treatments for Epilepsy

Cochrane DB of Syst Rev 2012;3:CD001903

Study: Systematic review of all studies of ketogenic and related diets. Included the review of 4 RCTs, 6 prospective studies and 5 retrospective studies.

Population: Adults and children with diagnosed epilepsy of any type.

Intervention: Ketogenic diet, control (placebo diet, any treatment with known antiepileptic properties)

Main outcome measure: Seizure control at 3, 6, 12 mo.

Results: Studies showed a response rate of at least 38-50% seizure reduction at 3 mo. This response was maintained for up to a year. A range of side effects were reported. The most frequent were gastrointestinal effects (30%).

Conclusion: The ketogenic diet is a valid option for people with medically-intractable epilepsy.
Table 42. Comparison of Simple and Complex Febrile Seizures

<table>
<thead>
<tr>
<th>Simple/Benign (70-80%)</th>
<th>Complex/Atypical (20-30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration &lt;15 min (95% &lt;5 min)</td>
<td>Duration &gt;15 min</td>
</tr>
<tr>
<td>Generalized tonic-clonic</td>
<td>Focal onset or focal features during seizure</td>
</tr>
<tr>
<td>No recurrence in 24-h period</td>
<td>Recurrent seizures (&gt;1 in 24-h period)</td>
</tr>
<tr>
<td>No neurological impairment or developmental delay before or after seizure</td>
<td>Previous neurological impairment or neurological deficit after seizure</td>
</tr>
</tbody>
</table>

Workup
- history: determine focus of fever, description of seizure, medications, trauma history, development, family history
- exam: LOC, signs of meningitis, neurological exam, head circumference, focus of infection
- septic work-up including LP if suspecting meningitis (strongly consider if child <12 mo; consider if child is 12-18 mo; only if meningeal sign present if child >18 mo)
- if simple febrile seizure, investigations only for determining focus of fever
- EEG not warranted unless complex febrile seizure or abnormal neurologic findings

Management
- counsel and reassure patient and parents:
  - febrile seizures do not cause brain damage
  - very small risk of developing epilepsy: 9% in child with multiple risk factors (i.e. development or neurological abnormalities prior to seizure, family history of complex febrile seizure, multiple simple febrile seizure); 2% in child with febrile simple seizures compared to 1% in general population
  - 33% chance of recurrence (mostly within 1 yr of first seizure and in children <1 yr old)
  - antipyretics (e.g. acetaminophen) and fluids for comfort (though neither prevent seizure)
  - prophylaxis not recommended
  - if high risk for recurrent or prolonged seizures, have rectal or sublingual lorazepam at home
  - treat underlying cause of fever

Recurrent Headache
- see Neurology, N38

Differential Diagnosis
- primary headache: tension, migraine, cluster
- secondary headache: see Neurology, N39

General Assessment
- if unremarkable history and neurological and general physical exam is negative, most likely diagnosis is migraine or tension-type headache
- CT or MRI if history or physical reveals red flags
- inquire about level of disability, academic performance, after-school activities

MIGRAINE
- 4-5% of school aged children; F>M after puberty
- heterogeneous autosomal dominant inheritance with incomplete penetrance (majority of patients have a positive family history)

Types
- common (no aura): most common in children, often with intense nausea and vomiting
- classic (with aura)
- complicated: basilar, ophthalmoplegic, confusional, hemiplegic

Clinical Features
- infancy: spells of irritability, sleepiness, pallor, and vomiting
- young child: periodic headaches with nausea and vomiting that is relieved by rest
- older child: usually unilateral throbbing headaches with photophobia or phonophobia

Prognosis and Treatment
- >50% undergo spontaneous prolonged remission after 10 yr of age
- non-pharmacological treatment and prophylaxis: rest in quiet, dark room, avoid triggers (poor sleep, stress, chocolate, caffeine), biofeedback techniques, exercise, magnesium supplementation
- pharmacological treatment: early analgesia (e.g. ibuprofen), sumatriptan or other tryptans if >12 yr of age
- pharmacological prophylaxis: β-blockers (e.g. propranolol), antihistamines, antidepressants (e.g. amitriptyline/nortriptyline), calcium-channel blockers, anticonvulsants (e.g. divalproex sodium)
TENSION HEADACHES

Clinical Features
- usually bilateral pressing tightness (aching, non-throbbing) anywhere on the cranium
- building in intensity; lasting 30 min-days
- no nausea/vomiting, not aggravated by physical activity

Management
- reassurance, supportive counseling (e.g. explain how stress may cause a headache)
- rule out refractory errors in eyesight
- mild analgesia (NSAIDs, acetaminophen)

ORGANIC HEADACHES
- organic etiology often suggested with occipital headache especially in pre-school aged child and red flags (e.g. ataxia)
- with increased ICP
  - etiology: brain tumours, hydrocephalus, meningitis, encephalitis, cerebral abscess, pseudotumour cerebri, subdural hematoma
  - characteristics: diffuse early morning headaches, early morning vomiting, headache worsened by increased ICP (cough, sneeze, Valsalva); as ICP increases, headache is constant and child is lethargic and irritable
- without increased ICP
  - etiology: cerebral arteriovenous malformation (AVM), aneurysm, collagen vascular diseases, subarachnoid hemorrhage, stroke

Hypotonia
- decreased resistance to passive movements – “floppy baby”

Differential Diagnosis
- central
  - chromosomal (Down, Prader-Willi, Fragile X syndromes)
  - metabolic (hypoglycemia, kernicterus)
  - perinatal problems (asphyxia, ICH)
  - endocrine (hypothyroidism, hypopituitarism)
  - infections (TORCH)
  - CNS malformations
  - dysmorphic syndromes
- peripheral
  - motor neuron (e.g. spinal muscular atrophy, polio)
  - peripheral nerve (e.g. Charcot-Marie-Tooth syndrome)
  - neuromuscular junction (e.g. myasthenia gravis)
  - muscle fibres (e.g. mitochondrial myopathy, muscular dystrophy, myotonic dystrophy)

History and Physical
- proper assessment of tone requires accurate determination of gestational age
- differentiate between upper motor neuron from lower motor neuron signs; spontaneous posture (spontaneous movement, movement against gravity, frog-leg position); muscle weakness; joint mobility (hyperextensibility); muscle bulk, presence of fasciculations
- postural maneuvers:
  - traction response: pull to sit, look for flexion of arms to counteract traction and head lag
  - axillary suspension: suspend infant by holding at axilla and lifting; hypotonic babies will slip through grasp because of low shoulder girdle tone
  - ventral suspension: infant is prone and supported under the abdomen by one hand; infant should be able to hold up extremities; inverted “U” posturing demonstrates hypotonia, i.e. baby will drape self over examiner’s arms
- dysmorphic features, cognitive ability, reflexes, power

Investigations
- rule out systemic disorders (e.g. blood glucose, CK and serum/urine investigations for multiple etiologies including mitochondrial causes)
- neuroimaging: MRI/MRS when indicated
- EMG, muscle biopsy/NCS
- chromosome analysis, genetic testing, metabolic testing, neuromuscular testing

Treatment
- depends on etiology: some treatments available for specific diagnosis
- counsel parents on prognosis and genetic implications
- refer patients for specialized care, refer for rehabilitation, OT, PT, assess feeding ability
Cerebral Palsy (CP)

Definition
• a symptom complex, not a disease
• non-progressive central motor impairment syndrome due to insult to or anomaly of the immature CNS
• incidence: 1.5-2.5 per 1000 live births (industrialized nations)
• life expectancy is dependent on the degree of mobility and intellectual impairment, not on severity of CNS lesion

Etiology
• often obscure, no definite etiology identified in 1/3 of cases
• 10% related to intrapartum asphyxia; 10% due to postnatal insult (infections, asphyxia, prematurity with intraventricular hemorrhage and trauma)
• association with low birth weight babies

Clinical Presentation

Table 43. Types of Cerebral Palsy

<table>
<thead>
<tr>
<th>Type</th>
<th>% of Total CP</th>
<th>Characteristics</th>
<th>Area of Brain Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spastic</td>
<td>70-80%</td>
<td>Truncal hypotonia in 1st yr, Increased tone, increased reflexes, clonus</td>
<td>UMN of pyramidal tract</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Affects one limb (monoplegia), one side of body (hemiplegia), both legs (diplegia), both arms and legs (quadriplegia)</td>
<td>Diplegia associated with periventricular leukomalacia in premature babies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quadriplegia associated with HIE (asphyxia), associated with higher incidence of MR</td>
</tr>
<tr>
<td>Athetoid/Dyskinetic</td>
<td>10-15%</td>
<td>Athetosis (involuntary writhing movements), chorea (involuntary jerky movements); Can involve face, tongue (results in dysarthria)</td>
<td>Basal ganglia (may be associated with kernicterus)</td>
</tr>
<tr>
<td>Ataxic</td>
<td>&lt;5%</td>
<td>Poor coordination, poor balance (wide based gait), Can have intention tremor</td>
<td>Cerebellum</td>
</tr>
<tr>
<td>Mixed</td>
<td>10-15%</td>
<td>More than one of the above motor patterns</td>
<td></td>
</tr>
</tbody>
</table>

Other Signs
• uncoordinated swallowing \rightarrow aspiration
• microcephaly (25%)
• seizures
• mental retardation, learning disabilities
• delay in motor milestones
• visual, hearing impairment

Investigations
• may include metabolics, chromosome studies, serology, neuroimaging, EMG, EEG (if seizures), ophthalmology, audiology

Treatment
• maximize potential through multidisciplinary services such as primary care physician, OT, PT, SLP, school supports, etc.
• orthopedic management (e.g. dislocations, contractures, rhizotomy)
• management of symptoms: spasticity (baclofen, Botox®), constipation (stool softeners)

Neurocutaneous Syndromes

characterized by tendency to form tumours of the CNS, PNS, viscera and skin

Neurofibromatosis Type I (NF-1)
• autosomal dominant but 50% are the result of new mutations
• also known as von Recklinghausen disease
• incidence 1:3000, mutation in NF1 gene on 17q11.2 (codes for neurofibromin protein)
• learning disorders, abnormal speech development and seizures are common
• diagnosis of NF-1 requires 2 or more of:
  • ≥6 café-au-lait spots (>5 mm if prepubertal, >1.5 cm if postpubertal)
  • ≥2 neurofibromas of any type or one plexiform neurofibroma
  • ≥2 Lisch nodules (hamartomas of the iris)
  • optic glioma
  • freckling in the axillary or inguinal region
  • a distinctive bony lesion (e.g. sphenoid dysplasia, cortical thinning of long bones)
  • a first degree relative with confirmed NF-1

In neurocutaneous syndromes, the younger the child at presentation, the more likely they are to develop mental retardation.
**Neurofibromatosis Type II (NF-2)**
- autosomal dominant
- incidence 1:33,000
- characterized by predisposition to form intracranial, spinal tumours
- diagnosed when either bilateral vestibular schwannomas found, or a first-degree relative with NF-2 and either a neurofibroma, meningioma, glioma, or schwannoma
- also associated with posterior subcapsular cataracts
- treatment consists of monitoring for tumour development and surgery

**Sturge-Weber Syndrome**
- port-wine nevus syndrome in V1 distribution with associated angiomatous malformations of the brain causing contralateral hemiparesis and hemiatrophy
- also associated with seizure, glaucoma and mental retardation

**Tuberous Sclerosis**
- autosomal dominant inheritance; 50% new mutations
- adenoma sebaceum (angiokeratomas on face, often in malar distribution), Shagreen patch (isolated raised plaque over lower back, buttocks), “ash leaf” hypopigmentation seen with Wood’s lamp (UV light)
- cardiac rhabdomyomas, kidney angiomyolipoma, mental retardation and seizures
- cerebral cortex tubers (areas of cerebral dysplasia); subependymal nodules (SEN) may evolve into giant cell astrocytomas (may cause obstructive hydrocephalus)
- calcifications within the SEN are seen on CT, MRI (especially around the foramen of Monro)
  - these may obstruct the foramen and cause hydrocephalus

---

**Acute Disseminated Encephalomyelitis (ADEM)**

**Epidemiology**
- median age of onset 5-8 yr; male predominance
- annual incidence in North America is estimated to be 0.4 per 100,000 children <20 yr of age

**Pathophysiology**
- immune-mediated inflammatory disorder of the CNS; characterized by a widespread demyelination predominantly affecting the white matter of the brain and spinal cord (similar to multiple sclerosis)
- usually preceded by a viral infection or vaccination
- absence of clear precedent event has been reported in 26% of patients

**Clinical Presentation**
- often occurs 2 d to 4 wk after a clinically evident infection or vaccination
- clinical course is rapidly progressive, develops over hours to maximum deficits within days
- headache, nausea, vomiting, pyrexia, malaise
- rapid onset encephalopathy, multifocal deficits, seizures
- pyramidal syndrome, cerebellar ataxia, brainstem involvement

**Investigations**
- LP: CSF showing variable pleocytosis and oligoclonal banding
- MRI: large, multifocal, poorly marginated regions of demyelination affecting bilateral subcortical white matter, and deep grey matter (thalamus, basal ganglia); lesions show complete or partial resolution on follow-up, with absence of new clinically silent lesions

**Treatment**
- high dose corticosteroids and supportive measures

**Prognosis**
- favourable, though some residual deficits often exist
**Respirology**

**Approach to Dyspnea**

- see Table 1, *Average Vitals at Various Ages*, P3

![Diagram](https://via.placeholder.com/150)

**Upper Respiratory Tract Diseases**

- see *Otolaryngology*, OT44
- diseases above the thoracic inlet characterized by inspiratory stridor, hoarseness, and suprasternal retractions
- differential diagnosis of stridor: croup, bacterial tracheitis, epiglottitis, foreign body aspiration, subglottic stenosis (congenital or iatrogenic), laryngomalacia/tracheomalacia (collapse of airway cartilage on inspiration)

**Table 44. Common Upper Respiratory Tract Infections in Children**

<table>
<thead>
<tr>
<th></th>
<th>Croup (Laryngotracheobronchitis)</th>
<th>Bacterial Tracheitis</th>
<th>Epiglottitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomy</strong></td>
<td>Subglottic laryngitis</td>
<td>Subglottic tracheitis</td>
<td>Supraglottic laryngitis</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Common in children &lt;6 yr, with peak incidence between 7-36 mo Common in fall and early winter</td>
<td>Rare All age groups</td>
<td>Very rare – due to Hib vaccination Usually older (2-6 yr)</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Parainfluenza (75%) Influenza A and B RSV Adenovirus</td>
<td>S. aureus H. influenzae α-hemolytic strep Pneumococcus Moraxella catarrhalis</td>
<td>H. influenzae β-hemolytic strep</td>
</tr>
<tr>
<td><strong>Clinical Presentation</strong></td>
<td>Common Prodrome: rhinorrhea, pharyngitis, cough, ≤ low-grade fever Symptoms: Hoarse voice Barking cough Stridor Worse at night</td>
<td>Similar symptoms as croup but more rapid deterioration with high fever Toxic appearance Does not respond to croup treatments</td>
<td>Toxic appearance Rapid progression 4 Ds – drooling, dysphagia, distress Stridor Tripod position Sternal recession Anxious Fever (&gt;39°C)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Clinical diagnosis CXR in atypical presentation: &quot;steeple sign&quot; from subglottic narrowing</td>
<td>Clinical diagnosis Endoscopy: definitive diagnosis</td>
<td>Clinical diagnosis Avoid examining the throat to prevent further respiratory exacerbation</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>No evidence for humidified O₂ Dexamethasone: PO 1 dose Racemic epinephrine: nebulized, 1-3 doses, q1-2h Intubation if unresponsive to treatment</td>
<td>Usually requires intubation IV antibiotics</td>
<td>Intubation Antibiotics Prevented with Hib vaccine</td>
</tr>
</tbody>
</table>
Lower Respiratory Tract Diseases

- obstruction of airways below thoracic inlet, produces more expiratory sounds
- classic symptom: wheezing

Differential Diagnosis of Wheezing

- common
  - asthma: recurrent wheezing episodes, identifiable triggers; typically over 6 yr
  - bronchiolitis: first episode of wheezing; usually under 1 yr
  - recurrent aspiration: often neurological impairment
  - pneumonia: fever, cough, malaise
- uncommon
  - foreign body: acute unilateral wheezing and coughing
  - cystic fibrosis: prolonged wheezing, unresponsive to therapy
  - bronchopulmonary dysplasia: often develops after prolonged ventilation in the newborn
- rare
  - congestive heart failure
  - mediastinal mass
  - bronchiolitis obliterans
  - tracheobronchial anomalies

Pneumonia

Etiology
- inflammation of pulmonary tissue, associated with consolidation of alveolar spaces

Clinical Presentation
- incidence is greatest in first year of life with viral cause being most common in children <5 yr
- cough, wheeze, stridor
- CXR: diffuse, streaky infiltrates bilaterally
- bacterial causes may present with cough, fever, chills, dyspnea, more dramatic CXR changes (e.g. lobar consolidation, pleural effusion)

Management
- see Table 45
- supportive therapy: hydration, antipyretics, humidified O₂

<table>
<thead>
<tr>
<th>Age</th>
<th>Bacterial</th>
<th>Viral</th>
<th>Atypical Bacteria</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>GBS</td>
<td>CMV, Herpes virus</td>
<td>Mycoplasma hominis</td>
<td>ampicillin + gentamicin / tobramycin (add erythromycin if suspect Chlamydia)</td>
</tr>
<tr>
<td></td>
<td>E. coli</td>
<td>RSV, Influenza virus</td>
<td>Ureaplasma urealyticum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Listeria</td>
<td>Parainfluenza virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 months</td>
<td>S. aureus</td>
<td>CMV, RSV, RSV</td>
<td>Chlamydia trachomatis</td>
<td>cefuroxime OR ampicillin ± erythromycin OR clarithromycin</td>
</tr>
<tr>
<td></td>
<td>H. influenzae</td>
<td>Influenza virus</td>
<td>Ureaplasma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S. pneumoniaiae</td>
<td>Parainfluenza virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B. pertussis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months –</td>
<td>S. pneumoniaiae</td>
<td>RSV</td>
<td>M. pneumoniae, TB</td>
<td>amoxicillin (if mild) OR ampicillin OR cefuroxime</td>
</tr>
<tr>
<td>5 years</td>
<td>S. aureus</td>
<td>Adenovirus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H. influenzae</td>
<td>Influenza virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>S. pneumoniaiae</td>
<td>Influenza virus</td>
<td>Mycoplasma pneumoniae</td>
<td>erythromycin OR clarithromycin (1st line)</td>
</tr>
<tr>
<td></td>
<td>H. influenzae</td>
<td>Varicella</td>
<td>(most common)</td>
<td>OR ampicillin</td>
</tr>
<tr>
<td></td>
<td>S. aureus</td>
<td>Adenovirus</td>
<td>Chlamydia pneumoniae</td>
<td>OR cefuroxime</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TB</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Legionella pneumophila</td>
<td></td>
</tr>
</tbody>
</table>

Bronchiolitis

Definition
- LRTI that has wheezing and signs of respiratory distress

Epidemiology
- the most common LRTI in infants, affects 50% of children in first 2 yr of life; peak incidence at 6 mo, winter or early spring
- increased incidence of asthma in later life

Etiology
- respiratory syncytial virus (RSV) (>50%), parainfluenza, influenza, rhinovirus, adenovirus, M. pneumoniae (rare)
Clinical Presentation
- prodrome of URTI with cough and fever
- feeding difficulties, irritability
- wheezing, respiratory distress, tachypnea, tachycardia, retractions, poor air entry lasting for 5-6 d

Investigations
- CXR (only in severe disease, poor response to therapy, chronic episode)
  - air trapping, peribronchial thickening, atelectasis, increased linear markings
- nasopharyngeal swab
  - direct detection of viral antigen (immunofluorescence)
- WBC can be normal

Treatment
- self-limiting disease with symptoms usually lasting 2-3 wk
- mild distress
  - supportive: oral or IV hydration, antipyretics for fever, O₂
- moderate to severe distress
  - as above ± intubation and ventilation as needed
  - consider rebetol (Ribavirin®) in high risk groups: bronchopulmonary dysplasia, CHD, congenital lung disease, immunodeficient
- monthly RSV- Ig or palivizumab (monoclonal antibody against the F-glycoprotein of RSV) is protective against severe disease in high risk groups; case fatality rate <1%
- antibiotics have no therapeutic value unless there is secondary bacterial pneumonia
- indications for hospitalization:
  - hypoxia: O₂ saturation <92% on initial presentation
  - persistent resting tachypnea >60/min and retractions after several salbutamol masks
  - past history of chronic lung disease, hemodynamically significant cardiac disease, neuromuscular problem, immunocompromised
  - young infants <6 mo old (unless extremely mild)
  - significant feeding problems
  - social problem (e.g. inadequate care at home)

Asthma
Definition
- see Respirology, R6
- characterized by recurrent episodes of airway hyperreactivity, bronchospasm and inflammation; reversible small airway obstruction
- very common, presents most often in early childhood
- associated with other atopic diseases such as allergic rhinitis or atopic dermatitis

Clinical Presentation
- episodic bouts of wheezing, dyspnea, tachypnea, cough (usually at night/early morning, with activity or cold exposure)
- physical exam may reveal hyper-resonant chest, prolonged expiration, wheeze

Triggers
- URTI (viral or Mycoplasma), weather (cold exposure, humidity changes), allergens (pets), irritants (cigarette smoke), exercise, emotional stress, drugs (Aspirin®, β-blockers)

Classification
- mild asthma
  - occasional attacks of wheezing or coughing (<2/wk)
  - symptoms respond quickly to inhaled bronchodilator
  - never needs systemic corticosteroids
- moderate asthma
  - more frequent episodes with symptoms persisting and chronic cough
  - decreased exercise tolerance
  - sometimes needs systemic corticosteroids
- severe asthma
  - daily and nocturnal symptoms
  - frequent ER visits and hospitalizations
  - usually needs systemic corticosteroid

Bronchodilators for Bronchiolitis
- Cochrane DB Syst Rev 2010;12:CD001266
- Study: Meta-analysis of prospective, randomized, double-blinded, placebo-controlled trials.
- Patients: 1912 infants (28 trials) up to 24 mo old with bronchiolitis.
- Intervention: Bronchodilators (including albuterol, salbutamol, terbutaline, ipratropium bromide, and adrenergic agents) given oral, subcutaneous, or nebulized vs. placebo.
- Main outcome: Oxygen saturation.
- Results: No clinically significant difference for infants treated with bronchodilators vs. placebo for bronchiolitis. Given the costs and side effects it is not recommended to use bronchodilators as management for bronchiolitis in infants.
Management

- **acute**
  - \( O_2 \) (keep \( O_2 \) saturation >92%) and fluids if dehydrated
  - \( \beta_2 \)-agonists: salbutamol (Ventolin\(^\text{®}\)) 0.03 cc/kg (max 1 cc) in 3 cc NS q20min by mask until improvement, then masks hourly if necessary
  - ipratropium bromide (Atrovent\(^\text{®}\)) if severe: 1 cc added to each of first 3 salbutamol masks
  - steroids: prednisone (2 mg/kg in ER, then 1 mg/kg daily x 4 d) or dexamethasone (0.3 mg/kg/d); in severe disease, use IV steroids
  - continue to observe- can discharge patient if asymptomatic for 2-4 h after last dose

- **chronic**
  - education, emotional support, avoid allergens or irritants, develop an “action plan”
  - exercise program (e.g. swimming)
  - monitor respiratory function with peak flow meter (improves self-awareness of status)
  - PFTs for children >6 yr
  - reliever therapy: short acting \( \beta_2 \)-agonists (e.g. salbutamol)
  - controller therapy (first line therapy for all children): low dose daily inhaled corticosteroids
  - second line therapy for children <12 yr: moderate dose of daily inhaled corticosteroids
  - second line therapy for children >12 yr: antileukotriene OR long acting \( \beta_2 \)-agonist in conjunction with low dose inhaled corticosteroids
    - leukotriene receptor antagonist monotherapy may be considered an alternative second line therapy
  - severe asthma unresponsive to first and second line treatments injection immunotherapy
  - aerochamber for children using daily inhaled corticosteroids

- indications for hospitalization
  - pre-treatment \( O_2 \) saturation <92%
  - past history of life-threatening asthma (ICU admission)
  - unable to stabilize with masks q4h
  - concern over environmental issues or family’s ability to cope

Cystic Fibrosis (CF)

- see Respirology, R11

Etiology

- 1 per 3000 live births, mostly Caucasians
- autosomal recessive, \( CFTR \) gene found on chromosome 7 (\( \Delta F508 \) mutation in 70%, but >1600 different mutations identified) resulting in a dysfunctional chloride channel on the apical membrane of cells
- leads to relative dehydration of airway secretions, resulting in impaired mucociliary transport and airway obstruction
- in Ontario, CF is routinely screened in the newborn

Clinical Presentation

- neonatal
  - meconium ileus
  - prolonged jaundice
  - antenatal bowel perforation
- infancy
  - pancreatic insufficiency with steatorrhea and failure to thrive (despite voracious appetite)
  - anemia, hypoproteinemia, hyponatremia
- childhood
  - heat intolerance
  - wheezing or chronic cough
  - recurrent chest infections (\( S. \) aureus, \( P. \) aeruginosa, \( H. \) influenzae)
  - hemoptysis
  - nasal polyps
  - \( \beta_2 \) distal intestinal obstruction syndrome, rectal prolapse
  - clubbing of fingers
- older patients
  - chronic obstructive pulmonary disease
  - infertility (males); decreased fertility (female)

Investigations

- sweat chloride test x 2 (>60 mEq/L)
  - false positive tests: malnutrition, atopic dermatitis, hypothyroidism, hypoparathyroidism, glycogen storage disease type, adrenal insufficiency, G6PD, Klinefelter syndrome, technical issues, autonomic dysfunction, familial cholestasis syndrome
  - false negative tests: technical problem with test, malnutrition, skin edema, mineralocorticoids
Management
• nutritional counselling
  • high calorie diet, pancreatic enzyme replacements, fat soluble vitamin supplements
• management of chest disease
  • physiotherapy, postural drainage
  • exercise
  • bronchodilators
  • aerosolized DNAse and inhaled hypertonic saline
  • antibiotics: depends on sputum C&S (e.g. cephalosporin, cloxacillin, ciprofloxacin, inhaled tobramycin)
  • lung transplantation
• genetic counselling

Complications
• respiratory failure, pneumothorax (poor prognostic sign), cor pulmonale (late), pancreatic fibrosis with diabetes mellitus, gallstones, cirrhosis with portal hypertension, infertility (male)
• early death (current median survival in Canada is 46.6 yr)

Rheumatology

Evaluation of Limb Pain

Table 46. Differential Diagnosis of Limb Pain

<table>
<thead>
<tr>
<th>Cause</th>
<th>&lt;3 yr</th>
<th>3-10 yr</th>
<th>&gt;10 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trauma</strong></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient synovitis</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JIA</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Spondyloarthritis</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>HSP</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Anatomic/Orthopedic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legg-Calve-Perthes disease</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Slipped capital femoral epiphysis</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Osgood-Schlatter disease</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td><strong>Neoplastic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Bone tumour</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemophilia (hemarthrosis)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td><strong>Pain Syndromes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growing pains</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>

• must rule out infection, malignancy or an acute orthopedic condition

History
• limp/weight-bearing status
• morning stiffness
• systemic symptoms (fever, rash, weight loss, fatigue)
• past medical illness, intercurrent infection, travel, sick contact history
• family history (arthritis, bleeding disorders, sickle cell anemia, IBD, psoriasis)
Physical
• joint exam (swelling, erythema, warmth, tenderness, deformity, ROM)
• adjacent structures (bone, tendon, muscle, skin)
• gait
• leg length
• neurologic exam

Investigations
• basic: CBC and differential, blood smear, ESR, CRP, x-ray
• as indicated: blood (ANA, RF, culture, viral/bacterial serology, CK, PTT, sickle cell screen, immunoglobulins, complement), urinalysis, synovial fluid (cell count, Gram stain, culture), TB skin test, imaging, BM aspiration, slit lamp exam

Growing Pains
Epidemiology
• age 2-12 yr, M=F

Clinical Presentation
• diagnosis of exclusion
• intermittent, non-articular pain in childhood with normal physical exam findings
• pain at night, often limited to the calf, shin or thigh; typically short-lived and bilateral
• relieved by heat, massage, mild analgesics
• child is well, asymptomatic during the day, no functional limitation
• possible family history of growing pains

Management
• lab investigations not necessary if typical presentation; reassurance and supportive management

Transient Synovitis of the Hip
• benign, self limited disorder, usually occurs after upper respiratory tract infection, pharyngitis, otitis media

Epidemiology
• age 3-10 yr, M>F

Clinical Presentation
• afebrile or low-grade fever, pain typically occurs in hips, knees (referred from hip); painful limp but capable of moving hip through ROM (pain not as pronounced as in joint or bone infections)
• symptoms resolve over 7-10 d

Investigations
• WBC within normal limits; ESR and CRP may be mildly elevated
• joint effusions may be seen on imaging
• diagnosis of exclusion (r/o septic arthritis and osteomyelitis)

Treatment
• symptomatic and anti-inflammatory medications

Septic Arthritis

Table 47. Microorganisms Involved in Septic Arthritis/Osteomyelitis

<table>
<thead>
<tr>
<th>Age</th>
<th>Pathogens</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>GBS, S. aureus, GNB</td>
<td>cloxacillin + aminoglycoside or cefotaxime</td>
</tr>
<tr>
<td>Infant (1-3 mo)</td>
<td>Strep. sp., Staph. sp., H. influenzae; Pathogens as per neonate</td>
<td>cloxacillin + cefotaxime</td>
</tr>
<tr>
<td>Child</td>
<td>S. aureus, S. pneumoniae, GAS</td>
<td>cefazolin</td>
</tr>
<tr>
<td>Adolescent</td>
<td>As above; also N. gonorrhoeae</td>
<td>cefazolin</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>As above; also Salmonella</td>
<td>cefotaxime</td>
</tr>
</tbody>
</table>

GBS = group B Strep; GNB = Gram-negative bacilli; GAS = group A Strep

Adapted from Tse SML, Laxer RM. Pediatrics in Review 2006;27:170-179
Juvenile Idiopathic Arthritis (JIA)

- a heterogeneous group of conditions characterized by persistent arthritis in children <16 yr
- arthritis defined:
  1. joint swelling/effusion OR
  2. >2 of the following:
     - decreased range of motion
     - tenderness or pain on motion
     - increased warmth
- diagnosis
  - arthritis in ≥1 joint(s)
  - duration ≥6 wk
  - onset age <16 yr old
  - with exclusion of other causes of arthritis
  - classification defined by features/number of joints affected in the first 6 mo of onset

Systemic Arthritis (Still’s disease)

- onset at any age, M=F
- once or twice daily fever spikes (>38.5ºC) ≥2 wk; children usually acutely unwell during fever episodes
- extra-articular features: erythematous “salmon-coloured” maculopapular rash, lymphadenopathy, hepatosplenomegaly, leukocytosis, thrombocytosis, anemia, serositis
- arthritis may occur weeks to months later
- high ESR, CRP, WBC, platelet count

Oligoarticular Arthritis (arthritis of 1-4 joints)

- onset early childhood, F>M
- persistent: affects no more than 4 joints during the disease course
- extended: affects more than 4 joints after the first six months
- typically affects large joints: knees > ankles, elbows, wrists; hip involvement unusual
- ANA positive ~60-80%, rheumatoid factor (RF) negative
- screening eye exams for asymptomatic anterior uveitis (occurs in ~30%)
- complications: knee flexion contracture, quadriceps atrophy, leg-length discrepancy, growth disturbances

Polyarticular Arthritis (arthritis of 5 or more joints)

- RF negative
  - onset: 2-4 yr and 6-12 yr, F>M
  - symmetrical involvement of large and small joints of hands and feet, TMJ, cervical spine
- RF positive
  - onset: late childhood/early adolescence, F>M
  - similar to the aggressive form of adult rheumatoid arthritis
  - severe, rapidly destructive, symmetrical arthritis of large and small joints
  - may have rheumatoid nodules at pressure points (elbows, knees)
  - unremitting disease, persists into adulthood

Enthesitis-Related Arthritis

- onset: late childhood/adolescence, M>F
- arthritis and/or enthesitis
- weight bearing joints, especially hip and intertarsal joints
- risk of developing ankylosing spondylitis in adulthood

Psoriatic Arthritis

- onset: 2-4 yr and 9-11 yr, F>M
- arthritis and psoriasis OR arthritis and at least two of:
  - dactylitis, nail abnormalities, or family history of psoriasis in a 1st degree relative
  - asymmetric or symmetric small or large joint involvement

Undifferentiated

- arthritis of unknown cause that persists for 6 wk and either does not fulfill criteria for any category or fulfills criteria for more than one category

Management

- goals of therapy: eliminate inflammation, prevent joint damage, promote normal growth and development as well as normal function, minimize medication toxicity
- exercise to maintain range of motion (ROM) and muscle strength
- multidisciplinary approach: OT/PT, social work, orthopedics, ophthalmology, rheumatology
- 1st line drug therapy: NSAIDs, intra-articular corticosteroids
2nd line drug therapy:
- DMARDs: methotrexate, sulfasalazine, leflunamide
- corticosteroids: acute management of severe arthritis, systemic symptoms of JIA, topical eye drops for uveitis
- biologic agents

Reactive Arthritis

- see Rheumatology, RH23
- arthritis (typically the knee) follows bacterial infection especially with *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Chlamydia*, and most commonly *Streptococcus* (post-streptococcal reactive arthritis)
- typically resolves spontaneously
- may progress to chronic illness or Reiter's syndrome (urethritis, conjunctivitis)

Lyme Arthritis

- see Infectious Diseases, ID26
- caused by spirochete *Borrelia burgdorferi*
- incidence highest among 5-10 yr olds
- do not treat children <8 yr old with doxycycline (may cause permanent tooth discoloration)

Systemic Lupus Erythematosus (SLE)

- see Rheumatology, RH11
- autoimmune illness affecting multiple organ systems
- incidence 1 per 1000, more commonly age >10, F:M = 10:1
- childhood-onset SLE vs. adult-onset SLE:
  - children have more active disease
  - children are more likely to have renal disease
  - children receive more intensive drug therapy and sustain more damage

Vasculitides

HENOCHE-SCHÖNLEIN PURPURA (HSP)
- most common vasculitis of childhood, peak incidence 4-10 yr, M:F = 2:1
- vasculitis of small vessels
- often have history of URTI 1-3 wk before onset of symptoms

Clinical Presentation
- clinical triad: 1) palpable purpura, 2) abdominal pain, 3) arthritis
- skin: palpable, non-thrombocytopenic purpura in lower extremities and buttocks, edema, scrotal swelling
- joints: arthritis/arthritis involving large joints associated with painful edema
- GI: abdominal pain, GI bleeding, intussusception
- renal: microscopic hematuria, IgA nephropathy, proteinuria, hypertension, renal failure in <5%

Management
- mainly supportive
- anti-inflammatories for joint pain, corticosteroids for select patients
- monitor for protein on urinalysis every month for 6 mo, checking for renal disease, which may develop late (immunosuppressive therapy if severe)

Prognosis
- self-limited, resolves within 4 wk
- recurrence in about one third of patients
- long term prognosis dependent on severity of nephritis
KAWASAKI DISEASE
• acute vasculitis of unknown etiology (likely triggered by infection)
• medium-sized vasculitis with predilection for coronary arteries
• most common cause of acquired heart disease in children in developed countries
• peak age: 3 mo – 5 yr; Asians > Blacks > Caucasians

Diagnostic Criteria
• fever persisting 5 d or more AND
• 4 of the following features:
  1. bilateral conjunctival injection
  2. red infected fissured lips, strawberry tongue, injected pharynx
  3. changes of the peripheral extremities
     • acute phase: peripheral edema, peripheral erythema
     • subacute phase: peeling from tips of fingers and toes
  4. polymorphous rash
  5. cervical lymphadenopathy >1.5 cm in diameter
• exclusion of other diseases (e.g. scarlet fever, measles)
• atypical Kawasaki disease: less than 5 of 6 diagnostic features but coronary artery involvement

Management
• high (anti-inflammatory) dose of ASA while febrile
• low (anti-platelet) dose of ASA in subacute phase until platelets normalize or longer if coronary artery involvement
• IV immunoglobulin (2 g/kg) within 10 d of onset reduces risk of coronary aneurysm formation
• baseline 2D-ECHO and follow up periodic 2D-ECHO (usually at 6 wk)

Complications
• coronary artery vasculitis with aneurysm formation occurs in 20-25% of untreated children, <5% if receive IVIG within 10 d of fever
• 50% of aneurysms regress within 2 yr
• anticoagulation for multiple or large coronary aneurysms
• risk factors for coronary disease: male, age <1 or >9 yr, fever >10 d, Asian or Hispanic ethnicity, thrombocytopenia, hyponatremia

Common Medications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetaminophen (Tylenol®)</td>
<td>10-15 mg/kg/dose PO q4-6h prn</td>
<td>Analgesic, antipyretic</td>
<td>Not to exceed 60 mg/kg/d or 4 g/d Causes hepatotoxicity at high doses</td>
</tr>
<tr>
<td>amoxicillin (Amoxil®)</td>
<td>80-90 mg/kg/d PO divided q8h</td>
<td>Otitis media</td>
<td></td>
</tr>
<tr>
<td>dexamethasone</td>
<td>0.6 mg/kg PO x 1</td>
<td>Croup</td>
<td>Acute asthma</td>
</tr>
<tr>
<td>fluticasone (Flovent®)</td>
<td>moderate dose – 250-500 µg/d divided bid high dose – &gt;500 µg/d divided bid</td>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>ibuprofen (Advil®)</td>
<td>5-10 mg/kg/dose PO q6-8h</td>
<td>Analgesic, antipyretic</td>
<td>Cautious use in patients with liver impairment, history of GI bleeding or ulcers</td>
</tr>
<tr>
<td>iron</td>
<td>6 mg/kg/d elemental iron OD or divided bid</td>
<td>Anemia</td>
<td>SE: dark stool, constipation, dark urine</td>
</tr>
<tr>
<td>omeprazole</td>
<td></td>
<td>GERD</td>
<td>SE: headache, diarrhea, nausea, abdominal pain</td>
</tr>
<tr>
<td>ondansetron</td>
<td></td>
<td>Post-op nausea and vomiting, gastroenteritis, cyclic vomiting</td>
<td>SE: QTc prolongation, orally disintegrating tablets contain phenylalanine (caution in phenylketonuria patients)</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>3-5 mg/kg/d PO OD or bid</td>
<td>Seizures</td>
<td>SE: CNS depression</td>
</tr>
<tr>
<td>polyethylene glycol 3350 (PEG)</td>
<td></td>
<td>Disimpaction: 1-1.5 g/kg/d for 3 d Maintenance: Starting dose at 0.4-1 g/kg</td>
<td></td>
</tr>
</tbody>
</table>
Table 48. Commonly Used Medications in Pediatrics (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>prednisone</td>
<td>1-2 mg/kg/d PO</td>
<td>Asthma</td>
<td>Oral prednisone is bitter tasting, consider using prednisolone</td>
</tr>
<tr>
<td>prednisolone</td>
<td>3-4 mg/kg/d PO</td>
<td>ITP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>then taper to 1-2 mg/kg/d PO once platelet count &gt; 30 x 10^9/L</td>
<td>Nephrotic syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60 mg/m²/d PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>salbutamol (Ventolin®)</td>
<td>0.01-0.03 mL/kg/dose in 3 mL normal saline via nebulizer q4h</td>
<td>Acute asthma</td>
<td>Can cause tachycardia, hypokalemia, restlessness</td>
</tr>
<tr>
<td></td>
<td>100-200 µg/dose pm, max 4-8 puffs frequency q4h</td>
<td>Maintenance treatment or asthma</td>
<td></td>
</tr>
</tbody>
</table>

References

Cardiology
Garc L. Sinus tachycardia. UpToDate, 2012.

Endocrinology

Gastroenterology

General Topics
Hospital for Sick Children handbook of pediatric emergency medicine. Sudbury: Jones and Bartlett, 2008.
Publicly funded immunization schedules for Ontario. August 2011.

Genetic Disorders and Developmental Disorders
Blake KD, Prasad C. CHARGE syndrome, orphenet. J Rare Diseases 2006;1.

Hematology

Infectious Disease and Immunizations
References


Neonatology

Neurology

Pharmacology

Respiratory

Rheumatology

Web-based Resources
Available from: http://www.cda-adc.ca.
Available from: http://www.abouitchdshelth.ca.
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acronyms</td>
<td>2</td>
</tr>
<tr>
<td>Basic Anatomy Review</td>
<td>2</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td></td>
</tr>
<tr>
<td>Brachial Plexus</td>
<td></td>
</tr>
<tr>
<td>Face</td>
<td></td>
</tr>
<tr>
<td>Skin Lesions and Masses</td>
<td>5</td>
</tr>
<tr>
<td>DDx of Skin Lesions/Masses</td>
<td></td>
</tr>
<tr>
<td>Surgical Management of Malignant Skin Lesions</td>
<td></td>
</tr>
<tr>
<td>Basic Surgical Techniques</td>
<td>6</td>
</tr>
<tr>
<td>Sutures and Suturing</td>
<td></td>
</tr>
<tr>
<td>Excision</td>
<td></td>
</tr>
<tr>
<td>Skin Biopsy Types and Techniques</td>
<td></td>
</tr>
<tr>
<td>Wounds</td>
<td>8</td>
</tr>
<tr>
<td>Causal Conditions</td>
<td></td>
</tr>
<tr>
<td>Principles of Wound Healing</td>
<td></td>
</tr>
<tr>
<td>Contaminated and Infected Wounds</td>
<td></td>
</tr>
<tr>
<td>Dressings</td>
<td></td>
</tr>
<tr>
<td>Reconstruction</td>
<td></td>
</tr>
<tr>
<td>Soft Tissue Infections</td>
<td>14</td>
</tr>
<tr>
<td>Erysipelas</td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td></td>
</tr>
<tr>
<td>Necrotizing Fasciitis</td>
<td></td>
</tr>
<tr>
<td>Ulcers</td>
<td>15</td>
</tr>
<tr>
<td>Lower Limb Ulcers</td>
<td></td>
</tr>
<tr>
<td>Pressure Ulcers</td>
<td></td>
</tr>
<tr>
<td>Burns</td>
<td>16</td>
</tr>
<tr>
<td>Burn Injuries</td>
<td></td>
</tr>
<tr>
<td>Pathophysiology of Burn Wounds</td>
<td></td>
</tr>
<tr>
<td>Diagnosis and Prognosis</td>
<td></td>
</tr>
<tr>
<td>Indications for Transfer to Burn Centre</td>
<td></td>
</tr>
<tr>
<td>Acute Care of Burn Patients</td>
<td></td>
</tr>
<tr>
<td>Special Considerations</td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>22</td>
</tr>
<tr>
<td>Traumatic Hand</td>
<td></td>
</tr>
<tr>
<td>General Management</td>
<td></td>
</tr>
<tr>
<td>Hand Infections</td>
<td></td>
</tr>
<tr>
<td>Amputations</td>
<td></td>
</tr>
<tr>
<td>Tendons</td>
<td></td>
</tr>
<tr>
<td>Fractures and Dislocations</td>
<td></td>
</tr>
<tr>
<td>Dupuytren's Disease</td>
<td></td>
</tr>
<tr>
<td>Carpal Tunnel Syndrome</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid Hand</td>
<td></td>
</tr>
<tr>
<td>Brachial Plexus</td>
<td>28</td>
</tr>
<tr>
<td>Craniofacial Injuries</td>
<td>28</td>
</tr>
<tr>
<td>Approach to Facial Injuries</td>
<td></td>
</tr>
<tr>
<td>Mandibular Fractures</td>
<td></td>
</tr>
<tr>
<td>Maxillary Fractures</td>
<td></td>
</tr>
<tr>
<td>Nasal Fractures</td>
<td></td>
</tr>
<tr>
<td>Naso-orbital Ethmoid Fractures</td>
<td></td>
</tr>
<tr>
<td>Zygomatic Fractures</td>
<td></td>
</tr>
<tr>
<td>Orbital Floor Fractures</td>
<td></td>
</tr>
<tr>
<td>Breast Surgery</td>
<td>32</td>
</tr>
<tr>
<td>Breast Reconstruction</td>
<td></td>
</tr>
<tr>
<td>Breast Tissue Expanders</td>
<td></td>
</tr>
<tr>
<td>Breast Reduction</td>
<td></td>
</tr>
<tr>
<td>Aesthetic Surgery</td>
<td>33</td>
</tr>
<tr>
<td>Aesthetic Procedures</td>
<td></td>
</tr>
<tr>
<td>Pediatric Plastic Surgery</td>
<td>34</td>
</tr>
<tr>
<td>Craniofacial Anomalies</td>
<td></td>
</tr>
<tr>
<td>Congenital Hand Anomalies</td>
<td></td>
</tr>
<tr>
<td>References</td>
<td>35</td>
</tr>
</tbody>
</table>
**Basic Anatomy Review**

### Skin

![Split and full (whole) thickness skin grafts](image)

1. **Thin**
2. **Medium**
3. **Thick**

**Epidermis**
- Upper (papillary)

**Dermis**
- Lower (reticular)

**Subcutaneous tissue**

**BONES AND NERVES**

1. Radius
2. Scaphoid
3. Trapeziun
4. Trapezoid
5. Capitate
6. Ulna
7. Lunate
8. Pisiform
9. Triquetrum
10. Hamate
11. Metacarpal bones

**Hand**

![Carpal bones](image)

![Sensory distribution in the hand](image)

**Acronyms**

- ABI: ankle-brachial index
- APL: abductor pollicis longus
- ATLS: advanced trauma life support
- BMR: basal metabolic rate
- CMC: carpo-metacarpal
- CVD: cerebrovascular disease
- CSF: cerebrospinal fluid
- D5W: 5% dextrose in water
- DIP: distal interphalangeal joint
- DIP: distal interphalangeal joint
- DM: diabetes mellitus
- EPB: extensor pollicis brevis
- EMG: electromyography
- ENT: ear, nose, throat
- EDM: extracranial movement
- FTSG: full thickness skin graft
- GBS: group B Streptococcus
- HBA: hypertension
- HTN: hypertension
- IGAP: inferior gluteal artery perforator
- I&D: incision and drainage
- ICP: intracranial pressure
- IP: interphalangeal
- MCV: metacarpal phalangeal joint
- MCP: metacarpal phalangeal joint
- NS: normal saline
- NSADs: nonsteroidal anti-inflammatory drugs
- OM: otitis media
- ORIF: open reduction internal fixation
- PIP: proximal interphalangeal joint
- PIP: proximal interphalangeal joint
- PVD: peripheral vascular disease
- RA: rheumatoid arthritis
- RL: Ringer’s lactate
- RMM: range of motion
- SGAP: superior gluteal artery perforator
- SIAH: syndrome of inappropriate antidiuretic hormone
- SIEA: superficial inferior epigastric artery
- SLP: speech language pathology
- SDF: superior orbital fissure
- STSG: split thickness skin graft
- TMJ: temporomandibular joint
- TRAM: transverse rectus abdominus myocutaneous
- UCL: ulnar collateral ligament
- UV: ultraviolet

**Supplied mainly by C**

**Supplied mainly by D**

- A: Superficial palmar arch
- B: Deep palmar arch
- C: Ulnar artery
- D: Radial artery
TENDONS

Figure 5. Flexor tendon insertion at PIP and DIP

Figure 6. Extensor mechanism of digits

Figure 7. Carpal tunnel

Figure 8. Extensor compartments of the wrist (dorsal view and cross-sectional view)

1. Extensor retinaculum
2. Palmar longus tendon
3. Ulnar artery
4. Extensor pollicis brevis
5. Extensor carpi radialis longus
6. Extensor pollicis longus (EPL tendon passes around Lister’s tubercle)
7. Extensor digiti minimi
8. Extensor indicis
9. Abductor pollicis longus
10. Extensor carpi ulnaris

Carpal Bone Mnemonic
- So (Scaphoid)
- Long (Lunate)
- To (Triquetrum)
- Pinky (Pisiform)
- Here (Hamate)
- Comes (Capitate)
- The (Trapezium)
- Thumb (Trapezoid)

Flexor Tendons
All require OR repair.

Extensor Tendons
ER repair unless proximal/multiple tendons.
Brachial Plexus

Figure 9. Brachial plexus anatomy

Face

Figure 10. Skull and facial bones
**Skin Lesions and Masses**

**DDx of Skin Lesions/Masses**

- for background information and medical management, see *Dermatology*
- for biopsy techniques, see PL7

**Surgical Management of Malignant Skin Lesions**

- surgical treatment for all malignant skin lesions involve total excision of the primary lesion
- excision margin of lesion depends on the diameter and depth
- for decisions regarding reconstruction using flaps or skin grafts, see *Reconstruction*, PL11

**Precursors of Malignant Lesions**

<table>
<thead>
<tr>
<th>Basal Cell Carcinoma</th>
<th>Squamous Cell Carcinoma</th>
<th>Malignant Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>No known precursor</td>
<td>Actinic keratosis</td>
<td>Dysplastic nevus</td>
</tr>
<tr>
<td></td>
<td>Bowen’s disease</td>
<td>Lentigo maligna</td>
</tr>
<tr>
<td></td>
<td>Bowenoid papulosis</td>
<td>Giant congenital nevus</td>
</tr>
<tr>
<td></td>
<td>Paget’s disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukoplakia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erythroplasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Surgical Margins**

**Table 2. Surgical Margins for Basal Cell Carcinoma**

<table>
<thead>
<tr>
<th>Diameter of Lesion</th>
<th>Surgical Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 cm or less</td>
<td>3 mm</td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>5 mm</td>
</tr>
</tbody>
</table>

**Table 3. Surgical Margins for Squamous Cell Carcinoma**

<table>
<thead>
<tr>
<th>Diameter or Location of Lesion</th>
<th>Surgical Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 cm or less *</td>
<td>4 mm *</td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>6 mm</td>
</tr>
<tr>
<td>High risk (facial)</td>
<td>6 mm</td>
</tr>
<tr>
<td>Low risk (elsewhere)</td>
<td>4 mm</td>
</tr>
</tbody>
</table>

*For a high risk lesion that is <2 cm in diameter, use a 6 mm margin
Table 4. Surgical Margins for Malignant Melanoma

<table>
<thead>
<tr>
<th>Depth of Lesion</th>
<th>Surgical Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>0.5 cm</td>
</tr>
<tr>
<td>&lt;1 mm</td>
<td>1 cm</td>
</tr>
<tr>
<td>1.01-1.99 mm</td>
<td>1-2 cm</td>
</tr>
<tr>
<td>≥2 mm</td>
<td>2 cm</td>
</tr>
</tbody>
</table>

Basic Surgical Techniques

Sutures and Suturing

ANESTHESIA
- debride and irrigate before injecting anesthetic
- toxicity of mixtures (i.e. lidocaine + bupivicaine) is no greater than its individual components

Table 5. Toxic Limit and Duration of action (1 cc of 1% solution contains 10 mg lidocaine)

<table>
<thead>
<tr>
<th></th>
<th>Without Epinephrine</th>
<th>With Epinephrine (vasoconstrictor, limits bleeding)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine (Xylocaine®)</td>
<td>5 mg/kg, lasts 45-60 min</td>
<td>7 mg/kg, lasts 2-6 h</td>
</tr>
<tr>
<td>Bupivicaine (Marcaine®)</td>
<td>2 mg/kg, lasts 2-4 h</td>
<td>3 mg/kg, lasts 3-7 h</td>
</tr>
</tbody>
</table>

IRRIGATION AND DEBRIDEMENT
- irrigate copiously with a physiologic solution such as Ringer’s lactate or normal saline to remove surface clots, foreign material, and bacteria
- debride all obviously devitalized tissue, irregular or ragged wounds must be excised to produce sharp wound edges that will assist healing when approximated

SUTURES
- use of a particular suture material is highly dependent on surgeon preference. However, skin should be closed with a non absorbable when trauma
- suture material divided by two categories (see Table 6)

Table 6. Suture Materials: Absorbable vs. Non-absorbable and Monofilament vs. Multifilament

<table>
<thead>
<tr>
<th>Suture Materials</th>
<th>Uses</th>
<th>Examples</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorbable</td>
<td>Deep sutures under short-term tension</td>
<td>Plain gut®, Vicryl®, Polysorb®</td>
<td>loses at least 50% of their strength in 4 wk; eventually absorbed</td>
</tr>
<tr>
<td></td>
<td>Skin closure in children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-absorbable</td>
<td>Skin closure</td>
<td>Nylon, polypropylene, stainless steel</td>
<td>Lower likelihood of wound dehiscence</td>
</tr>
<tr>
<td></td>
<td>Sites of long term tension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monofilament</td>
<td>Contaminated and infected wounds (lower likelihood of bacterial trapping in suture material)</td>
<td>Monosof®, Monocryl®, Biosyn®</td>
<td>Slides through tissue with less friction; more memory/stiffness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifilament</td>
<td>AVOID in contaminated wounds (increased likelihood of bacterial trapping)</td>
<td>Vicryl® and Silk</td>
<td>Less memory/stiffness thus easier to work with</td>
</tr>
</tbody>
</table>

Steps to Ensuring Good Suturing

Cosmesis:
- Incisions should be made along relaxed skin tension lines
- Attain close apposition of wound edges
- Minimize tension on skin by closing in layers
- Evert wound edges
- Use appropriately sized suture for skin closure (5-0, 6-0 on face; 3-0, 4-0 elsewhere)
- Ensure equal width and depth of tissue on both sides
- Remove sutures within 5-7 d from the face, 10-14 d from scalp/torsq/ extremities

Basic Suturing Techniques

Basic Suture Methods (Figure 12)
- simple interrupted: can be used in almost all situations
- sub-cuticular: good cosmetic result but weak, used in combination with deep sutures; not used in trauma
- vertical mattress: for areas difficult to evert (e.g. dorsum of the hand)
- horizontal mattress: evertting, time saving
- continuous over and over (aka “running”, “baseball stitch”): time saving, good for hemostasis

Basic Principles
- minimize tissue trauma: follow curve of needle, handle wound edges gently (use toothed forceps), use just enough tension to approximate edges (do not strangulate)
- use the finest needle and suture possible
- ensure good cosmesis (see sidebar)
Other Skin Closure Materials

- tapes: may be indicated for superficial wounds and those with opposable edges. Tape cannot be used on actively bleeding wounds. When placed across the incision, will prevent surface marks and can be used primarily or after surface sutures have been removed. Tape burns may occur if there is excessive tension or swelling around the incision
- skin adhesives: e.g. 2-octylcyanoacrylate (e.g. Dermabond®) works well on small areas without much tension or shearing. May cause irreversible tattooing
- staples: steel-titanium alloys that incite minimal tissue reaction (healing is comparable to wounds closed by suture)

Excision

- incise along relaxed skin tension lines to minimize appearance of scar (Figure 13)
- use elliptical incision to prevent “dog ears” (heaped up skin at end of incision)
- if needed, undermine skin edges to decrease wound tension
- use layered closure including dermal sutures when wound is deeper than superficial (decreases tension)

Skin Biopsy Types and Techniques

SHAVE BIOPSY
- used for superficial lesions where sampling of the full thickness of the dermis is not necessary
- most suitable lesions for shave biopsies are either elevated above the skin or have pathology confined to the epidermis (e.g. seborrheic or actinic keratoses, skin tags, warts, and superficial basal cell or squamous cell carcinomas)
- rapid, requires little training, and does not require sutures for closure
- should not be used for pigmented lesions – an unsuspected melanoma cannot be properly staged if partially removed

PUNCH BIOPSY
- involves the removal of a core-shaped piece of tissue, performed with round, disposable knives ranging in diameter from 2 to 10 mm
- allows sampling of the deep dermis
- can be used for the diagnosis and treatment of small pigmented lesions and atypical moles
- punch biopsy wounds can be closed with suture or left to heal by secondary intention. Punches greater than 3 mm may produce scarring and are best closed with one or two sutures
- has low incidence of infection, bleeding, nonhealing, significant scarring

EXCISIONAL BIOPSY
- performed for lesions that require complete removal for diagnostic or therapeutic purposes
- performed for lesions that cannot be adequately punch biopsied due to size, depth, or location
- requires the greatest amount of expertise and time
- always requires sutures for closure

TECHNIQUE

General
- all biopsies performed in clinic are done using aseptic technique, but are not sterile
- sterile gloves are indicated for biopsies and excisions in all patients

Preparing the Site
- common skin antiseptics (betadine, chlorhexidine) can be used to prepare the biopsy site
- chlorhexidine is used in concentrations ranging from 0.5-4%. This higher concentration cannot be used on the face as it could get into the eyes and may burn or cause damage
- mark the intended lesion and surgical margins with a surgical marker since they may be temporarily obliterated following injection of the anesthetic
- for all biopsies, a sterile drape technique is indicated. A fenestrated surgical drape is placed around the biopsy site after the area is cleansed and anesthetized

Anesthesia
- most commonly used local anesthetic is 1% or 2% lidocaine
- small amounts of epinephrine are added to constrict blood vessels, decrease bleeding, prolong anesthesia, and limit lidocaine toxicity. The local with epinephrine can be injected directly into the lesion
- local anesthetics with epinephrine may be used anywhere in the body including the digits
- epinephrine should be avoided in patients with history of vascular compromise
- a field block should be performed for larger lesions by placing a ring of anesthetic around the surgical site, advancing and injecting through a site that has been previously anesthetized
Wounds

Causal Conditions

- laceration: cut or torn tissue
- abrasion: superficial skin layer is removed, variable depth
- contusion: injury caused by forceful blow to the skin and soft tissue; entire outer layer of skin intact yet injured
- avulsion: tissue/limb forcefully separated from surrounding tissue, either partially or fully; “de-gloving”
- puncture wounds: opening relatively small as compared with depth (e.g. needle)
  - includes bite wounds
- crush injuries: caused by compression
- thermal and chemical wounds

Principles of Wound Healing

- wound: disruption of the normal anatomical relationships of tissue as a result of injury

STAGES OF WOUND HEALING

- see Figure 14
- growth factors released by tissues play an important role
- scar is mature once it has completed the final stage

FACTORS INFLUENCING WOUND HEALING

Local (reversible/controllable):
- mechanical (local trauma, tension)
- blood supply (ischemia/circulation)
- temperature
- technique and suture materials
- retained foreign body
- infection
- hematoma/seroma (↑ infection rate)
- venous hypertension
- peripheral vascular disease

General (often irreversible):
- age
- nutrition (protein, vitamin C, O₂)
- smoking
- chronic illness (e.g. diabetes, cancer, CVD)
- immunosuppression (steroids, chemo, radiation)
- collagen vascular disease
- tissue irradiation
- retained foreign body
- tissue irradiation
- infection
- hematoma/seroma (↑ infection rate)
- chronic illness (e.g. diabetes, cancer, CVD)
- immunosuppression (steroids, chemo, radiation)
- collagen vascular disease
- tissue irradiation
- retained foreign body
- tissue irradiation
- infection

PHASE | PROCESS
--- | ---
1. Inflammatory Phase (Reactive) (Days 1-6) | 1. Hemostasis – vasoconstriction + platelet plug
- Limits damage, prevents further injury
- Debris and organisms cleared via inflammatory response:
  - Neutrophils (24-48 h)
  - Macrophages: critical to wound healing by orchestrating growth factors for collagen production (48-96 h)
  - Lymphocytes: role poorly defined (5-7 d)
2. Proliferative Phase (Regenerative) (Day 4 – Week 3) | 1. Collagen synthesis (mainly type III)
2. Angiogenesis
3. Epithelialization
- Fibroblasts attracted and activated by macrophage growth factors
- Reparative process: re-epithelialisation, matrix synthesis, angiogenesis (relieves ischemia)
- Tensile strength begins to increase at days 4-5
3. Remodeling Phase (Maturation) (Week 3 – 1 year) | 1. Contraction
2. Scarring
3. Remodeling of scar
- Increasing collagen organization and stronger crosslinks
- Type I collagen replaces Type III until normal 4:1 ratio achieved
- Peak tensile strength at 60 d – 80% of preinjury strength

Figure 14. Stages of wound healing

Myofibroblasts are the cells responsible for wound contraction. They do this at a rate of less than 0.75 mm/d.
ABNORMAL HEALING

Hypertrophic Scar
• scar remains roughly within boundaries of original injury
• red, raised, widened, frequently pruritic
• common sites: back, shoulder, sternum
• treatment: pressure garments, silicone gel sheeting, corticosteroid injection, surgical excision if other options fail (however, may still recur), typically improves with time

Keloid Scar
• scar extends beyond boundaries of original injury
• frequently pruritic, often painful; collagen in whorls rather than bundles
• common sites: sternum, deltoid, earlobe; more common in darker skinned people
• treatment: pressure garments, silicone gel sheeting, corticosteroid injection, radiation therapy ± surgical excision as a last resort

Chronic Wound
• fails to heal primarily within 4-6 wk
• common chronic wounds include diabetic, pressure and venous stasis ulcers
• treatment: may heal with meticulous wound care; may also require surgical intervention
• Marjolin's ulcer: squamous cell carcinoma arising in a chronic wound secondary to genetic changes caused by chronic inflammation → consider biopsy of chronic wound

WOUND CLOSURE

Primary (1°) Closure (First Intention)
• definition: wound closure by direct approximation of edges within hours of wound creation (i.e. with sutures, staples, skin graft, etc.)
• indication: recent (<6 h, longer with facial wounds), clean wounds
• contraindications: animal/human bites (except on face), crush injuries, infection, long time lapse since injury (>6-8 h), retained foreign body

Secondary (2°) Closure/Spontaneous Healing (Second Intention)
• definition: wound left open to heal spontaneously (epithelialization 1 mm/d from wound margins in concentric pattern), contraction (myofibroblasts) and granulation – maintained in inflammatory phase until wound closed; requires dressing changes; inferior cosmetic result
• indication: when 1° closure not possible or indicated (see Primary Closure, above)

Tertiary (3°) Closure/Delayed Primary Closure (Third Intention)
• definition: intentionally interrupt healing process (e.g. with packing), then wound can be closed at 4-10 d post-injury after granulation tissue has formed and there is <10^6 bacteria/gram of tissue
• indication: contaminated (high bacterial count), long time lapse since initial injury, severe crush component with significant tissue devitalization
• prolongation of inflammatory phase decreases bacterial count and lessens chance of infection after closure

Contaminated and Infected Wounds

Definitions
• contamination: the presence of non-replicating microorganisms within a wound
• colonization: the presence of replicating microorganisms within a wound
• infection: greater than 10^5 microorganisms in a wound without intact epithelium, a wound may also be infected with small amounts of a very virulent organism (e.g. GBS)

Management of Acute Contaminated Wound (<24 h)
• cleanse and irrigate open wound with physiologic solution (NS or RL)
• evaluate for injury to underlying structures (vessels, nerve, tendon and bone)
• control active bleeding
• debridement: removal of foreign material, devitalized tissue, old blood
  • surgical debridement: blade and irrigation if indicated
• systemic antibiotics are commonly indicated for obvious infection, wound older than 8 h, severely contaminated, immunocompromised, involvement of deeper structures (e.g. joints, fractures)
• ± tetanus toxoid 0.5 mL IM ± tetanus immunoglobulin 250 U deep IM (see Table 7 and Table 8)
• ± post-exposure treatment of
  • hepatitis B, HIV, hepatitis C (if titres confirmed at 6 mo)

Risk Factors for Infection
• Virulence of the infecting microorganism
• Amount of bacteria present
• Host resistance
• re-evaluate in 24-48 h for signs of deep infection
  ▪ open infected portion of wound by removing sutures if evidence of infection (i.e. erythema, warmth, pain, discharge)

### Table 7. Risks for Tetanus

<table>
<thead>
<tr>
<th>Wound Characteristics</th>
<th>Tetanus-Prone</th>
<th>Not Tetanus-Prone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since injury</td>
<td>&gt;6 h</td>
<td>&lt;6 h</td>
</tr>
<tr>
<td>Depth of injury</td>
<td>&gt;1 cm</td>
<td>&lt;1 cm</td>
</tr>
<tr>
<td>Mechanism of Injury</td>
<td>Crush, burn, gunshot, frostbite, puncture through clothing, farming injury</td>
<td>Sharp cut (e.g. clean knife, clean glass)</td>
</tr>
<tr>
<td>Devitalized tissue</td>
<td>Present</td>
<td>Not present</td>
</tr>
<tr>
<td>Contamination (e.g. soil, dirt, saliva, grass)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Retained foreign body</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

### Table 8. Tetanus Immunization Recommendations

<table>
<thead>
<tr>
<th>History of Tetanus Immunization</th>
<th>Clean, Minor Wounds</th>
<th>All Other Wounds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Td or Tdap*</td>
<td>Tdap**</td>
</tr>
<tr>
<td>Uncertain or &lt;3 doses of immunization</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3 doses received in immunization series</td>
<td>No~</td>
<td>No</td>
</tr>
</tbody>
</table>

* 0.5 mL of combined tetanus and diphtheria toxoids ± acellular pertussis
** Tetanus immune globulin, 250 U given at a separate site from Td/Tdap
~ Yes, if >10 yr since last booster
§ Yes, if >5 yr since last booster

**Management of Contaminated Wounds (>24 h, including ulcers)**

- irrigation and debridement
  ▪ traumatic tattooing can occur if foreign materials left in wound
- systemic antibiotics indicated if there is concern of infection (e.g. redness, swelling, pain, clinically unwell)
- topical antimicrobials: beneficial for minor wounds, but no additional benefit for wounds requiring systemic antibiotics. May aid in healing of chronic wounds
- closure: final closure via secondary intention (most common), delayed wound closure (3º closure), skin graft or flap; successful closure depends on bacterial count of ≤10⁵/cm³ prior to closure and frequent dressing changes

**BITES**

- see [Emergency Medicine, ER46](#)

**Dog and Cat Bites**

- pathogens: *Pasteurella multocida, S. aureus, S. viridans*
- investigations: same as for human bites; see below
- treatment: Clavulin® (500 mg PO q8h started immediately – amoxicillin + clavulanic acid)
  ▪ consider rabies prophylaxis if animal has symptoms of rabies or unknown animal
  ▪ ± rabies lg (20 IU/kg around wound, or 1M) and 1 of the 3 types of rabies vaccines
    (1.0 mL IM in deltoid, repeat on days 3, 7, 14, 28)
  ▪ aggressive irrigation with debridement
  ▪ healing by secondary intention is mainstay of treatment
  ▪ only consider primary closure for bite wounds on the face; otherwise primary closure is contraindicated
  ▪ contact Public Health if animal status unknown

**Human Bites**

- pathogens: *Staphylococcus > α-hemolytic Streptococcus > Eikenella corrodens > Bacteroides*
- mechanism: most commonly over dorsum of MCP from a punch in mouth; “fight-bite”
- serious, as mouth has 10⁹ microorganisms/mL, which get trapped in joint space when fist unclenches and overlying skin forms an air-tight covering ideal for anaerobic growth – can lead to septic arthritis
- investigations:
  ▪ radiographs prior to therapy to rule out foreign body (e.g. tooth) or fracture
  ▪ culture for aerobic and anaerobic organisms, Gram stain
- treatment:
  ▪ urgent surgical exploration of joint, drainage and debridement of infected tissue
  ▪ wound must be copiously irrigated
  ▪ Clavulin® 500 mg PO q8h, clindamycin 300 mg PO q6h + ciprofloxacin 500 mg PO q12h (if allergic to penicillin) + secondary closure
  ▪ splint
Dressings

- there is no one dressing for any given type of wound. Dressing selection depends on the wound characteristics
  - as the wound progresses through healing it will require different types of dressings, therefore, routine inspection is recommended
  - principles of dressings:
    - moist vs. dry wounds (see Table 9)
    - purpose of dressings should be to keep wound appropriately moist (i.e. moistening dry wounds or removing excess exudate/blood from wet wounds)
    - clean vs. infected wounds
      - clean wounds can be dressed with petroleum based gauze, which is non-adhering to epithelializing tissue; requires secondary dressing
      - infected wounds can be dressed with iodine gauze, silver-containing, or antimicrobial dressings
    - wide-based vs. cavitary/tunneling wounds
      - cavitary or tunnelling wounds (i.e. through a fascial layer) can be packed with saline-soaked (non-infected), betadine-soaked (infected) ribbon gauze, or other easily retrievable one-piece moisture providing dressing

Table 9. Recommended Dressings for Wound Type

<table>
<thead>
<tr>
<th>Wound Depth</th>
<th>Exudate Level</th>
<th>Dressing Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial</td>
<td>Lightly exuding</td>
<td>Films (Opsite®, hydrogels (Intrasite®, Na-gel®, Duoderm®))</td>
</tr>
<tr>
<td></td>
<td>Any exudate level</td>
<td>Contact layers</td>
</tr>
<tr>
<td>Superficial to Deep</td>
<td>Light to moderately exuding wounds</td>
<td>Amorphous gels, hydrogels, hydrocolloids (Duoderm®, Tegaderm®), collagen, hypertonic saline gauze (Mesalt®)</td>
</tr>
<tr>
<td></td>
<td>Moderately to heavily exuding wounds</td>
<td>Foams (Mepilex®, Allevyn®), alginites (Sorbsan®, Kaltostat®), hypertonic saline gauze, hydrofibre (Aquacel®)</td>
</tr>
</tbody>
</table>

Table adapted from Grabb & Smith’s Plastic Surgery 6th Edition Chapter 3, Table 3.3

Reconstruction

SKIN GRAFTS

Definition
- skin that is harvested from a donor site and transferred to the recipient site and that does not carry its own blood supply. Survival requires the generation of new blood vessels from the recipient site bed. They are classified according to the depth of dermis they contain: full thickness (entire epidermis + dermis) vs. split-thickness (epidermis + partial dermis)

Donor Site Selection
- must consider size, hair pattern, texture, thickness of skin, and colour (facial grafts best if taken from “blush zones” above clavicle e.g. pre/post auricular or neck)
- partial thickness grafts usually taken from inconspicuous areas (e.g. buttocks, lateral thighs, etc.)

Partial Thickness Skin Graft Survival
- 3 phases of skin graft “take”
  1. plasmatic imbibition: diffusion of nutrition from recipient site (first 48 h)
  2. inosculation: vessels in graft connect with those in recipient bed (day 2-3)
  3. neovascular ingrowth: graft revascularized (day 3-5)
- requirements for survival
  - bed: well-vascularized (unsuitable: bone, tendon, heavily irradiated, infected wounds, etc.)
  - contact between graft and recipient bed: fully immobile (decreased shearing and hematoma formation)
  - staples, sutures, splinting, and appropriate dressings (pressure) are used to prevent movement of graft and hematoma or seroma formation
  - site: low bacterial count (<10^5/cm³, to prevent infection)

Classification of Skin Grafts
1. by species
   - autograft: from same individual
   - allograft (homograft): from same species, different individual
   - xenograft (heterograft): from different species (e.g. porcine)
2. by thickness: see Table 10
Table 10. Skin Grafts

<table>
<thead>
<tr>
<th></th>
<th>Split Thickness Skin Graft</th>
<th>Full Thickness Skin Graft</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Epidermis and part of dermis</td>
<td>Epidermis and all of dermis</td>
</tr>
<tr>
<td><strong>Donor Site</strong></td>
<td>More sites</td>
<td>Limited donor sites (full thickness skin loss, must be closed 1st or with STSG)</td>
</tr>
<tr>
<td><strong>Healing of Donor Site</strong></td>
<td>Re-epithelialization via dermal appendages in graft and wound edges</td>
<td>Primary closure</td>
</tr>
<tr>
<td><strong>Re-harvesting</strong></td>
<td>~10 d (faster on scalp)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Graft Take</strong></td>
<td>Easier; shorter nutrient diffusion distance</td>
<td>Lower rate of survival (thicker, slower vascularization)</td>
</tr>
<tr>
<td><strong>Contraction</strong></td>
<td>Less 1st contraction, greater 2nd contraction (less with thicker graft)</td>
<td>Greater 1st contraction, less 2nd contraction</td>
</tr>
<tr>
<td><strong>Aesthetic</strong></td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>Can be meshed for greater area (see below)</td>
<td>May use on face and fingers</td>
</tr>
<tr>
<td><strong>Advantage</strong></td>
<td>Takes well in less favourable conditions, can cover a larger area</td>
<td>Resists contraction, texture/pigment more normal</td>
</tr>
<tr>
<td><strong>Disadvantage</strong></td>
<td>Contracts significantly, abnormal pigmentation, high susceptibility to trauma</td>
<td>Requires well vascularized bed</td>
</tr>
<tr>
<td><strong>Uses</strong></td>
<td>Large areas of skin, granulating tissue beds</td>
<td>Face (colour match), site where thick skin or decreased contracture is desired (e.g. finger)</td>
</tr>
</tbody>
</table>

**mesh graft**
- **advantages**
  - Prevents accumulation of fluids (e.g. hematoma, seroma)
  - Covers a larger area
  - Best for contaminated recipient site
- **disadvantages**
  - Poor cosmetic result (“alligator hide” appearance)
  - Has significant contracture

**common reasons for graft loss:** hematoma/seroma, infection, mechanical force (e.g. shearing, pressure)

**OTHER GRAFTS**

Table 11. Various Tissue Grafts

<table>
<thead>
<tr>
<th>Graft Type</th>
<th>Use</th>
<th>Preferred Donor Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>Repair rigid defects</td>
<td>Cranial, rib, iliac, fibula</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Restore contour of ear and nose</td>
<td>Ear, nasal septum, costal cartilage</td>
</tr>
<tr>
<td>Tendon</td>
<td>Repair damaged tendon</td>
<td>Palmaris longus, planaris</td>
</tr>
<tr>
<td>Nerve</td>
<td>Conduit for regeneration across nerve gap</td>
<td>Sural, antebrachial cutaneous, medial brachial cutaneous</td>
</tr>
<tr>
<td>Vessel</td>
<td>Bridge vascular gaps</td>
<td>Forearm or foot vessels for small vessels, saphenous vein for larger vessels</td>
</tr>
<tr>
<td>Dermis</td>
<td>Contour restoration (± fat for bulk)</td>
<td>Thick skin of buttock or abdomen</td>
</tr>
<tr>
<td>Fat</td>
<td>Contour restoration</td>
<td>Abdomen, any area with fat available</td>
</tr>
</tbody>
</table>

**FLAPS**
- **Definition:** tissue transferred from one site to another with a known blood supply (random, pedicled or named); not dependent on neovascularization, unlike a graft
- **May Consist of:** skin, subcutaneous tissue, fascia, muscle, bone, other tissue (e.g. omentum)
- **Classification:** based on blood supply to skin (random, axial) and anatomic location (local, regional, distant)
- **Indications for Flaps**
  - Reconstruction: replaces tissue loss due to trauma or surgery
  - Provides skin and temporary soft tissue coverage through which surgery can be carried out later
  - Improves blood supply to poorly vascularized bed (e.g. bone)
- **Complications:** flap loss due to hematoma, seroma, infection, poor flap design, extrinsic compression (dressing too tight) or vascular failure/thrombosis, fat necrosis (in free flaps)
Random Pattern Flaps (see Figure 15)
- blood supply by dermal and subdermal plexus to skin and subdermal tissue with random vascular supply
- limited length:width ratio to ensure adequate blood supply (typically 2:1)
- flap choice is often a combination of available tissue, location of reconstruction site with respect to donor site, and surgeon preference
- types
  - rotation: cover wounds of various sizes; common use: sacral pressure sores
  - transposition: smaller in size compared to rotation flaps and advancement flaps; commonly used on certain areas of the face using adjacent areas of excess skin laxity
  - Z-plasty: used to reorient a scar, lengthen the line of a scar or to break up a scar
  - advancement flaps (V-Y, Y-V)
    - single/bipedicle V-Y flaps: wounds with lax surrounding tissue; the pedicle is the deep tissue underlying the flap

Axial Pattern Flaps (Arterialized)
- flap contains a well defined artery and vein
- allows greater length:width ratio (5-6:1)
- types
  - peninsular flap: skin and vessel intact in pedicle (see Figure 16)
  - island flap: vessel intact, pedicle is better defined (see Figure 17)
  - free flap: vascular supply anastomosed at recipient site by microsurgical techniques
- can be sub-classified according to tissue content of flap:
  - e.g. musculocutaneous/myocutaneous (e.g. transverse rectus abdominal myocutaneous) vs. fasciocutaneous

Free Flaps
- transplanting expendable donor tissue from one part of the body to another by isolating and dividing a dominant artery and veins to a flap and performing a microscopic anastomosis between these and the vessels in the recipient wound
- survival rates >95%
- types: muscle and skin (common), bone, jejunum, omentum
  - e.g. radial forearm, scapular, latissimus dorsi

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal</th>
<th>Arterial Insufficiency</th>
<th>Venous Insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colour</td>
<td>Pink</td>
<td>Pale</td>
<td>Purple or blue</td>
</tr>
<tr>
<td>Temperature</td>
<td>Warm</td>
<td>Cool</td>
<td>Warm or cool</td>
</tr>
<tr>
<td>Arterial Pulse (Doppler)</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Turgor</td>
<td>Soft, but with tissue turgor</td>
<td>Decreased</td>
<td>Increased (i.e. tense)</td>
</tr>
</tbody>
</table>
# Soft Tissue Infections

## Table 13. Classification of Soft Tissue Infections by Depth

<table>
<thead>
<tr>
<th>Infection</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erysipelas</td>
<td>Superficial with subcutaneous tissue involvement</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>Full thickness with subcutaneous tissue involvement</td>
</tr>
<tr>
<td>Fasciitis</td>
<td>Fascia</td>
</tr>
<tr>
<td>Myositis</td>
<td>Muscle</td>
</tr>
</tbody>
</table>

## Erysipelas

**Definition**
- acute skin infection that is more superficial than cellulitis

**Etiology**
- typically caused by Group A β-hemolytic *Streptococcus*

**Clinical Features**
- intense erythema, induration, and **sharply demarcated borders** (differentiates it from other skin infections)

**Treatment**
- penicillin or first generation cephalosporin (e.g. cefazolin or cephalexin)

## Cellulitis

**Definition**
- non-suppurative infection of skin and subcutaneous tissues

**Etiology**
- skin flora most common organisms: *S. aureus*, β-hemolytic *Streptococcus*
- immunocompromised: Gram-negative rods and fungi

**Clinical Features**
- source of infection
  - trauma, recent surgery
  - PVD, diabetes – cracked skin in feet/toes
  - foreign bodies (IV, orthopaedic pins)
- systemic symptoms (fever, chills, malaise)
- pain, tenderness, edema, erythema with poorly defined margins, regional lymphadenopathy
- can lead to ascending lymphangitis (visible red streaking in skin proximal to area of cellulitis)

**Investigations**
- CBC, blood cultures
- culture and Gram stain wound/aspirate from wound if open wound
- plain radiographs if suspect foreign body or abscess
  - r/o bone invasion (osteomyelitis)

**Treatment**
- antibiotics: first line – cephalexin 500 mg PO q6h or cloxacillin 500 mg PO q6h x 7 d; if complicated (e.g. lymphangitis, DM) consider IV cefazolin 1-2 g q8h
- outline area of erythema to monitor success of treatment
- immobilize and splint (hands)

## Necrotizing Fasciitis

**Definition**
- rapidly spreading, very painful infection of the deep fascia with necrosis of tissues
- some bacteria create gas that can be felt as crepitus and be seen on x-rays
- infection spreads rapidly along deep fascial plane and is **limb and life threatening**

**Etiology**
- Type I: polymicrobial (less aggressive)
- Type II: monomicrobial, usually β-hemolytic *Streptococcus*
Clinical Features
- pain out of proportion to clinical findings and beyond border of erythema, edema, tenderness, ± crepitus (subcutaneous gas from anaerobes) ± fever
- infection spreads very rapidly
- patients may look deceptively well at first, but may rapidly become very sick/toxic
- late findings:
  - skin turns dusky blue and black (secondary to thrombosis and necrosis)
  - induration, formation of bullae
  - cutaneous gangrene, subcutaneous emphysema

Investigations
- a clinical diagnosis
- CT scan only if suspect it is not necrotizing fasciitis (looking for abscess, myonecrosis, etc.)
- severely elevated CK: usually means myonecrosis (late sign)
- hemostat easily passed along fascial plane; fascial biopsy to rule out in equivocal situations

Treatment
- rigorous resuscitation (ABCs)
- urgent surgical debridement: remove all necrotic tissue, copious irrigation
- IV antibiotics: as appropriate for clinical scenario; consider penicillin 4 million IU IV q4h or clindamycin 900 mg IV q6h until final cultures available
- urgent consultation with infectious disease specialist is recommended

Ulcers

Lower Limb Ulcers

Traumatic Ulcers (Acute)
- failure of lesions to heal, usually due to compromised blood supply and unstable scar
- usually over bony prominence ± edema ± pigmentation changes ± pain
- treatment: debridement of ulcer and compromised tissue, left to heal via secondary intention with dressings, may need reconstruction with local or distant flap in select cases, vascular status of limb must be assessed clinically and via vascular studies (i.e. sonographically)

Non-Traumatic Ulcers (Chronic)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Venous (70% vascular ulcers)</th>
<th>Arterial</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Valvular incompetence</td>
<td>2° to small and/or large vessel disease (be aware of risk factors)</td>
<td>Peripheral neuropathy: decreased sensation</td>
</tr>
<tr>
<td>History</td>
<td>Dependent edema, trauma</td>
<td>Arteriosclerosis, claudication</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Venous HTN</td>
<td>Usually &gt; 45 yr</td>
<td></td>
</tr>
<tr>
<td>Common Distribution</td>
<td>Medial malleolus</td>
<td>Distal locations</td>
<td>Pressure point distribution</td>
</tr>
<tr>
<td>Appearance</td>
<td>Yellow exudates, Granulation tissue</td>
<td>Pale/white, necrotic base ± dry eschar covering</td>
<td>Necrotic base</td>
</tr>
<tr>
<td>Wound Margins</td>
<td>Irregular</td>
<td>Even (“punched out”)</td>
<td>Irregular or “punched out” or deep</td>
</tr>
<tr>
<td>Depth</td>
<td>Superficial</td>
<td>Deep</td>
<td>Superficial/deep</td>
</tr>
<tr>
<td>Surrounding Skin</td>
<td>Venous stasis discolouration (brown)</td>
<td>Thin shiny dry skin, hairless, cool</td>
<td>Thin dry skin ± hyperkeratotic border</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypersensitive/ischemic</td>
</tr>
<tr>
<td>Pulses</td>
<td>Normal distal pulses</td>
<td>Decreased distal pulses</td>
<td>Decreased pulses likely</td>
</tr>
<tr>
<td>Vascular Exam</td>
<td>ABI &gt; 0.9, Doppler; abnormal venous system</td>
<td>ABI &lt; 0.9</td>
<td>ABI is inaccurately high</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulsus on elevation, rubor on dependency</td>
<td>Usually associated with arterial disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delayed venous filling</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Moderately painful</td>
<td>Extremely painful</td>
<td>Painless</td>
</tr>
<tr>
<td></td>
<td>Increased with leg dependency, decreased with elevation</td>
<td>Decreased with dependency, increased with leg elevation and exercise (claudication)</td>
<td>No claudication or rest pain</td>
</tr>
<tr>
<td></td>
<td>No rest pain</td>
<td>Rest pain</td>
<td>Associated paresthesia, anesthesia</td>
</tr>
<tr>
<td>Treatment</td>
<td>Leg elevation, rest</td>
<td>Rest, no elevation, no compression</td>
<td>Control diabetes</td>
</tr>
<tr>
<td></td>
<td>Compression at 30 mmHg</td>
<td>Most wound dressing ± topical and/or systemic antibiotics</td>
<td>Careful wound care</td>
</tr>
<tr>
<td></td>
<td>(stockings or elastic bandages)</td>
<td>Most wound dressing ± topical and/or systemic antibiotics</td>
<td>Foot care</td>
</tr>
<tr>
<td></td>
<td>Most wound dressings ± topical, systemic antibiotics</td>
<td>Modify risk factors (smoking, diet, exercise, etc.)</td>
<td>Orthotics</td>
</tr>
<tr>
<td></td>
<td>± skin grafts</td>
<td>Vascular surgical consultation</td>
<td>Early intervention for infections (topical and/or systemic antibiotics)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treat underlying conditions (DM, proximal arterial occlusion, etc.)</td>
<td>Vascular surgical consultation</td>
</tr>
</tbody>
</table>
Pressure Ulcers

Common Sites
- over bony prominences; 95% on lower body

Stages of Development
1. hyperemia: disappears 1 h after pressure removed
2. ischemia: follows 2-6 h of pressure
3. necrosis: follows >6 h of pressure
4. ulcer: necrotic area breaks down – N.B. skin is like tip of an iceberg

Classification (National Pressure Ulcer Advisory Panel 2007)
Stage I: nonblanchable erythema present >1 h after pressure relief, skin intact
Stage II: partial-thickness skin loss
Stage III: full-thickness skin loss into subcutaneous tissue, but not through fascia
Stage IV: through fascia into muscle, bone, tendon, or joint
  ▪ if an eschar is present, must fully debride before staging possible

Prevention
- good nursing care (clean dry skin, frequent repositioning), special beds or mattress (Kin Air®), proper nutrition, activity, early identification of individuals at risk (e.g. immobility, incontinence, paraplegia, etc.)

Treatment
- depends on individual patient and condition
- treat underlying medical issues including nutrition
- continue with preventative measures (pressure relief)
- wound debridement, moisture retentive or antimicrobial dressing, regular reassessment
- topical antimicrobials at treating physician’s discretion, systemic antibiotics for infections
- assess for possible reconstruction

Complications
- cellulitis, osteomyelitis, sepsis, gangrene

Burns

Burn Injuries

Causal Conditions
- thermal (flame contact, scald)
- chemical
- radiation (UV, medical/therapeutic)
- electrical

Most Common Etiology
- children: scald burns
- adults: flame burns

Table 15. Skin Function and Burn Injury

<table>
<thead>
<tr>
<th>Skin Function</th>
<th>Consequence of Burn Injury</th>
<th>Intervention Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermoregulation</td>
<td>Prone to lose body heat</td>
<td>Must keep patient covered and warm</td>
</tr>
<tr>
<td>Control of fluid loss</td>
<td>Loss of large amounts of water and protein from the skin and other body tissues</td>
<td>Adequate fluid resuscitation is imperative</td>
</tr>
<tr>
<td>Mechanical barrier to bacterial invasion and immunological organ</td>
<td>High risk of infection</td>
<td>Antibiotic ointments (systemic if signs of specific infection present) Tetanus prophylaxis if necessary</td>
</tr>
</tbody>
</table>
Pathophysiology of Burn Wounds

- amount of tissue destruction is based on temperature, time of exposure, and specific heat of the causative agent (see Figure 18)
- **zone of hyperemia**: vasodilation from inflammation; entirely viable, cells recover within 7 d; contributes to systemic consequences seen with major burns
- **zone of stasis (edema)**: decreased perfusion; microvascular sludging and thrombosis of vessels results in progressive tissue necrosis → cellular death in 24-48 h without proper treatment
  - factors favoring cell survival: moist, aseptic environment, rich blood supply
  - zone where appropriate early intervention has most profound effect in minimizing injury
- **zone of coagulation (ischemia)**: no blood flow to tissue → irreversible cell damage → cellular death/necrosis

Diagnosis and Prognosis

- burn size (see Figure 19)
  - % of TBSA burned: rule of 9s for 2° and 3° burns only (children <10 yr old use Lund-Browder chart – see Figure 20)
  - for patchy burns, surface area covered by patient’s palm (fingers closed) represents approximately 1% of TBSA
- age: more complications if <3 or >60 yr old
- depth: difficult to assess initially – history of etiologic agent and time of exposure helpful (see Table 16)
- location: face and neck, hands, feet, perineum are critical areas requiring special care of a burn unit (see Indications for Transfer to Burn Centre, PL18)
- inhalation injury: can severely compromise respiratory system
- associated injuries (e.g. fractures)
- co-morbid factors (e.g. concurrent disability, alcoholism, seizure disorders, chronic renal failure) can exacerbate extent of injury

![Figure 19. Rule of 9s for TBSA](image)
Table 16. Burn Depth (1st, 2nd, 3rd degree)

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Traditional Nomenclature</th>
<th>Depth</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema/Superficial</td>
<td>First degree</td>
<td>Epidermis</td>
<td>Painful, sensation intact, erythema, blanchable</td>
</tr>
<tr>
<td>Superficial-Partial</td>
<td>Second degree</td>
<td>Into superficial dermis</td>
<td>Painful, sensation intact, erythema, blisters with clear fluid, blanchable, hair follicles present</td>
</tr>
<tr>
<td>Thickness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep-Partial Thickness</td>
<td>Second degree</td>
<td>Into deep (reticular) dermis</td>
<td>Insensate, difficult to distinguish from full thickness, does not blanch, some hair follicles still attached, softer than full thickness burn</td>
</tr>
<tr>
<td>Full Thickness</td>
<td>Third degree</td>
<td>Through epidermis and dermis</td>
<td>Insensate (nerve endings destroyed), hard leathery eschar that is black, grey, white, or cherry red in colour, hairs do not stay attached, may see thrombosed veins</td>
</tr>
<tr>
<td>Fourth degree</td>
<td></td>
<td>Injury to underlying tissue structures (e.g. muscle, bone)</td>
<td></td>
</tr>
</tbody>
</table>

American Burn Association Criteria

- total 2° and 3° burns >10% TBSA
- burns involving the face, hands, feet, genitalia, perineum, or major joints
- 3° burns in any age group
- electrical burns, including lightning (internal injury underestimated by TBSA)
- chemical burns
- inhalation injury (may lead to respiratory distress)
- burns associated with major trauma/serious illness
- burned children in hospitals without appropriate child burn care
- burns in patients who will require special social, emotional, or rehabilitative intervention.

Acute Care of Burn Patients

- adhere to ATLS protocol
- resuscitation using Parkland formula to restore plasma volume and cardiac output
  - 4 cc R/L/kg/% TBSA over first 24 h (1/2 within first 8 h of sustaining burn, 1/2 in next 16 h)
• extra fluid administration required if
  - burn >80% TBSA
  - 4\textdegree\ burns
  - associated traumatic injury
  - electrical burn
  - inhalation injury
  - delayed start of resuscitation
  - pediatric burns
• monitor resuscitation
  - urine output is best measure: maintain at >0.5 cc/kg/h (adults) and 1.0 cc/kg/h (children <12 yr)
  - maintain a clear sensorium, HR <120/min, MAP >70 mmHg
• burn specific care
  - relieve respiratory distress: intubation and/or escharotomy (see sidebar)
  - prevent and/or treat burn shock: 2 large bore IVs
  - identify and treat immediate life-threatening conditions (e.g. inhalation injury, CO poisoning)
  - determine TBSA affected first, since depth is difficult to determine initially (easier to determine after 24 h)
• tetanus prophylaxis if needed
  - all patients with burns >10% TBSA, or deeper than superficial partial thickness, need 0.5 cc tetanus toxoid
  - also give 250 U of tetanus Ig if prior immunization is absent/unclear, or the last booster >10 yr ago
• baseline laboratory studies (Hb, UA, BUN, CXR, electrolytes, ECG, cross-match, ABG, carboxyhemoglobin)
• cleanse, debride, and treat the burn injury (antimicrobial dressings)
• early excision and grafting important for outcome

Respiratory Problems
• 3 major causes
  - burn eschar encircling chest
    - distress may be apparent immediately
  - perform escharotomy to relieve constriction
  - CO poisoning
    - may present immediately or later
    - treat with 100% O\textsubscript{2} by facemask (decreases half-life of carboxyhemoglobin from 210 to 59 min) until carboxyHb <10%
  - smoke inhalation leading to pulmonary injury
    - chemical injury to alveolar basement membrane and pulmonary edema (insidious onset)
    - risk of pulmonary insufficiency (up to 48 h) and pulmonary edema (48-72 h)
    - watch for secondary bronchopneumonia (3-25 d) leading to progressive pulmonary insufficiency
    - intubate patient with any signs of inhalation injuries

Burn Wound Healing

Table 17. Burn Shock Resuscitation (Parkland Formula)

<table>
<thead>
<tr>
<th>Time</th>
<th>Fluid Administration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hour 0-24</td>
<td>4 cc RL/kg/% TBSA</td>
<td>1/2 of total in first 8 h from time of injury and 1/2 of total in next 16 h from time of injury</td>
</tr>
<tr>
<td>Hour 24-30</td>
<td>0.35-0.5 cc plasma/kg/%TBSA</td>
<td></td>
</tr>
<tr>
<td>&gt;Hour 30</td>
<td>5% D5W at rate to maintain normal serum sodium</td>
<td></td>
</tr>
</tbody>
</table>

*Do not forget to add maintenance fluid to resuscitation

Table 18. Burn Wound Healing

<table>
<thead>
<tr>
<th>Depth</th>
<th>Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree</td>
<td>No scarring. Complete healing</td>
</tr>
<tr>
<td>Second degree (Superficial partial)</td>
<td>Spontaneously re-epithelialize in 7 to 14 d from retained epidermal structures ± residual skin discolouration Hypertrophic scarring uncommon. Grafting rarely required</td>
</tr>
<tr>
<td>Deep second degree (Deep partial)</td>
<td>Re-epithelialize in 14-35 d from retained epidermal structures Hypertrophic scarring frequent Grafting recommended to expedite healing</td>
</tr>
<tr>
<td>Third degree (Full thickness)</td>
<td>Re-epithelialize from the wound edge Grafting flap necessary to replace dermal integrity, limit hypertrophic scarring</td>
</tr>
<tr>
<td>Fourth degree</td>
<td>Often results in amputations</td>
</tr>
</tbody>
</table>

If not requiring amputation, needs flap for coverage after debridement (do not reepithelialize – cannot graft)
Treatment
- 3 stages
  1. assessment: depth determined
  2. management: specific to depth of burn and associated injuries
  3. rehabilitation
- first degree
  - treatment aimed at comfort
    - topical creams (pain control, keep skin moist) ± aloe
    - oral NSAIDs (pain control)
- superficial second degree
  - daily dressing changes with topical antibiotics, polyporous, may use a temporary biological or synthetic covering to close the wound; leave blisters intact unless circulation impaired or unless over joint inhibiting motion
- deep second degree and third degree
  - prevent infection and sepsis (significant cause of death in burn patients)
  - most common organisms: S. aureus, P. aeruginosa and C. albicans
    - day 1-3 (rare): Gram-positive
    - day 3-5: Gram-negative (Proteus, Klebsiella)
  - topical antimicrobials: prevent bacterial infection (from skin flora, gut flora or caregiver) and secondary sepsis (see Table 19)
  - remove dead tissue
  - surgically debride necrotic tissue, excise to viable (bleeding) tissue

Other Considerations in Burn Management

Table 19. Topical Antibiotic Therapy for Burns

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Penetration</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver nitrate (0.5% solution)</td>
<td>None</td>
<td>Minimal, may cause methemoglobinemia, stains (black), leaches sodium from wounds</td>
</tr>
<tr>
<td>Nanocrystalline silver-coated dressing (Acticoat®)</td>
<td>None or transient</td>
<td>Medium, does not penetrate eschar. Preferred over silver sulfadiazine and silver nitrate</td>
</tr>
<tr>
<td>Silver sulfadiazine (cream) (Silvadene®)</td>
<td>Minimal</td>
<td>Medium, does not penetrate eschar. Slowed healing, leukopenia, mild inhibition of epithelialization</td>
</tr>
<tr>
<td>Mafenide acetate (solution/cream) (Sulfamylon®)</td>
<td>Moderate</td>
<td>Well, penetrates eschar. Mild inhibition of epithelialization, may cause metabolic acidosis with wide application</td>
</tr>
</tbody>
</table>

- early excision and grafting is the mainstay of treatment
- initial dressing should decrease bacterial proliferation
- indication for skin graft: deep 2° or 3° burn that is > size of a quarter
- prevention of wound contractures: pressure dressings, joint splints, early physiotherapy

Other Considerations in Burn Management

Vascular Permeability and Edema

Immunosuppression

Renal Failure (2° to ↓ Renal Blood Flow)

- Increased Gut Mucosal Permeability (GI Bleed Risk)
- Progressive Pulmonary Insufficiency
- Hypermetabolism
- Altered Hemodynamics (↓ CO, ↑ SVR)

Risk Factors for Infection of Burn Wounds

Patient Related
- Extent: >30% TBSA
- Depth: full-thickness and deep partial-thickness
- Patient age (higher risk with very young and very old)
- Co-morbidities
- Wound dryness
- Wound temperature
- Secondary impairment of blood flow to wound
- Acidosis

Microbial Factors
- Density >10^6 organisms per gram tissue
- Motility
- Virulence and metabolic products (endotoxin, exotoxin, permeability factors, other factors)
- Antimicrobial resistance

Figure 21. Systemic effects of severe burns
- nutrition
  - hypermetabolism: TBSA >40% have BMR 2-2.5x predicted
  - calories, vitamin C, vitamin A, Ca^2+, Zn^2+, Fe^2+
- immunosuppression and sepsis
  - must keep bacterial count <10^8 bacteria/g of tissue (blood culture may not be positive)
  - signs of sepsis: sudden onset of hyper/hypothermia, unexpected CHF or pulmonary edema, development of ARDS, ileus >48 h post-burn, mental status changes, azotemia, thrombocytopenia, hypofibrinogenemia, hyper/hypoglycemia (especially if burn >40% TBSA)
- GI bleed may occur with burns >40% TBSA (usually subclinical)
  - treatment: tube feeding or NPO, antacids, H2 blockers (preventative)
- renal failure secondary to under resuscitation, drugs, myoglobin, etc.
- progressive pulmonary insufficiency
  - can occur after: smoke inhalation, pneumonia, cardiac decompensation, sepsis
- wound contracture and hypertrophic scarring
  - largely preventable with timely wound closure, splinting, pressure garments and physiotherapy

Meta-Analysis of Early Excision of Burns 2006;32:145-150
Purpose: To determine if early excision and grafting is superior (or equivalent) to conservative treatment and delayed grafting once the burn eschar has separated.
Methods: A literature review was completed seeking prospective randomized controlled trials comparing early excision (<7 d) and immediate grafting against treatment with dressings followed by grafting post-eschar separation. All ages and burn severities were included. Outcomes were mortality, blood transfusions, wound healing time and length of hospital stay.
Results: A total of 361 patients from 7 randomized controlled trials were included in the meta-analysis. 180 patients received early intervention and 181 received conservative management. There was no significant difference in mortality in patients with inhalational injury. Early excision and grafting in patients without inhalational injury resulted in significantly reduced mortality (RR 0.36, p<0.05) and decreased length of hospitalization by 0.09 d (p<0.05). The number of patients requiring blood transfusion was significantly higher with early excisional management (SMD 1.85, p<0.05). There was no significant difference in wound healing time between the two groups.
Conclusion: Early excision of burns (<7 d) is beneficial in reducing mortality in patients without inhalational injury, along with reducing length of time spent in hospital.

Figure 19. Flowchart of work up and treatment of burns

Figure 20. Tissue physiology of burn wounds
Special Considerations

CHEMICAL BURNS
- major categories: acid burns, alkaline burns, phosphorous burns, chemical injection injuries
- common agents: cement, hydrofluoric acid, phenol, tar
- mechanism of injury: chemical solutions coagulate tissue protein leading to necrosis
  - acids → coagulation necrosis
  - alkalines → saponification followed by liquefactive necrosis
- severity related to: type of chemical (alkali worse than acid), temperature, volume, concentration, contact time, site affected, mechanism of chemical action, degree of tissue penetration
- burns are deeper than they initially appear and may progress with time

Treatment (general)
- ABCs, monitoring
- remove contaminated clothing and brush off any dry powders before irrigation
- irrigation with water for 1-2 h under low pressure (contraindicated in heavy metal burns, such as sodium, potassium, magnesium, and lithium; in these cases soak in mineral oil instead)
- inspect eyes, if affected: wash with saline and refer to ophthalmology
- inspect nails, hair and webspaces
- correct metabolic abnormalities and tetanus prophylaxis if necessary
- local wound care 12 h after initial dilution (debridement)
- wound closure same as for thermal burn
- beware of underestimated fluid resuscitation, renal, liver, and pulmonary damage

ELECTRICAL BURNS
- depth of burn depends on voltage and resistance of the tissue (injury more severe in tissues with high resistance)
- often presents as small punctate burns on skin with extensive deep tissue damage which requires debridement
- electrical burns require ongoing monitoring as latent injuries can occur
- watch for system specific damages and abnormalities:
  - abdominal: intraperitoneal damage
  - bone: fractures and dislocations especially of the spine and shoulder
  - cardiopulmonary: anoxia, ventricular fibrillation, arrhythmias
  - muscle: myoglobinuria indicates significant muscle damage → compartment syndrome
  - neurological: seizures and spinal cord damage
  - ophthalmology: cataract formation (late complication)
  - renal: ATN resulting from toxic levels of myoglobin and hemoglobin
  - vascular: vessel thrombosis → tissue necrosis (increased Cr, K⁺ and acidity), decrease in RBC (beware of hemorrhages/delayed vessel rupture)

Treatment
- ABCs, primary and secondary survey, treat associated injuries
- monitor: hemochromogenuria, compartment syndrome, urine output
- wound management: topical agent with good penetrating ability (silver sulfadiazine or mafenide acetate)
- debride non-viable tissue early and repeat prn (every 48 h) to prevent sepsis
- amputations frequently required

FROSTBITE
- see Emergency Medicine, ER45
Table 20. Key Features of the History and Physical Exam of the Injured Hand in the Emergency Department

| HISTORY | | 
| Key Questions | Age | Hand dominance | Occupation | Time and place of accident | Mechanism of injury | Tetanus status |

| PHYSICAL EXAM | Structure | Examination |
| Position of finger | Abnormal cadence (fingers normally slightly flexed), scissoring |
| Deformity | Bony or specific (e.g., mallet, swan neck) |
| Bruising or swelling | May indicate underlying skeletal injury |
| Sweating pattern | May indicate denervation |
| Anatomical structures beneath | If open laceration, need to explore within wound (under sterile conditions) |

| Vascular Status | Radial and ulnar arteries | Allen's Test (see sidebar) |
| Digital arteries | Capillary refill (<2-3 s) |
| Temperature and skin turgor | For each test, need to compare both sides |

| Sensory (refer to Figure 3) | Median nerve | Dorsal radial tip of index finger |
| Ulnar nerve | Dorsal ulnar tip of little finger |
| Radial nerve | Dorsal web space of the thumb |
| Digital nerves | 2 point discrimination of each finger |

| Motor Function | Median nerve | Extrinsic muscles: flex DIP of index finger ("OK sign") |
| Intrinsic muscles: thumb to ceiling with palm up |
| Ulnar nerve | Extrinsic muscles: flex DIP of little finger Intrinsic muscles: abduct index finger ("Peace sign") or patient able to hold piece of paper between adducted fingers and resist pulling |
| Radial nerve | Extrinsic muscles: extend thumb ("thumb's up") and wrist |

| Range of Motion | Tendons, bones, joints, nerves | Assess active and passive range of motion of wrist extension/flexion/ulnar/radial deviation, finger abduction/adduction/flexion/extension, thumb flexion/extension/abduction/adduction/circumflexion |

| Tendons | Flexor digitorum profundus (FDP) | Stabilize PIP joint in extension, ask patient to flex fingers (at DIP) (see Figure 22) |
| Flexor digitorum superficialis (FDS) | Stabilize non-exam fingers in extension (neutralizes FDP) and ask patient to flex examination finger (see Figure 23) |

| Palpation | Bones | Focal tenderness or abnormal alignment |
| Joints | Instability may indicate ligamentous injury or dislocation |

General Management

Nerves
- direct repair for a clean injury within 14 d and without concurrent major injuries → otherwise secondary repair
- epineural repair of digital nerves with minimal tension
- post-operative: dress wound, elevate hand and immobilize
- Tinel's sign (cutaneous percussion over the repaired nerve) produces paresthesias and defines level of nerve regeneration
  - Wallerian degeneration occurs in the first 2 wk, which is why there is no Tinel's sign till after this time period
  - a peripheral nerve regenerates at 1 mm/d
  - paresthesias felt at area of percussion because re-growth of myelin (Schwann cells) is slower than axonal re-growth → percussion on exposed free-end of axon generates paresthesia
Vessels
- often associated with nerve injury (anatomical proximity)
- control bleeding with direct pressure and hand elevation
- if digit devascularized, optimal repair within 6 h
- dress, immobilize, and splint hand with finger tips visible
- monitor colour, capillary refill, skin turgor, fingertip temperature post-revascularization

Tendons
- most tendon lacerations require primary repair
- many extensors are repaired in the emergency room, flexors are repaired in the operating room within 2 wk
- avoid excessive immobilization (specific protocols for flexors, 2-3 wk for extensors) to minimize stiffness and facilitate rehabilitation

Bones
- see Fractures and Dislocations, PL25

Nailbed
- remove nail to examine underlying nailbed under digital block anesthesia
- irrigate wound and nail thoroughly
- suture repair of nailbed with catgut suture
- replace cleaned nail, which acts as splint for any underlying distal phalangeal fracture and prevents adhesion formation between nail fold and nailbed

Hand Infections

Principles
- trauma is most common cause
- 5 cardinal signs: rubor (red), calor (hot), tumour (swollen), dolor (painful) and functio laesa (loss of function)
- 90% caused by Gram-positive organisms
- most common organisms (in order) – S. aureus, S. viridans, Group A Streptococcus, S. epidermidis, and Bacteroides melaninogenicus (MRSA becoming more common)

TYPES OF INFECTIONS

Deep Palmar Space Infections
- uncommon, involve thenar or mid-palm, treated in OR

Felon
- definition: subcutaneous abscess in the fingertip that commonly occurs following severe paronychia or a puncture wound into the pad of digit; may be associated with osteomyelitis
- treatment: elevation, warm soaks, cloxacillin 500 mg PO q6h (if in early stage); if obvious abscess then I&D and PO cloxacillin

Flexor Tendon Sheath Infection
- \textit{Staphylococcus} > \textit{Streptococcus} > Gram-negative rods
- definition: acute suppurative tenosynovitis commonly caused by a penetrating injury and can lead to tendon necrosis and rupture if not treated
- clinical features: Kanavel’s 4 cardinal signs:
  1. point tenderness along flexor tendon sheath (earliest and the most important)
  2. severe pain on passive extension of DIP (second most important)
  3. fusiform swelling of entire digit
  4. flexed posture (increased comfort)
- treatment
  - OR incision and drainage, irrigation, IV antibiotics, and resting hand splint until infection resolves

Herpetic Whitlow
- HSV-1, HSV-2
- definition: painful vesicle(s) around fingertip
  - often found in medical/dental personnel and children
- clinical features: can be associated with fever, malaise and lymphadenopathy
  - patient is infectious until lesion has completely healed
- treatment: routine culture and viral prep protection (cover), consider oral acyclovir; do not break blisters, as this can spread infection

Paronychia
- acute = \textit{Staphylococcus}; chronic = \textit{Candida}
- definition: infection (granulation tissue) of soft tissue around fingernail (beneath eponychial fold)
• **etiology**  
  - acute paronychia: a “hangnail”, artificial nails, and nail biting  
  - chronic paronychia: prolonged exposure to moisture  
• **treatment**  
  - acute paronychia: warm compresses and cephalaxin 500 mg PO q6h ± drainage if abscess present  
  - chronic paronychia: anti-fungals with possible debridement and marsupialization, removal of nail plate

### Amputations

**Hand or Finger**  
- emergency management: injured patient and amputated part require attention  
  - **patient**: x-rays, NPO, clean wound and irrigate with NS, dress stump with nonadherent, cover with dry sterile dressing, tetanus and antibiotic prophylaxis (cephalosporin/erythromycin)  
  - **amputated part**: x-rays, gently irrigate with RL, wrap amputated part in a NS/RL soaked sterile gauze and place inside waterproof plastic bag, place in a container, then place container on ice

- **indications for replantation**  
  - **age**: children often better results than adults  
  - **level of injury**: proximal, thumb and multiple digit amputations are higher priority  
  - **nature of injury**: clean cut injuries have higher successful replantation rate; avulsion and crush injuries are relative contraindications to replant  
- if replant contraindicated manage stump with revision amputation  
  - would only allow a fingertip injury to heal by secondary intention

### Tendons

**Common Extensor Tendon Deformities**

<table>
<thead>
<tr>
<th>Injury</th>
<th>Definition</th>
<th>Zone</th>
<th>Etiology/Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mallet Finger</strong></td>
<td>DIP flexed with loss of active extension (see Figure 25)</td>
<td>1</td>
<td>Forced flexion of the extended DIP joint leading to extensor tendon rupture at DIP joint (e.g. sudden blow to tip of the finger)</td>
<td>Splint DIP in extension for 6 wk followed by 2 wk of night splinting. If inadequate improvement after 6 wk, check splinting routine and recommend 4 more wk of continuous splinting</td>
</tr>
<tr>
<td><strong>Boutonniere Deformity</strong></td>
<td>PIP flexed, DIP hyperextended (see Figure 26)</td>
<td>3</td>
<td>Injury or disease affecting the extensor tendon insertion into the dorsal base of the middle phalanx (laceration, volar dislocation, acute forceful flexion of PIP)</td>
<td>Splint PIP in extension and allow active DIP motion</td>
</tr>
</tbody>
</table>
| **Swan Neck Deformity** | PIP hyperextended, DIP flexed (see Figure 27) | 3    | Trauma (PIP volar plate injury) Associated with RA and old, untreated mallet deformity | Splint to prevent PIP hyperextension or DIP flexion  
  Consider arthrodesis/arthroplasty |

**De Quervain’s Tenosynovitis (zone 7; most common cause of radial wrist pain)**  
- **definition**: inflammation in 1st extensor compartment (APL and EPB)  
- **clinical features**:  
  - +ve Finkelstein’s test (pain over the radial styloid induced by making fist, with thumb in palm, and ulnar deviation of wrist)  
  - pain localized to the 1st extensor compartment  
  - tenderness and crepitant over radial styloid may be present  
  - differentiate from CMC joint arthritis (CMC joint arthritis will have a positive grind test, whereby crepitus and pain are elicited by axial pressure to the thumb)  
- **treatment**:  
  - mild: NSAIDs, splinting and steroid injection into the tendon sheath (successful in over 60% of cases)  
  - severe: surgical release of stenotic tendon sheaths (APL and EPB); remember there may be 2 or more sheaths

**Ganglion Cyst (zone 7)**  
- **definition**:  
  - fluid-filled synovial lining that protrudes between carpal bones or from a tendon sheath; most commonly carpal in origin  
  - most common soft tissue tumour of hand and wrist (60% of masses)  

---

[Images and diagrams are not transcribed.]
• **clinical features:**
  - most common around scapholunate ligament junction
  - 3 times more common in women than in men
  - more common in younger individuals
  - can be large or small – may drain internally so size may wax and wane
  - often non-tender although tenderness increased when cyst smaller (from increased pressure within smaller cyst sac)

• **treatment:**
  - conservative treatment: watch and wait
  - aspiration (recurrence rate 65%)
  - consider operative excision of cyst and stalk (recurrence is possible)
  - steroids if painful

**Common Flexor Tendon Deformities** (see Figure 28)

• flexor tendon zones (important for prognosis of tendon lacerations)
  - “no-man’s land”:
    - between distal palmar crease and mid-middle phalanx
    - zone where superficialis and profundus lie enmeshed together
    - recovery of glide very difficult after injury

**Stenosing Tenosynovitis (trigger finger/thumb)**

• **definition:** inflammation of synovium causes size discrepancy between tendon and sheath/pulley (most commonly at A-1 pulley) = locking of thumb or finger in flexion/extension

• **etiology:** idiopathic or associated with RA, diabetes, hypothyroidism and gout

• **clinical features:**
  - thumb, ring and long fingers most commonly affected
  - patient complains of catching, snapping or locking of affected finger
  - tenderness to palpation/nodule at palmar aspect of MCP over A-1 pulley
  - women are 4 times more likely than men to be affected

• **conservative treatment:**
  - NSAIDs
  - steroid injection
  - surgical flexor tendon release
  - injections less likely to be successful in patients with DM or symptoms greater than 6 mo

• **surgical treatment:**
  - incise A-1 flexor tendon pulley to permit unrestricted, full active finger motion

**Fractures and Dislocations**

• for fracture principles, see [Orthopedics, OR5](#)

**FRACTURES**

• about 90% of hand fractures are stable in flexion (lock/prevent extension)

• **position of function** (like a hand holding a pop can) (see Figure 29):
  - wrist extension 15°
  - MCP flexion 45°
  - IP flexion (slight)
  - thumb abduction/rotation
  - contraindications: post repair of flexor tendons, median/ulnar nerve injury

• **position of safety** (see Figure 30):
  - wrist extension 45° (position most beneficial for hand function if immobilized)
  - MCP flexion 60° (maximal collateral ligament stretch)
  - PIP and DIP in full extension (maximal volar plate origin stretch)
  - thumb abduction and opposition (functional position)
  - stiffness secondary to immobilization is the most important complication; Tx = early motion

**Distal Phalanx Fractures**

• most commonly fractured bone in the hand

• usual mechanism is crush injury and thus accompanied by soft tissue injury

• subungual hematoma is common and must be decompressed if painful or nail removed

• treatment consists of 3 wk of digital splinting (with IP joint movement preserved)

**Proximal and Middle Phalanx Fractures**

• check for: rotation, scissoring (overlap of fingers on making a fist), shortening of digit

• undisplaced or minimally displaced: closed reduction (if extra-articular) buddy tape to neighbouring stable digit, elevate hand, motion in guarded fashion 10-14 d post injury

• displaced, non-reducible, not stable with closed reduction, or rotational or scissoring deformity: percutaneous pins (K-wires) or ORIF, and splint
Metacarpal Fractures

- generally accept varying degrees of deviation before reduction required: up to 10° (D2), 20° (D3), 30° (D4), or 40° (D5)
- **Boxer's fracture (extra-articular):** acute angulation of neck of metacarpal of little finger into palm (see Figure 31)
  - mechanism: blow on the distal-dorsal aspect of closed fist
  - loss of prominence of metacarpal head, volar displacement of head
  - check for scissoring of fingers on making a fist
  - up to 30-40° angulation may be acceptable
  - closed reduction should be considered to decrease the angle
  - if stable ulnar gutter splint x 3 wk with PIP and DIP joints free
- **Bennett's fracture (intra-articular):** fracture/dislocation of the base of the thumb metacarpal (see Figure 32)
  - unstable fracture
  - abductor pollicis longus pulls MC shaft proximally and radially causing adduction of thumb
  - treat with percutaneous pinning, thumb spica x 6 wk
- **Rolando's fracture (intra-articular):** T- or Y-shaped fracture of the base of the thumb metacarpal (see Figure 33)
  - treat with ORIF with K-wire

**DISLOCATIONS**

- must be reduced as soon as possible

**PIP and DIP Dislocations (PIP more common than DIP)**

- usually dorsal dislocation (commonly from hyperextension)
- if closed dislocation: closed reduction and splinting (30° flexion for PIP and full extension for DIP) or buddy taping and early mobilization (prolonged immobilization causes stiffness)
- open injuries are treated with wound care, closed or open reduction and antibiotics

**MCP Dislocations (relatively rare)**

- dorsal dislocations much more common than volar dislocations
- dorsal dislocation of proximal phalanx on metacarpal head; most commonly index finger (hyperextension)
- two types of dorsal dislocation:
  - simple (reducible with manipulation): treat with 2 wk of splinting at 30° MCP flexion
  - complex (volar plate blocks reduction): treat with open reduction and A1 pulley release + extension-blocking splint at 30° flexion (2 wk) then 10° flexion (2 wk)

**Ulnar Collateral Ligament (UCL) Injury**

- forced abduction of thumb (e.g. ski pole injury)
- **skier's thumb:** acute UCL injury
- **gamekeepers thumb:** chronic UCL injury
- **evaluation:** radially deviate joint in full extension and at 30° flexion and compare with non-injured hand. UCL rupture is presumed if injured side deviates more than 30° in full extension or more than 15° in flexion
- **Stener's lesion:** the UCL has bony attachments to the adductor aponeurosis and the proximal ligament can displace while the distal attachment remains deep to the aponeurosis, forming a barrier that blocks healing and leads to chronic instability; requires surgery

**Dupuytren’s Disease**

**Definition**

- contraction of longitudinal palmar fascia, forming nodules (usually painless), fibrous cords and eventually flexion contractures at the MCP and interphalangeal joints (see Figure 34)
- flexor tendons not involved
- Dupuytren's diathesis: early age of onset, strong family history, and involvement of sites other than palmar aspect of hand

**Epidemiology**

- genetic disorder, unusual in patients from African and Asian countries, high incidence in northern Europeans, men > women, often presents in 5th-7th decade of life, associated with but not caused by alcohol use and diabetes

**Clinical Features**

- order of digit involvement (most common to least common): ring > little > long > thumb > index
- may also involve feet (Lederhosen’s) and penis (Peyronie’s – see *Urology*, U29)
Clinical Features

- Investigations
  - indications for percutaneous release:
    - functional impairment
    - MCP joint contractures >30°
    - any PIP contracture
    - rapidly progressive disease
  - may recur, especially in Dupuytren's diathesis

Surgical Treatment of Common Problems

- General Principles
  - non-surgical treatments form the foundation in the management of the rheumatoid hand
  - surgery only for patients whose goals (improved cosmesis or function) may be achieved

Rheumatoid Hand

General Principles

- non-surgical treatments form the foundation in the management of the rheumatoid hand
- surgery only for patients whose goals (improved cosmesis or function) may be achieved

Surgical Treatment of Common Problems

- synovitis: requires tendon repair if ruptured; can lead to carpal tunnel syndrome and trigger finger
- ulnar drift: MCP arthroplasty, resection of distal ulna, soft tissue reconstruction around wrist
- thumb deformities: can be successfully treated by arthrodesis (surgical fixation of joint to promote bone fusion)

Carpal Tunnel Syndrome

Definition

- median nerve compression at the level of the flexor retinaculum as opposed to pronator teres syndrome

Etiology

- median nerve entrapment at wrist
- primary cause is idiopathic
- secondary causes: space occupying lesions (tumours, hypertrophic synovial tissue, fracture callus, and osteophytes), metabolic and physiological (pregnancy, hypothyroidism, acromegaly, and RA), infections, neuropathies (associated with DM or alcoholism), and familial disorders
- job/hobby repetitive trauma, especially forced wrist flexion

Epidemiology

- female: male = 4:1, most common entrapment neuropathy

Clinical Features

- sensory loss in median nerve distribution i.e. radial 3.5 digits (see Figure 3)
- discriminative touch often lost first
- classically, patient awakened at night with numb/painful hand, relieved by shaking/dangling/rubbing
- decreased light touch and 2-point discrimination, especially fingertips
- advanced cases: thenar wasting/weakness
- ± Tinel's sign (tingling sensation on percussion of nerve)
- ± Phalen's sign (wrist flexion induces symptoms)

Investigations

- clinical diagnosis
- NCV and EMG may confirm, but do not exclude, the diagnosis

Treatment

- avoid repetitive wrist and hand motion, wrist splints when repetitive wrist motion required
- conservative: night time splinting to keep wrist in neutral position
- medical: NSAIDs, local corticosteroids injection, oral corticosteroids
- surgical decompression: transverse carpal ligament incision to decompress median nerve
- indications for surgery: numbness and tingling ± sensory loss, weakness ± muscle atrophy, unresponsive to conservative measures
- complications of surgery: injury to median motor branch, palmar cutaneous branch or superficial transverse vascular arch, local pain (pilar pain), and scar formation

Radiographic Evolution of the Rheumatoid Hand

- Earliest sign: erosion of the ulnar styloid
- Progression: characterized by symmetrical joint space narrowing and erosions of the carpal bones, MCP and PIP (with DIP relatively spared)
- Late stage: Swan neck and Boutonniere deformities

Tests:

- Phalen's test: Sensitivity: 0.75, Specificity: 0.47
- Tinel's test: Sensitivity: 0.60, Specificity: 0.67
- Carpal Tunnel Compression Test: Sensitivity: 0.87, Specificity: 0.90

Results/Conclusions: The correlation between the probability of CTS predicted by the regression model and the panel of clinicians was 0.71. Clinical diagnostic criteria that contributed significantly to the model were:

1. Numbness and tingling in median nerve distribution
2. Nocturnal numbness
3. Weakness and/or atrophy of the thenar musculature
4. Tinel's sign
5. Phalen's test
6. Loss of 2-point discrimination

Accuracy of the Clinical Assessment for Carpal Tunnel Syndrome

- Phalen's:
  - Sensitivity: 0.75, Specificity: 0.47
- Tinel's:
  - Sensitivity: 0.60, Specificity: 0.67
- Carpal Tunnel Compression Test:
  - Sensitivity: 0.87, Specificity: 0.90

Hand Surgery Update 1986; p.223
Brachial Plexus

Etiology
- common causes of brachial plexus injury: complication of childbirth and trauma
- other causes of injury: compression from tumours, ectopic ribs

Common Palsies

Table 22. Named Neonatal Palsies of the Brachial Plexus

<table>
<thead>
<tr>
<th>Palsy</th>
<th>Location of Injury</th>
<th>Mechanism of Injury</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne-Erb Palsy</td>
<td>Upper brachial plexus (C5-C6)</td>
<td>Head/shoulder distraction (e.g. motorcycle)</td>
<td>Waiter’s tip deformity (shoulder internal rotation, elbow extension, wrist flexion)</td>
</tr>
<tr>
<td>Klumpke’s Palsy</td>
<td>Lower brachial plexus (C7-T1)</td>
<td>Traction on abducted arm</td>
<td>May include Horner’s syndrome (“claw hand”)</td>
</tr>
</tbody>
</table>

Differential Diagnosis
- trauma (blunt, penetrating)
- thoracic outlet syndrome
  - neurogenic: associated with cervical rib; compression of C8/T1
  - vascular: pain or sensory symptoms without cervical rib; cessation of radial pulse with provocative maneuvers
- tumour
  - schwannoma: well-defined margins makes it easier for total resection
  - neurofibromas: associated with neurofibromatosis type I
  - other: e.g. Pancoast syndrome (apical lung tumour)
- neuropathy (compressive, post-irradiation, viral, diabetic, idiopathic)

Investigations
- EMG
- MRI: gold standard for identifying soft tissue masses
- CT myelogram: better than MRI for identification of nerve root avulsion and identification of pseudomeningocele. Important for preoperative identification of patients likely to require neurotisation procedures (especially for patients with blunt trauma)

Management

Table 23. Management of Brachial Plexus Injuries

<table>
<thead>
<tr>
<th>Type</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Penetrating Trauma</td>
<td>Usually improves (unless expanding mass, e.g. hematoma)</td>
</tr>
<tr>
<td>Concussive/compressive</td>
<td>If no continued insult, follow for 3-4 mo for improvement</td>
</tr>
<tr>
<td>Traction/stretch</td>
<td>Surgery if no significant improvement and/or residual paresis at 6 mo of age</td>
</tr>
<tr>
<td>Obstetric palsy</td>
<td></td>
</tr>
<tr>
<td>Penetrating Trauma</td>
<td>Sharp or vascular injury</td>
</tr>
<tr>
<td>Explore immediately in OR</td>
<td></td>
</tr>
</tbody>
</table>

Craniofacial Injuries

- low velocity vs. high velocity injuries determine degree of damage
- fractures cause bruising, swelling and tenderness → loss of function
- frequency: nasal > zygomatic > mandibular > maxillary
- management: can wait 5-10 d for swelling to decrease before ORIF required
Approach to Facial Injuries

- ATLS protocol
- inspect, palpate, clinical assessment for injury to underlying structures (e.g. facial nerve)
- visual assessment
- tetanus prophylaxis
- radiological evaluation
- wound irrigation with NS/RL and remove foreign materials
- conservative debridement of detached or nonviable tissue
- repair when patient's general condition allows (soft tissue injury: <8 h preferable)

Investigations (see Table 24)
- CT:
  - axial and coronal (specifically request 1.5 mm cuts): for fractures of upper and middle face (not good for mandible)
  - indicated for high velocity trauma, complex facial fractures, orbital floor, panface fractures, pre-op assessment
- panorex radiograph: shows entire upper and lower jaw; best for isolated mandible fracture as patient must be able to sit

Table 24. Imaging of the Craniofacial Skeleton

<table>
<thead>
<tr>
<th>Structure</th>
<th>Appropriate Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandible</td>
<td>Panoramic (panorex)*</td>
</tr>
<tr>
<td></td>
<td>CT</td>
</tr>
<tr>
<td>Zygomatic and orbital bones</td>
<td>CT scan*</td>
</tr>
<tr>
<td></td>
<td>Water’s view (occipitomental, A-P “from below”), Town’s, AP</td>
</tr>
<tr>
<td>Nasal bones</td>
<td>No x-ray required – clinical</td>
</tr>
<tr>
<td>Maxilla</td>
<td>CT scan – axial and coronal*</td>
</tr>
</tbody>
</table>

*Best imaging method

Treatment
- consultation when indicated (dentistry, ophthalmology)
- re-establish normal occlusion
- pursue normal eye function
- restore stability of face and appearance

Complications
- diplopia/enophthalmos/blindness
- intracranial pathology such as CSF leak, bleeding and SIADH
- sinusitis
- functional abnormalities (i.e. malocclusion)
- infection – extremely rare
- poor cosmesis; need for 2° surgery

Mandibular Fractures

always two points of injury since it is a ring structure (includes fractures and dislocations)
commonly at sites of weakness (condylar neck, angle of mandible, region of 3rd molar or canine tooth)

Etiology
- anterior force: bilateral fractures
- lateral force: ipsilateral subcondylar and contralateral angle or body fracture
- note: classified as open if fracture into tooth bearing area (alveolus)

Clinical Features
- pain, swelling, difficulty opening mouth (“trismus”)
- malocclusion, asymmetry of dental arch
- damaged, loose, or lost teeth
- palpable “step” along mandible
- numbness in V3 distribution
- intra-oral lacerations or hematoma (sublingual)
- chin deviating toward side of a fractured condyle

Patients with major facial injuries are at risk of developing upper airway obstruction (displaced blood clots, teeth or fracture fragments; swelling of pharynx and larynx; loss of support of hyomandibular complex → retroposition of tongue). Also at risk of ocular injury.

Suspect C-spine injury with any facial trauma. C-spine evaluation before radiographs are ordered.

Consider intracranial trauma; rule out skull fracture.

Signs of Basal Skull Fracture
- Battle’s sign (bruised mastoid process)
- Hemotympanum
- Raccoon eyes (periorbital bruising)
- CSF otorrhea

Facial bone injuries with orbit involved require ophthalmology consult.
Classification

Table 25. Mandibular Fracture Classifications by Anatomic Region (refer to Figure 35)

<table>
<thead>
<tr>
<th>Areas/Boundaries</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symphysis</td>
<td>Midline of the mandible; between the central incisors from the alveolar process through the inferior border of the mandible</td>
</tr>
<tr>
<td>Body*</td>
<td>From the symphysis to the distal alveolar border of the third molar</td>
</tr>
<tr>
<td>Angle</td>
<td>Triangular region between the anterior border of the masseter and the posterosuperior insertion of the masseter distal to the third molar</td>
</tr>
<tr>
<td>Ramus</td>
<td>Part of the mandible that extends posterosuperiorly into the condylar and coronoid processes</td>
</tr>
<tr>
<td>Condylar</td>
<td>Area of condylar process of mandible</td>
</tr>
<tr>
<td>Subcondylar</td>
<td>Area below the condylar neck (i.e. sigmoid notch) of the mandible</td>
</tr>
<tr>
<td>Corooid Process</td>
<td>Area of the coronoid process of mandible</td>
</tr>
</tbody>
</table>

*Most common mandibular fracture type

Treatment
- maxillary and mandibular arch bars wired together (intramaxillary fixation) or ORIF
- antibiotics to cover against *S. aureus* and anaerobes

Complications
- malocclusion, malunion
- tooth loss, and possible sensation loss
- TMJ ankylosis

Maxillary Fractures

Table 26. Le Fort Classification (refer to Figure 36)

<table>
<thead>
<tr>
<th>Le Fort I</th>
<th>Le Fort II</th>
<th>Le Fort III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative Name</td>
<td>Guerin fracture</td>
<td>Pyramidal fracture</td>
</tr>
<tr>
<td>Type of Fracture</td>
<td>Horizontal</td>
<td>Pyramidal</td>
</tr>
<tr>
<td>Structures Involved</td>
<td>Piniform aperture</td>
<td>Nasal bones</td>
</tr>
<tr>
<td>Maxillary sinus</td>
<td>Medial orbital wall</td>
<td>Maxilla</td>
</tr>
<tr>
<td>Pterygoid plates</td>
<td>Pterygoid plates</td>
<td>Pterygoid plates</td>
</tr>
<tr>
<td>Anatomical Result</td>
<td>Maxilla divided into 2 segments</td>
<td>Maxillary teeth separated from face</td>
</tr>
</tbody>
</table>

Nasal Fractures

Etiology
- lateral force → more common, good prognosis
- anterior force → can produce more serious injuries
- most common facial fracture

Clinical Features
- epistaxis/hemorrhage, deviation/flattening of nose, swelling, periorbital ecchymosis, tenderness over nasal dorsum, crepitus, septal hematoma, respiratory obstruction, subconjunctival hemorrhage
- depression and splaying of nasal bones causing a saddle deformity
- important to clinically assess for naso-orbital ethmoid (NOE) fractures

Treatment
- in the absence of complications, no treatment required
- closed reduction with Asch or Walsham forceps under anesthesia, pack nostrils with Adaptic®, nasal splint for 7 d
- best reduction immediately (<6 h) or when swelling subsides (5-7 d)
- rhinoplasty may be necessary later for residual deformity (30%)

Always drain septal hematomas as this is a cause of septal necrosis with perforation (saddle nose deformity).
Naso-orbital Ethmoid Fractures

**Etiology**
- fractures of the nasal and ethmoid bones of the medial orbit
- problematic and may lead to greatest change in facial appearance
- Markowitz-Manson classification:
  - Type 1: Single, central fragment, medial canthal ligament intact
  - Type 2: Comminuted central fragment, medial canthal ligament intact
  - Type 3: Severe comminution of central fragment and disrupted medial canthal ligament

**Clinical Presentation**
- telecanthus (increased intercanthal distance secondary to medial canthal ligament disruption)
- orbital rim step-off
- similar to nasal fractures (see Nasal Fractures, PL30)

**Treatment**
- surgical repair to restore intercanthal distance, nasal projection and orbital anatomy

Zygomatic Fractures

- 3 categories (see Figure 37)
  1. fracture restricted to zygomatic arch
  2. depressed fracture of zygomatic complex (zygoma)
  3. unstable fracture of zygomatic complex (tetrapod fracture) – separations occur at maxilla, frontal bone, temporal bone and orbital rim

**Clinical Features**
- flattening of malar prominence (view from above)
- pain over fractures on palpation
- numbness in V2 distribution (infraorbital and superior dental nerves)
- palpable step deformity in bony orbital rim (especially inferiorly)
- often associated with fractures of the orbital floor
- ipsilateral epistaxis; trismus (lock jaw)

**Treatment**
- if undisplaced, stable and no symptoms, then soft diet; no treatment necessary
- ophthalmologic evaluation if suspected orbital injury
- uncomplicated zygomatic arch fractures can be elevated using Gillies approach: leverage on the anterior part of the zygomatic arch via a temporal incision; stabilization often unnecessary
- ORIF for displaced or unstable fractures of zygomatic complex

Orbital Floor Fractures

- see Ophthalmology, OP42

**Definition**
- fracture of floor of orbit ± intact infraorbital rim (see Figure 38)
- may be associated with nasoethmoid fracture

**Etiology**
- blunt force to eyeball → sudden increase in intra-orbital pressure (e.g. baseball or fist)

**Clinical Features**
- check visual fields and acuity for injury to globe
- periorbital edema and bruising, subconjunctival hemorrhage
- ptosis, exophthalmos, exorbitism, or enophthalmos
- orbital rim step-offs with possible infraorbital nerve anesthesia
- vertical dystopia (abnormal displacement of the entire orbital cone in the vertical plane); diplopia looking up or down (entrapment of inferior rectus), limited EOM
- orbital entrapment:
  - clinical diagnosis that is a surgical emergency
  - diplopia with vertical gaze; limited EOM
  - severe pain or nausea and vomiting with eye movement
  - requires urgent ophthalmology evaluation and surgical repair
Investigations
• CT (diagnostic): axial and coronal views
• diagnostic manoeuvre for entrapment is **forced duction** test (pulling on inferior rectus muscle with forceps to ensure full ROM) under anesthesia

Treatment
• surgical repair indicated if: urgent repair for entrapment, floor defect >1 cm, any size defect with enophthalmos or persistent diplopia (>10 d)
• reconstruction of orbital floor with bone graft or alloplastic material
• ophthalmologic evaluation suggested

Complications
• persistent diplopia
• enophthalmos

**Superior Orbital Fissure Syndrome**
• fracture of SOF causing ptosis, proptosis, anesthesia in V1 distribution, and painful ophthalmoplegia (paralysis of CN III, IV, VI)
• uncommon complication seen in Le Fort II and III fractures (1/130)
• recovery time reported as 4.8-23 wk following operative reduction of fractures

**Orbital Apex Syndrome**
• fracture through optic canal with involvement of CN II at apex of orbit
• symptoms are the same as SOF syndrome plus vision loss
• treatment is urgent decompression of fracture in optic canal or steroids (emergency)

**Breast Surgery**

**Breast Reconstruction**

• integral part of breast cancer treatment
• two basic methods: implants (1-stage or 2-stage) or autologous tissue (see Table 27)
• may also require breast balancing procedure and nipple areola reconstruction

**Pre-Reconstruction Considerations**
• radiation: treatment before and after mastectomy is a relative contraindication to alloplastic reconstruction
• recipient tissue: skin sparing mastectomy allows for the use of implants without tissue expanders (1-stage process)
• donor tissue: limited availability of suitable donor tissue (lack of tissue, scar, previous surgery that interferes with blood supply) may prevent the use of autologous tissue reconstruction
• timing (immediate vs. delayed)
• contralateral breast: may not be possible to reconstruct a breast of the same size or shape as the contralateral breast. Breast reduction or mastopexy may be considered in opposite breast (see Table 28)
• other considerations: patient’s age and co-morbidities, prognosis, body weight, characteristics of chest wall and patient’s attitude

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Definition</th>
<th>Surgical Details</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Implant</strong></td>
<td>Use of synthetic material (silicone or saline implants)</td>
<td>With expanders (2 stages): Use tissue expanders before replacement with implants to help facilitate breast ptosis. (see Breast Tissue Expanders, PL33) Without expanders (1 stage): In skin-sparing mastectomy, enough skin is available for immediate placement of implant</td>
<td>Complications: capsular contraction (foreign body reaction to implants), rupture or leakage of implant, increased risk of infection, 35% revision rate over 5 yr</td>
</tr>
<tr>
<td><strong>Autologous Tissue</strong></td>
<td>Use of patient’s own tissue</td>
<td>Many flap options: DIEP, TRAM, latissimus dorsi, SIEA, SGAP, and IGAP</td>
<td>Offers reduced long-term morbidity and natural consistency</td>
</tr>
<tr>
<td><strong>Nipple Areola Reconstruction</strong></td>
<td>Final stage of breast reconstruction</td>
<td>Usually require tattooing for areola reconstruction Local vs. distant flap/graft: 1. Local: fish tail or skate flap most common; these flaps allow simultaneous nipple and areola reconstruction 2. Distant: opposite nipple, earlobe, abdominal skin, costal cartilage, labia</td>
<td>Usually performed 3 mo post-reconstruction</td>
</tr>
</tbody>
</table>

Table 27. Options for Breast Reconstruction
Breast Tissue Expanders

- types: textured vs. smooth, both with integrated port
- placement: sub-pectoral, total submuscular (pectoral/serratus)
- size: depends on contralateral breast and desired size
  - generally over-expanded to facilitate ptosis
- timing of expansion: begins when wound fully healed (usually 2 wk post-op), and implants are expanded weekly or bi-weekly until complete (up to 3 mo). Expanders are exchanged for implants after another 3 mo for consolidation of expanded skin

Breast Reduction

- reduction mammoplasty performed for relief of physical symptoms (e.g. shoulder groove, neck pain, back pain, shoulder pain, mastodynia), and to improve breast size and shape
- key steps of procedure:
  - incisions: circular around the areola, vertical from areola incision to infra-mammary fold, along the natural infra-mammary fold
  - removal of fat, breast tissue, and excess skin
  - possible need to move nipple and areola complex to higher position
- complications: infection, hemorrhage, decreased nipple sensation, inability to breast feed, breast/nipple asymmetry, nipple loss (partial or complete), skin loss/necrosis, fat necrosis

Aesthetic Surgery

Aesthetic Procedures

<table>
<thead>
<tr>
<th>Location</th>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head/Neck</td>
<td>Hair transplants</td>
<td>Aesthetic improvement of hair growth patterns using grafts or flaps</td>
</tr>
<tr>
<td></td>
<td>Otoplasty</td>
<td>Surgical correction of protruding ears</td>
</tr>
<tr>
<td></td>
<td>Brow lift</td>
<td>Surgical procedure to lift low brows</td>
</tr>
<tr>
<td>Face</td>
<td>Rhytidectomy</td>
<td>Surgical procedure to reduce wrinkling and sagging of the face and neck. “Face lift”</td>
</tr>
<tr>
<td></td>
<td>Blepharoplasty</td>
<td>Surgical procedure to shape or modify the appearance of eyelids by removing excess eyelid skin ± fat pads</td>
</tr>
<tr>
<td></td>
<td>Rhinoplasty</td>
<td>Intranasal surgical reconstruction of the nose</td>
</tr>
<tr>
<td></td>
<td>Genioplasty</td>
<td>Chin augmentation via osteotomy or synthetic implant to improve contour</td>
</tr>
<tr>
<td></td>
<td>Lip augmentation</td>
<td>Procedure to create fuller lips and to reduce wrinkles around the mouth using collagen injections, fat transferred from other body parts, or implantable materials</td>
</tr>
<tr>
<td>Skin</td>
<td>Chemical peel</td>
<td>Application of one or more exfoliating agents to the skin resulting in destruction of portions of the epidermis and/or dermis with subsequent tissue regeneration</td>
</tr>
<tr>
<td></td>
<td>Dermabrasion</td>
<td>Skin re-surfacing by sanding with a rapidly rotating abrasive tool. Often used to reduce scars, irregular skin surfaces and fine lines</td>
</tr>
<tr>
<td></td>
<td>Laser resurfacing</td>
<td>Application of laser to the skin which ultimately results in collagen reconfiguration and subsequent skin shrinking and tightening. Often used to reduce scars and wrinkles</td>
</tr>
<tr>
<td></td>
<td>Injectable fillers</td>
<td>An injectable substance is used to decrease frown lines, wrinkles and nasolabial folds. Substances include collagen, fat, hyaluronic acid and calcium hydroxyapatite</td>
</tr>
<tr>
<td>Other</td>
<td>Abdominoplasty</td>
<td>Removal of excess skin and repair of rectus muscle laxity (rectus diastasis). “Tummy tuck”</td>
</tr>
<tr>
<td></td>
<td>Breast augmentation</td>
<td>Surgical breast enhancement with silicone or saline implants (see Figure 39)</td>
</tr>
<tr>
<td></td>
<td>Calf augmentation</td>
<td>Augmentation of calf muscle with implants</td>
</tr>
<tr>
<td></td>
<td>Liposuction</td>
<td>Surgical removal of adipose tissue for body contouring (not a weight loss procedure)</td>
</tr>
<tr>
<td></td>
<td>Mastopexy</td>
<td>Surgical breast lift to elevate breast mound and tighten the skin envelope in ptotic breasts</td>
</tr>
<tr>
<td></td>
<td>Breast reduction</td>
<td>Surgical breast reduction for relief of physical symptoms</td>
</tr>
<tr>
<td></td>
<td>Sclerotherapy</td>
<td>Injection with a sclerosant to treat telangiectasias and varicose veins</td>
</tr>
</tbody>
</table>

Figure 39. Augmentation mammoplasty: incision lines and implant placement
Table 29. Pediatric Craniofacial Anomalies

<table>
<thead>
<tr>
<th>Definition</th>
<th>Epidemiology</th>
<th>Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleft Lip</td>
<td>Failure of fusion of maxillary and medial nasal processes</td>
<td>1 in 1000 live births (1 in 800 Caucasians, increased in Asians, decreased in Blacks) More common on the left (cleft of left lip/palate in boys has hereditary component)</td>
<td>Classified as incomplete/complete and uni/bilateral 2/3 cases: unilateral, left sided, male</td>
</tr>
<tr>
<td>Cleft Palate</td>
<td>Failure of fusion of lateral palatine/median palatine processes and nasal septum</td>
<td>Isolated cleft palate: 0.5 per 1000 (no racial variation) F &gt; M</td>
<td>Classified as incomplete/complete and uni/bilateral Isolated (common in females) or in conjunction with cleft lip (common in males)</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>Premature fusion of ≥1 cranial sutures Primary – abnormal suture, no known cause This may limit brain growth perpendicular to the suture and cause compensatory growth parallel to the fused suture</td>
<td>1 in 2000 live newborns; M:F = 52:48 Syndromes include: Crouzon’s, Apert’s, Saethre-Chotzen, Carpenter’s, Pfeiffer’s Jackson-Weiss and Boston-type syndromes</td>
<td>Syndromic – assoc. with genetic mutation Secondary (to microcephaly, hyperthyroid, rickets, etc.) Dx: irregular head shape, craniofacial abnormalities, x-ray</td>
</tr>
</tbody>
</table>

Figure 40. Types of cleft lips and palates

Table 30. American Society for Surgery of the Hand (ASSH) Classification of Congenital Hand Anomalies

<table>
<thead>
<tr>
<th>Classification</th>
<th>Example</th>
<th>Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of formation</td>
<td>Transverse absence (congenital amputation)</td>
<td>At any level (often below elbow/wrist)</td>
<td>Early prosthesis</td>
</tr>
<tr>
<td>Longitudinal absence</td>
<td>Absent humerus</td>
<td>Thalidomide-assoc.</td>
<td></td>
</tr>
<tr>
<td>Radial deficiency (radial club hand)</td>
<td>Radial deviation</td>
<td>Thumb hypoplasia M &gt; F</td>
<td>Physiotherapy + splinting Soft tissue release if splinting fails Distraction osteogenesis (Ilizarov) ± wedge osteotomy Tendon transfer Pollicization</td>
</tr>
<tr>
<td>Thumb hypoplasia</td>
<td>Degree ranges from small thumb with all components to complete absence</td>
<td>Depends on degree – may involve no treatment, webspace deepening, tendon transfer, or pollicization of index finger</td>
<td></td>
</tr>
<tr>
<td>Ulnar club hand</td>
<td>Rare, compared to radial club hand Stable wrist</td>
<td>Splinting and soft-tissue stretching therapies Soft-tissue release (if above fails) Correction of angulation (Ilizarov distraction)</td>
<td></td>
</tr>
<tr>
<td>Cleft hand</td>
<td>Autosomal dominant Often functionally normal (depending on degree)</td>
<td>First web space syndactyly release Osteotomy/tendon transfer of thumb (if hypoplastic)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 30. American Society for Surgery of the Hand (ASSH) Classification of Congenital Hand Anomalies (continued)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Example</th>
<th>Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of differentiation/ separation</td>
<td>Syndactyly</td>
<td>Fusion of ≥2 digits 1/3000 live births M:F = 2:1 Classified as partial/complete Simple (skin only) vs. complex (osseous or cartilaginous bridges)</td>
<td>Surgical separation before 6-12 mo of age Usually good result</td>
</tr>
<tr>
<td></td>
<td>Symbrachydactyly</td>
<td>Short fingers with short nails at fingertips</td>
<td>Digital separation (more difficult) Webspace deepening</td>
</tr>
<tr>
<td></td>
<td>Camptodactyly</td>
<td>Congenital flexion contracture (usually atPIP esp. 5th digit)</td>
<td>Early splinting Volar release Arthroplasty (rarely)</td>
</tr>
<tr>
<td></td>
<td>Clinodactyly</td>
<td>Radial or ulnar deviation Often middle phalanx</td>
<td>None (usually). If severe, osteotomy with grafting</td>
</tr>
<tr>
<td>Duplication</td>
<td>Polydactyly</td>
<td>Congenital duplication of digits May be radial (increased in Aboriginals and Asians) or central or ulnar (increased in Blacks)</td>
<td>Amputation of least functional digit Usually &gt; 1 yr of age (when functional status can be assessed)</td>
</tr>
<tr>
<td>Overgrowth</td>
<td>Macrodactyly</td>
<td>Rare</td>
<td>None (if mild) Soft tissue/bony reduction</td>
</tr>
<tr>
<td>Undergrowth</td>
<td>Brachydactyly</td>
<td>Short phalanges</td>
<td>Removal of non-functional stumps Osteotomies/tendon transfers Distraction osteogenesis Phalangeal/free toe transfer</td>
</tr>
<tr>
<td></td>
<td>Symbrachydactyly (brachysyndactyly)</td>
<td>Short webbed fingers</td>
<td>As above + syndactyly release</td>
</tr>
<tr>
<td>Constriction band syndrome</td>
<td>aka amniotic (annular) band syndrome</td>
<td>Variety of presentations</td>
<td>Urgent release for acute, progressive edema distal to band in newborn Other reconstruction is case-specific</td>
</tr>
<tr>
<td>Generalized skeletal abnormality</td>
<td>Achondroplasia, Marfan’s, Madelung’s</td>
<td>Variety of presentations</td>
<td>Treatment depends on etiology</td>
</tr>
</tbody>
</table>

### References

- General Plastic Surgery Concepts

- Hand
### Historical Context of Public Health

See Ethical, Legal and Organizational Aspects of Medicine, ELOAM17 for Canada Health Act

**Definitions**

- **population health**
  - health of the population as measured by health status indicators (e.g. life expectancy, low birth weight rates)
  - influenced by: physical, biological, social, environmental, and economic factors; personal health behaviours; health care services
  - refers to the prevailing or desired level of health in the population of a specific country/region/subset of population
  - considered to be more complex than the aggregate health status of individuals within a population

- **public health**
  - systematic organized efforts to protect, promote, and restore the health of the public
  - refers to the practices, procedures, institutions, and disciplines required to achieve the desired state of population health

- **public health and preventive medicine** (formerly called community medicine)
  - the postgraduate study of health and disease in the population or a specified community
  - five-year Royal College specialty training
  - goal: to identify and address health problems and evaluate the extent to which health services and others address these issues (http://rcpesc.medical.org/information/index.php?specialty=110&submit=Select)


### Public Health Services in Canada

**Mission:** to promote and protect the health of Canadians, and reduce health inequities through leadership, partnership, innovation, and action in public health

- local public health units and services within regional health authorities (in most provinces except Ontario, where local public health units are either autonomous or within local government) provide programs and activities for health protection, promotion, and disease prevention at local and regional levels
- catchment-area populations range from hundreds to thousands of people, covering areas of 15 to 1.5 million km²

### Legislation and Public Health in Canada

**Table 1. Legislation and Public Health in Canada**

<table>
<thead>
<tr>
<th>Federal</th>
<th>Provincial</th>
<th>Municipal (Ontario)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Canada</td>
<td>• Provides health services to First Nations, Aboriginal peoples, the Canadian military, and veterans</td>
<td>• Legislation is in the form of Acts and Regulations</td>
</tr>
<tr>
<td></td>
<td>• Approves new drugs and medical devices</td>
<td>• Local boards of health deliver programs mandated by provincial legislation</td>
</tr>
<tr>
<td></td>
<td>• Canadian Food Inspection Agency</td>
<td>• Boards of health are responsible for the delivery of most public health services, such as:</td>
</tr>
<tr>
<td></td>
<td>• Monitors food products</td>
<td>• Infectious disease control, including the follow-up of reported diseases and management of outbreaks</td>
</tr>
<tr>
<td></td>
<td>• Deals with animal-related infections</td>
<td>• Inspection of food premises including those in hospitals, nursing homes, and restaurants</td>
</tr>
<tr>
<td></td>
<td>• Regulates food labeling</td>
<td>• Family health services including pre-conception, preschool, school-aged, and adult health programs</td>
</tr>
<tr>
<td></td>
<td>• Public Health Agency of Canada (main Government of Canada agency responsible for public health)</td>
<td>• Tobacco control legislation enforcement</td>
</tr>
<tr>
<td></td>
<td>• An independent body created to strengthen public health capacity</td>
<td>• Assessment and management of local environmental health risks</td>
</tr>
<tr>
<td></td>
<td>• Focuses on preventing chronic diseases, preventing injuries, and responding to public health emergencies and infectious disease outbreaks</td>
<td>• Collection and dissemination of local health status reports</td>
</tr>
<tr>
<td></td>
<td>• Oversees immigration screening, protects Canadian borders (e.g. airport health inspection)</td>
<td>• Public dental health services to children</td>
</tr>
<tr>
<td></td>
<td>• Lobbies with the World Health Organization (WHO) on global health issues</td>
<td>• By-laws may be approved by municipal governments to facilitate public health issues</td>
</tr>
</tbody>
</table>

Source: The AFMC Primer on Population Health is the core text for the MCC and is available as an online resource on the AFMC website.

For the LMCC exam, it is recommended that you also read all of Chapter 15 in Shah CP. Public health and preventive medicine in Canada, 5th ed. Toronto: Elsevier, 2003

Topics covered include:
- Primary, secondary, tertiary and quaternary health care
- Physician remuneration, organization of primary care, new model of primary health care
- Services of other health care professionals: nurses, dentists, chiropractors, podiatrists, optometrists, midwives, pharmacists, and alternative health care providers
- Hospitals and acute care facilities
- Local public health units: departments: communicable disease control, women’s health and maternal and child health, health promotion, dental health, environmental health, population health assessment and health surveillance
- Home care
- Palliative care
- Services for mental illnesses
- Services for cancer patients
- Services for persons with special needs
- Voluntary agencies
- Self-help groups
- Telehealth

Historical Perspective
Over the last century, Public Health has evolved through three main epidemiological phases:
- **Infectious diseases:** controlled in the more developed world but an issue in less developed countries (e.g. polio, malaria)
- **Chronic diseases:** chronic diseases and other noncommunicable conditions have increased morbidity and mortality (e.g. heart disease and cancer due to risk factors and/or exposures)
- **Re-emerging infectious diseases:** new or re-emergent infections emerge due to unfamiliar or new pathogens, inefficient or inappropriate antibiotic use, travel, and global warming (e.g. HIV, drug resistant TB and malaria)

Five Core Functions for All Public Health Units
- Population health assessment
- Health, injury, and disease surveillance
- Health promotion
- Disease and injury prevention
- Health protection
Concepts of Health

- **disease**: abnormal, medically-defined changes in the structure or function of the human body
- **illness**: an individual’s experience or subjective perception of a lack of physical or mental well-being and consequent inability to function normally in social roles
- **impairment**: any loss or abnormality of psychological, physiological, or anatomical structure or function
- **disability**: any restriction or lack of ability to perform an activity within the range considered normal for a human being
- **handicap**: the disadvantage for an individual arising due to impairment and disability
  - limits or prevents the fulfillment of an individual’s normal role as determined by society and depends on age, sex, social, and cultural factors
  - changes the individual's relationship with the physical and social environment
- **health equity**: when all people have the opportunity to attain their full health potential and no one is “disadvantaged from achieving this potential because of their social position or other socially determined circumstance.” Differs from health equality
- **health equality**: defined as where populations have equal or similar health status. Health inequities are those which are considered unjust and/or preventable

Determinants of Health

- 1974: the Honourable Marc Lalonde, federal Minister of Health, presented the health field concept entitled *A New Perspective on the Health of Canadians* which included four areas that interact to determine health: human biology, environment, lifestyle, and health care
- since then this concept has been expanded to include numerous determinants of health (see below)

---

**Table 2. Health Determinants of Vulnerable Populations**

<table>
<thead>
<tr>
<th>Population</th>
<th>Definition</th>
<th>Psycosocial/ Socioeconomic</th>
<th>Physical Environment</th>
<th>Individual Behaviour</th>
<th>Population-Specific Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aboriginal Peoples</strong></td>
<td>Four specific groups: First Nations Status Indians (registered under the Indian Act), non-Status Indians, Métis, and Inuit</td>
<td>Low income, Family violence, Low education status, Unemployment, Homelessness, Longer length of disability</td>
<td>Crowded housing, Inefficient ventilation, Environmental toxins (botulism), TB declining but prevalence higher than rest of population</td>
<td>Smoking, Substance misuse, Excessive gambling, Poor nutrition, Sedentary lifestyle, High BMI, High risk sexual behaviours</td>
<td>Mental health awareness, Aboriginal-specific diabetes initiatives, Substance abuse treatment programs</td>
</tr>
</tbody>
</table>

---

**Definitions of Health**

- First multidimensional definition of health, as defined by the WHO in 1948: “A complete state of physical, mental and social well being and not merely the absence of illness.”
- WHO updated the definition (socio-ecological definition) of health in 1986: “The ability to identify and to realize aspirations, to satisfy needs, and to change or cope with the environment. Health is therefore a resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities.”
- Other definitions of health have since been proposed that incorporate other dimensions of health (e.g. “Health is a social, economic, and political issue and above all a fundamental human right” – The People’s Charter for Health)
Table 2. Health Determinants of Vulnerable Populations (continued)

<table>
<thead>
<tr>
<th>Determinants of Health</th>
<th>PH4</th>
<th>Determinants of Health</th>
<th>Toronto Notes 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Income and social status</td>
<td></td>
<td>• Education and literacy</td>
<td></td>
</tr>
<tr>
<td>• Social support networks</td>
<td></td>
<td>• Employment and working conditions</td>
<td></td>
</tr>
<tr>
<td>• Economic environment</td>
<td></td>
<td>• Physical environment</td>
<td></td>
</tr>
<tr>
<td>• Personal health practices and coping skills</td>
<td></td>
<td>• Healthy child development</td>
<td></td>
</tr>
<tr>
<td>• Biology and genetic endowment</td>
<td></td>
<td>• Health services</td>
<td></td>
</tr>
<tr>
<td>• Gender</td>
<td></td>
<td>• Culture</td>
<td></td>
</tr>
<tr>
<td>Source: Public Health Agency of Canada</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

New Immigrants to Canada

- Mandatory medical exams on entry to Canada by a designated medical practitioner:
  - Complete medical examination for all persons of all ages
  - Chest x-ray and report for persons 11 yr of age and over
  - Urinalysis for persons 5 yr of age and over
  - Syphilis serology for persons 15 yr of age and over
  - HIV testing for applicants 15 yr of age and over, as well as for those children who have received blood or blood products, have a known HIV-positive mother, or have an identified risk. An ELISA HIV screening test should be done for HIV 1 and HIV 2
  - Serum creatinine if the applicant has hypertension (resting blood pressure greater than 140/90 mmHg), a history of treated hypertension, diabetes, autoimmune disorder, persistent proteinuria, or kidney disorder

Example of Primary Prevention: Gardasil Vaccine and its Efficacy in the Prevention of Cervical Cancer

Gardasil® is a quadrivalent HPV vaccine covering strains 6,11,16,18. The efficacy of Gardasil® was studied in 4 randomized, double-blind, placebo controlled trials on females between 16 and 26 yr of age and was found to prevent nearly 100% of precancerous cervical changes for up to 4 yr after vaccination.

Example of Primary Prevention: The Obesity Prevention Campaign by the Ontario Medical Association (OMA)

The OMA campaign has involved calls for early action on menu labeling from leaders in the restaurant field, lobbying the provincial government to enact legislation requiring calorie contents to be listed on menus at chain restaurants and school cafeterias, and an education campaign to inform the public about the impact of caloric intake on weight gain and obesity.


Disease Prevention Strategies

- measures aimed at preventing the occurrence, interrupting through early detection and treatment, or slowing the progression of disease/mitigating the sequelae

Primary Prevention

- implemented to prevent disease from occurring
- immunization programs exist in most countries to address major causes of pediatric morbidity and mortality that are preventable by vaccines, e.g. measles, diphtheria, pertussis, tetanus, polio, and tuberculosis (not routine in Canada or the U.S.)
• additional immunizations are offered in Canada depending on jurisdiction: mumps, rubella, rotavirus, hepatitis B, Haemophilus influenzae type B, varicella, HPV, conjugated pneumococcal and meningococcal vaccines (see Pediatrics, P3)

**Secondary Prevention (Screening)**
• presumptive identification (not diagnosis) of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly
• types of screening
  ▪ mass screening: screening all members of a population for a disease (e.g. phenylketonuria (PKU) and hypothyroidism in all newborns)
  ▪ selective screening: screening of a specific subgroup of the population at risk for a disease (e.g. mammography in women >50 yr old)
  ▪ multiphasic screening: the use of many measurements and investigations to look for many disease entities (e.g. periodic health exam)

Table 3. Ideal Criteria for Screening Tests

<table>
<thead>
<tr>
<th>Disease</th>
<th>Test</th>
<th>Health Care System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes significant suffering and/or death</td>
<td>High specificity and sensitivity</td>
<td>Adequate capacity for reporting, follow-up, and treatment of positive screens</td>
</tr>
<tr>
<td>Natural history must be understood</td>
<td>Safe, rapid, easy, relatively inexpensive</td>
<td>Cost effective</td>
</tr>
<tr>
<td>Must have an asymptomatic stage that can be detected by a test</td>
<td>Acceptable to providers and to population</td>
<td>Sustainable program</td>
</tr>
<tr>
<td>Early detection and intervention must result in improved outcomes</td>
<td></td>
<td>Clear policy guidelines</td>
</tr>
<tr>
<td>Incidence is not too high or too low</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Tertiary Prevention**
• treatment and rehabilitation of disease after it has been diagnosed so as to prevent progression and permanent disability (e.g. HbA1c, eye, and foot monitoring for diabetes)

**Health Promotion Strategies**

Table 4. Disease Prevention versus Health Promotion Approach

<table>
<thead>
<tr>
<th>Disease Prevention</th>
<th>Health Promotion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health</strong> = absence of disease</td>
<td><strong>Health</strong> = positive and multidimensional concept</td>
</tr>
<tr>
<td>Medical model (passive role)</td>
<td>Participatory model of health</td>
</tr>
<tr>
<td>Aimed mainly at high-risk groups in the population</td>
<td>Aimed at the population in its total environment</td>
</tr>
<tr>
<td>Concerns a specific pathology</td>
<td>Concerns a network of issues</td>
</tr>
<tr>
<td>One-shot strategy</td>
<td>Diverse and complementary strategies</td>
</tr>
<tr>
<td>Directive and persuasive strategies</td>
<td>Facilitating and enabling approaches</td>
</tr>
<tr>
<td>Directive measures enforced in target groups</td>
<td>Incentive measures offered to the population</td>
</tr>
<tr>
<td>Focused mostly on individuals and groups of subjects</td>
<td>Focused on a person’s health status and environment</td>
</tr>
<tr>
<td>Preventive programs considered the affairs of professional groups from health disciplines</td>
<td>Non-professional organizations, civic groups, local, municipal, regional, and national governments necessary for achieving the goal of health promotion</td>
</tr>
</tbody>
</table>


**Healthy Public Policy**
• characterized by an explicit concern for health and equity in all areas of policy and by an accountability for health impact
• main aim: to create a supportive environment to enable people to lead healthy lives, thereby making healthy choices easier for citizens
• government sectors must take into account health as an essential factor when formulating policy and should be accountable for the health consequences of their policy decisions
• methods:
  ▪ fiscal: imposing additional costs (e.g. taxes on tobacco and alcohol)
  ▪ legislative: implementing legal deterrents (e.g. smoking bans, legal alcohol drinking age)
  ▪ social: improving health beyond providing universally funded health care (e.g. providing affordable housing)

Source: International Conference on Health Promotion, Adelaide, South Australia (1998)

**Community Development**
• process of community members identifying issues and problems affecting their community and subsequently developing the skills and capacity to implement change

Source: Labonte’s Model of Community Development

**Disease Prevention Strategies**
• **Primary**: before disease occurs (e.g. immunizations, seatbelt use, smoking cessation programs for lung cancer prevention)
• **Secondary**: early detection of disease (e.g. mammography, routine Pap smears)
• **Tertiary**: treatment and rehabilitation of existing disease (e.g. ACE inhibitor for hypertension)

Within these three stages of prevention there can be both:
• **Passive prevention**: measures that operate without the person’s active involvement (e.g. airbags in cars)
• **Active prevention**: measures that a person must do on their own (e.g. wearing a seatbelt)

**Ottawa Charter for Health Promotion (1986)**
Governments and health care providers should be involved in a health promotion process that includes:
• Building healthy public policy
• Creating supportive environments
• Strengthening community action
• Developing personal skills
• Re-orienting health services

**Jakarta Declaration on Health Promotion into the 21st Century (WHO 1993)**
• Reiterated the commitment to health promotion
• First of the health promotion conferences to involve the private sector
• Formally cited poverty as the greatest threat to health
• Priorities for health promotion:
  ▪ Promote social responsibility for health
  ▪ Increase investments for health development
  ▪ Consolidate and expand partnerships for health
  ▪ Increase community capacity and empower the individual
  ▪ Secure an infrastructure for health promotion

**4 Ps Influencing Health Marketing**
Product: good health
Price: what a person must give up if he or she accepts the product “pursuing good health”
Place: the distribution channels used to reach the consumer (e.g. distributing pamphlets at the doctor’s office)
Promotion: the way in which the product is promoted to the consumer
Community-Based Prevention
- public health service (prevention or promotion) focused on an entire community as opposed to only high-risk groups/individuals
- “community-based approaches” are population-based multifactorial initiatives that make use of community organization and social marketing to elicit change at the community level (e.g. Saskatoon’s In Motion program – see sidebar)
- numerous preventable risk factors are addressed by multiple health promotion strategies

Health/Social Marketing
- application of the principles of commercial marketing to promote healthy changes
- involves target group analysis and segmentation of the market for specific messages and promotion strategies
- employed by both the health system (e.g. pamphlets providing health information about HIV) and by industry (e.g. in medication advertisements)

Behaviour Change
- health education serves to:
  - increase knowledge and skills
  - encourage positive behaviour changes and discourage unhealthy choices
- health education is an important component of eliciting behaviour change
- behaviour is a result of three factors
  1. predisposing factors: knowledge, attitude, beliefs, values, intentions
  2. enabling factors: skills, supports
  3. reinforcing factors: health care professionals and the social context of family and community

Health Belief Model (1975)
- behaviours undertaken by individuals in order to remain healthy are a function of a set of interacting beliefs
- beliefs include an individual’s perception of his or her susceptibility to a disease, the severity of the disease, and the benefits and costs of health-related actions
- beliefs are modified by socio-demographic and psychosocial variables
- individuals must believe that the action will have positive consequences
- individuals must be in a state of readiness
- behaviour can be stimulated by cues to action, which are specific events that can encourage preventive health decisions and actions (e.g. physician recommendation, public advertising)

Stages of Change Model
- provides a framework in which the Health Belief Model is applied to facilitating behaviour change (e.g. quitting smoking)

1. Precontemplation: the individual is not seriously considering change (for various reasons) and is not interested in any kind of intervention
2. Contemplation: the individual begins to seriously consider making the change within the foreseeable future (often defined as six months)
3. Preparation: the individual begins experimenting, making small changes; he or she resolves to make a serious attempt in the future (usually defined as 30 days)
4. Action: the individual is actively involved in making the change, using different techniques
5. Maintenance: the individual must learn to successfully cope with temptations to return to the previous behaviour pattern

Risk Reduction Strategies
- risk reduction: lower the risk to health without eliminating it (e.g. avoiding sun to lower risk of skin cancer)
- harm reduction: tolerance of some degree of risk behaviour, while aiming to minimize the adverse outcomes associated with these behaviours (e.g. needle exchange programs)

Innovation-Diffusion Theory
- theory that describes the process by which health promotion efforts spread in populations
- aims to identify the most effective methods of health promotion within a population
- Roger’s diffusion theory illustrates the following hierarchy within populations:
  - innovators
  - early adopters (community leaders)
  - early majority
  - late majority
  - laggards

Saskatoon’s In Motion
- is a community-based strategy to increase physical activity through collaborative community efforts. 98% of all Saskatoon schools have now committed to meeting In Motion goals, including at least 30 min of daily physical activity per child. Elementary schools also report that students are active on one additional day per week compared to pre-program activity levels. In Motion is viewed as a best practice strategy and is now being implemented in communities and provinces across Canada.


Example of Harm Reduction Strategy
Summary of Findings from the Evaluation of a Pilot Medically Supervised Safer Injecting Facility
CMAJ 2006;175:1399-1404
Background: This study discusses the outcomes among a population of illicit injection drug users (IDUs) after initiating a supervised safe injecting facility in Vancouver, September 2003. Legal exemption by the Canadian government was granted such that an evaluation of its results be conducted over a 3 yr period.
Study Population: IDUs of the Vancouver area were allowed to inject previously obtained illicit drugs under the supervision of nurses and physicians. IDUs were offered addiction counseling and supports for appropriate community resources. A random sample of 670 IDUs was recruited and monitored from Dec 2003-July 2004.
Results: Characteristics of IDUs who used the safe injecting facility included age <30 yr; history of public drug use, homelessness, daily heroin and/or cocaine injection, and recent history of overdose. Mean measures of public order problems were taken 6 wk before and 12 wk after initiation of the safer injecting facility. It was found that the mean number of IDUs injecting daily in public, along with the mean number of publically discarded syringes were reduced by approximately half.
Conclusions: Overall, it has been found that the safer injecting facility in Vancouver has been successful in attracting IDUs at increased risk of HIV, overdose, and public injection of substances. This has resulted in lower incidences of public drug use, publicly discarded syringes and sharing of needles. Other studies associated with this one have demonstrated that there has been no increase in the drug dealing, drug related crimes, or rates of new IDUs in the area surrounding the safer injecting facility.

Characteristics of Innovations that Influence Positive Adaptability of the Change
- Simple
- Workable
- Reversible
- Flexible
- Advantageous
- Cost effective
- Low risk
- Compatible with value systems

Figure 2. Stages of change model

To ronto Notes 2014
Measurements of Health and Disease in a Population

Life Expectancy
• the expected number of years that an individual will live based on standardized death rates for the population
• usually qualified by country, gender, and age

Crude Death Rate
• mortality rate from all causes of death per 1000 in the population

Age Standardized Rate
• adjustment of the crude rate of a health-related event using a “standard” population
• standard population is one with a known number of persons in each age and sex group (e.g. the 1991 census data for Canada using 5-yr age intervals for males and females)
• standardization prevents bias which could be made by comparing crude rates from two dissimilar populations (e.g. crude death rates over a number of decades are not comparable as the population age distribution has changed with time)

Standardized Mortality Rate
• the ratio of the observed (actual) number of deaths to the expected number of deaths for a group (e.g. age, race, gender, etc.)
• useful for comparing populations that are significantly different in some aspect (e.g. the causes of death in more and less developed countries)

Infant Mortality Rate (IMR)
• number of deaths among children under 1 yr of age reported during a given time period divided by the number of live births reported during the same time period and expressed per 1000 live births per year

Maternal Mortality Rate (MMR)
• number of deaths of women during pregnancy and due to puerperal causes per 100,000 live births per year

Proportional Mortality Ratio (PMR)
• proportion of all deaths in a specified population over a given period of time attributable to a specific cause
  ▪ each cause is expressed as a percentage of all deaths, with the sum of all causes adding to 100%

Potential Years of Life Lost (PYLL)
• calculated for a population using the difference between the actual age at death and a standard/expected age at death
• increased weighting of mortality at a younger age

Disability Adjusted Life Year (DALY)
• quantitative indicator of the burden of diseases that reflects the total amount of disability-free life years lost
• includes loss from premature mortality and loss due to a degree of disability over a specific period of time; these disabilities can be physical or mental

Quality Adjusted Life Year (QALY)
• a value from 0 to 1 assigned to a yr of life based on perceived quality of life; a yr in “perfect” health is considered equal to 1 QALY, the value of a yr in ill health would be lowered based on the burden of disease
• it is possible to have “states worse than death” for example QALY <0 for extremely serious conditions

Epidemiology

Population
• a collection of individuals who share a common trait (most commonly applied to a geographic area but it could be another factor such as ethnic group)
**Sample**
- A selection of individuals from a population or set of observations
- Types:
  - Random: all are equally likely to be selected
  - Systematic: an algorithm is used to select a subset
  - Stratified: separate representations of more than one subgroup
  - Cluster: grouped in space/time to reduce costs
  - Convenience: non-random inclusion, usually volunteers

**Sample Size**
- Sample size contributes to the statistical precision of the observed estimate
- Increasing the sample size decreases the probability of type I and type II errors (see PH14)

**Bias**
- Non-random error leading to a deviation of inferences or results from the truth
- Any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth
  - **Lead-time**: Time between early diagnosis with screening and when diagnosis would have been made without screening
  - **Lead-time bias**: Over-estimation of survival when the estimate is made from the time of screening, instead of the later time when the disease would have been diagnosed without screening (see Figure 3)
  - **Incidence-prevalence bias**: When prevalent cases include long-term survivors who have a better prognosis than some incident cases
  - **Length-time bias**: Overestimation of the survival time due to the sampling of prevalent as opposed to incident cases
    - Selection of prevalent cases will favor the over-inclusion of longer-living cases rather than newly-diagnosed incident cases, some of whom may have short survival times
  - **Sampling bias**: Occurs with the selection of a sample that does not truly represent the population
    - Sampling procedures should be chosen to prevent or minimize bias
  - **Recall bias**: When individuals with a disease are more prone to recalling or believing they were exposed to a possible causal factor than those who are free of disease

**Figure 3. Lead time bias**

**Confounder**
- A variable that is related to both the exposure and outcome but is not measured or is not distributed equally between groups
- Distorts the apparent effect of an exposure or risk because it may not be possible to separate/ control for the contribution of a single causal factor to an effect (e.g., late maternal age could be a confounder in an investigation of birth order >4 and risk of developing Trisomy 21)

**Prevalence**
- Total number of cases in a population over a defined period of time (see sidebar)
- Two forms of prevalence
  - **Point prevalence**: Attemps to measure the frequency of all disease at one specific point in time, therefore knowledge of the time of onset of disease is not required
  - **Period prevalence**: Measure constructed from prevalence at a point in time, plus new cases and recurrences over a defined period of time
- Depends on **incidence rate** (see sidebar) and disease duration from onset to termination (cure or death)
- Favours the inclusion of chronic over acute cases and may be used to present a biased picture of the disease
- Prevalence studies are cross-sectional and cannot be used for causal inferences
- Prevalence figures are useful for determining the extent of a disease and can aid in the rational planning of facilities and services

**Sensitivity**
- Proportion of people with disease who are correctly identified by a positive test

**Specificity** (refer to sidebar)
- Proportion of people without disease who are correctly identified by having a negative test

---

**Incidence and Prevalence**

- **Incidence**: Number of new cases of disease in a time interval (measures the rate of new infections)
  - \[ \text{Incidence} = \frac{\text{number of new cases}}{\text{total population at risk} \times \text{per unit population}} \]
  - (e.g. 100,000)

- **Prevalence**: Number of existing cases of disease at a point in time (measures the frequency of disease at a point in time)
  - \[ \text{Prevalence} = \frac{\text{number of existing cases}}{\text{total population} \times \text{per unit population}} \]
  - (e.g. 100,000)

**SPIN**: Use a **Specific** test to rule **IN** a hypothesis. Note that specific tests have very few false positives. If you get a positive test, it is likely a true positive.

**SNOUT**: Use a **Sensitivity** test to rule **OUT** a hypothesis. Note that sensitive tests have very few false negatives. If you get a negative test, it is likely a true negative.
Figure 4. Understanding sensitivity and specificity

Figure 4a. Hypothetical population

Figure 4b. Results of diagnostic test on hypothetical population

Figure 4c. Sensitivity of test (e.g. 24/30 = 80% sensitive)

Figure 4d. Specificity of test (e.g. 56/70 = 80% specific)

Source: Loong TW. Understanding sensitivity and specificity with the right side of the brain. BMJ 2003;327:716-719

TP = True positive   TN = True negative   FP = False positive   FN = False negative

Likelihood Ratio (LR)
• LR+ indicates how much the probability of disease increases if the test is positive
• LR- indicates how much the probability of disease decreases if the test is negative

\[
LR+ = \frac{\text{Sensitivity}}{1 - \text{Specificity}} = \frac{TP/(TP+FN)}{FP/(TN+FP)}
\]

\[
LR- = \frac{1 - \text{Sensitivity}}{\text{Specificity}} = \frac{FN/(TP+FN)}{TN/(TN+FP)}
\]

Positive Predictive Value (PPV)
• Proportion of people with a positive test who have the disease

\[
PPV = \frac{TP}{TP + FP}
\]

Negative Predictive Value (NPV)
• Proportion of people with a negative test who are free of disease

\[
NPV = \frac{TN}{TN + FN}
\]

Pre-test Probability
• An estimate of the likelihood a particular patient has a given disease based on known factors such as clinical assessment prevalence of disease in the population. Together with a post-test probability this can be used to interpret a diagnostic test or a series of tests

\[
\text{Pre-test Odds} = \frac{\text{Prevalence}}{1 - \text{Prevalence}}
\]

Post-test Probability
• A revision of the probability of disease after a patient has been examined or a diagnostic test has been conducted
• Calculation process can be more explicit using results from epidemiologic studies, knowledge of the accuracy of tests and Bayes’ theorem
• The post-test probability from clinical examination is the basis of consideration when ordering diagnostic tests or imaging studies
• After each iteration the resultant post-test probability becomes the pre-test probability when considering new investigations

\[
\text{Post-test Odds} = \text{Pre-Test Odds} \times LR
\]

\[
\text{Post-test Probability} = \frac{\text{Post-test odds}}{\text{Post-test odds} + 1}
\]

Intention-To-Treat (ITT)
• A strategy for analyzing data in which all participants are included in the group to which they were assigned, whether or not they completed the requirements of that group
• This is to limit the bias introduced by issues of compliance and to simulate real world situations in which not all patients/providers adhere to the study allocation protocol

Relative Risk (RR)
• Ratio of the incidence of a health outcome among the exposed population to the incidence of the health outcome in the non-exposed population

\[
\text{Relative Risk (RR)} = \frac{\text{PPV}}{1 - \text{NPV}} = \frac{\frac{TP}{TP+FP}}{\frac{FN}{TN+FP}}
\]

Attributable Risk (AR)
• Rate of a health outcome attributable to a hypothetical risk factor for that outcome
• [Incidence in exposed population] - [Incidence in non-exposed]
• Attributable risk assumes causation

\[
\text{Attributable Risk} = \frac{\text{PPV} \times (1 - \text{NPV})}{\text{PPV} - (\text{PPV} \times (1 - \text{NPV}))}
\]

Advanced Neoplasia

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>68</td>
<td>147</td>
</tr>
<tr>
<td>Negative</td>
<td>216</td>
<td>2234</td>
</tr>
<tr>
<td>Total</td>
<td>284</td>
<td>2381</td>
</tr>
</tbody>
</table>

Sensitivity = 68/284 = 23.9%
Specificity = 2234/2381 = 93.8%

\[
\text{LR+} = \frac{0.239}{1 - 0.938} = 3.85
\]

\[
\text{LR-} = \frac{1 - 0.239}{0.938} = 0.81
\]

\[
\text{PPV} = \frac{68}{(68 + 147)} = 31.6%
\]

\[
\text{NPV} = \frac{2234}{(2234 + 216)} = 91.2%
\]

Figure 5. Clinical epidemiology definitions and practical example using FOBT testing in advanced colon cancer
Pre-test Probability
• an estimate of the likelihood a particular patient has a given disease based on known factors

Post-test Probability
• a revision of the probability of disease after a patient has been interviewed and examined
• calculation process can be more explicit using results from epidemiologic studies, knowledge of the accuracy of tests, and Bayes’ theorem
• the post-test probability from clinical examination is the basis of consideration when ordering diagnostic tests or imaging studies
  ▪ after each iteration the resultant post-test probability becomes the pre-test probability when considering new investigations


Effectiveness of Interventions

DEFINITIONS

Relative Risk Reduction (RRR)
• proportional reduction in rates of adverse outcomes between experimental and control participants in a trial

Absolute Risk Reduction (ARR)
• absolute arithmetic difference in rates of adverse outcomes between experimental and control participants in a trial
• it is hypothesized that events will occur more often in control group than in experimental group where the intervention is protective (e.g. a vaccine)

Absolute Risk Increase (ARI)
• absolute arithmetic difference in rates of adverse outcomes between control and experimental participants in a trial
• it is hypothesized that events will occur more often in experimental group than in control group when the intervention is harmful (e.g. alcohol excess)

Number Needed to Treat (NNT)
• number of patients who need to be treated to achieve one additional favourable outcome
• only one of many factors that should be taken into account in clinical or health system decision making (e.g. must take into account cost, ease, feasibility, etc. of intervention)
  ▪ a condition with death as a potential outcome can have a higher NNT (and be acceptable), as compared to an intervention to prevent an outcome with low morbidity, in which a low NNT would be necessary

Number Needed to Harm (NNH)
• number of patients who, if they received the experimental treatment, would lead to one additional patient being harmed, compared with patients who received the control treatment

Adherence (formerly compliance)
• degree to which a patient follows a treatment plan
Effectiveness, Efficacy, Efficiency

- three measurements indicating the relative value (beneficial effects vs. harmful effects) of an intervention
  - **efficacy**: the extent to which a specific intervention produces a beneficial result under ideal conditions
  - ideally, based on the results of a randomized control trial (the theoretical impact)
  - **effectiveness**: measures the benefit of an intervention under usual conditions of clinical care
    - considers both the efficacy of an intervention and its actual impact on the real world, taking into account access to the intervention, whether it is offered to those who can benefit from it, its proper administration, acceptance of intervention, and degree of adherence to intervention
  - **efficiency**: a measure of economy of an intervention with known effectiveness
    - considers the optimal use of resources (e.g. money, time, personnel, equipment, etc.)

### Types of Study Design

#### Qualitative vs. Quantitative

<table>
<thead>
<tr>
<th>Qualitative</th>
<th>Quantitative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generates hypothesis (Why? What does it mean?)</td>
<td>Tests hypothesis (What? How much/many?)</td>
</tr>
<tr>
<td>Inductive (specific to general): “bottom up”</td>
<td>Deductive (general to specific): “top down”</td>
</tr>
<tr>
<td>Observation → pattern → tentative hypothesis → theory</td>
<td>Theory → hypothesis → observation → confirmation</td>
</tr>
<tr>
<td>Sampling approach to obtain representative coverage of ideas or concepts</td>
<td>Sampling approach to obtain representative coverage of people in the population</td>
</tr>
<tr>
<td>Narrative: rich, contextual, and detailed information from a small number of participants</td>
<td>Numeric: frequency, severity, and associations from a large number of participants</td>
</tr>
</tbody>
</table>

Source: Adapted from http://phprimer.afmc.ca

#### Quantitative Research Methods

![Figure 7. Quantitative study designs](http://phprimer.afmc.ca)
# Observational Study Designs

- observational studies involve neither the manipulation of the exposure of interest nor randomization of the study subjects
- there are two main subtypes of observational studies: descriptive and analytic studies

## Descriptive Studies
- describe the events and rates of disease with respect to person, place and time and to estimate disease frequency and time trends
- first sets of studies and are used to generate an etiologic hypothesis, not test a hypothesis

## Analytic Studies
- observational studies used to test a specific hypothesis
- includes ecological studies, cohort studies, case-control studies, and cross-sectional studies

## Table 6. Observational Study Designs

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Ecological</th>
<th>Cross-Sectional</th>
<th>Case-Control (Figure 8)</th>
<th>Cohort (Figure 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Units of analysis are populations or groups of people, rather than individuals</td>
<td>Assessment of individuals with respect to presence and absence of exposures and diseases at the same point in time</td>
<td>Samples a group of people who already have a particular outcome (cases) and compares them to a similar sample group without that outcome (controls)</td>
<td>Subjects are sampled and, as a group, classified on the basis of presence or absence of exposure to a particular risk factor</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>Population (e.g., geographic areas)</td>
<td>Population (sample)</td>
<td>Two study sample populations are compared: cases and controls</td>
<td>One or more cohorts Cohort: group of people with common characteristics (e.g., year of birth) Divided into measured exposed vs. non-exposed groups</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>Accurate descriptions of the average exposure or risk of disease for a population Collect information from each person at one particular time Tabulate the numbers in groups (e.g., by presence or absence of disease/factor of interest) Make 2 x 2 table and compare groups Estimate prevalence</td>
<td>Collect information about exposures Select all the cases of a specific disease during a specific time frame Representative of spectrum of clinical disease Select control(s) Represent the general population To minimize risk of bias, may select more than one control group and/or match controls to cases (e.g., age, gender) Association can be concluded between the risk factor and the disease (odds ratio) Estimate incidence</td>
<td>Ask cases and controls about exposures Select all the cases of a specific disease during a specific time frame Representative of spectrum of clinical disease Select control(s) Represent the general population To minimize risk of bias, may select more than one control group and/or match controls to cases (e.g., age, gender) Association can be concluded between the risk factor and the disease (odds ratio) Estimate incidence</td>
<td>Subjects are followed for a specific period of time to determine development of disease in each exposure group Prospective: measuring from the exposure to the future outcomes – looking forward Retrospective: measuring from outcomes to possible risk factors or protective factors – looking back Collect information on factors from all persons at the beginning of the study Tabulate the number of persons who develop the disease or other measured outcomes of morbidity Provides estimates of incidence, relative risk, attributable risk</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Quick, easy to do Uses readily available data Generates hypothesis Determines association between variables Quick and uses limited resources Surveys with validated questions allows comparison between studies Used when disease in population is rare (less than 10% of population) due to increased efficiency Less costly and time consuming Shows an association between a factor and an outcome/several outcomes Stronger evidence for causation</td>
<td>Does not allow for assessment of temporal relationship or causation between variables Recall bias (see PH8) Recall bias (see PH8) Confounding Selection bias for controls Only one outcome can be measured</td>
<td>By itself, cannot establish causation Confounding factors are common as the cohort self-selects the exposure, or unknown/unknown factors are associated with the measured exposure Cost and duration of time needed to follow cohort</td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Poor generalizability to individual level (not direct assessment of causal relationship) Ecological fallacy: an incorrect inference about individuals in the population</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An example of a descriptive study is one that explores the rates of AIDS by age, sex, geographic distribution, and over time.

An example of an ecological study would be one looking at the association between smoking rates and lung cancer rates in different countries.

An example of an ecological fallacy would be concluding that red wine drinking leads to lower risk of death from CVS disease after an ecological study shows that France has a higher rate of red wine consumption and a lower rate of death from CVS causes.

An example of an ecological study is the Framingham Heart Study, which assesses the long-term cardiovascular risks of diet, exercise, medications such as Aspirin®, etc.

An example of a famous cohort study is the Framingham Heart Study, which assesses the long-term cardiovascular risks of diet, exercise, medications such as Aspirin®, etc.

An example of a famous case control study is by Sir Richard Doll who demonstrated the link between tobacco smoking exposure and lung cancer cases.

An example of an ecological study is that which examines the distribution of BMI by age in Ontario at a particular point in time.
Experimental Study Designs

- not discussed here are non-randomized control trials (e.g. allocation by clinic or other non-random basis – performed when randomization is not possible) and clinical trials (test treatments or laboratory tests in human subjects)

1. RANDOMIZED CONTROLLED TRIAL (RCT)

**Definition**
- subjects are assigned by random allocation to two or more groups, one of which is the control group, the other group(s) receive(s) an experimental intervention

**Subjects**
- individuals are separated into groups by a random process to ensure as much as possible equal distribution of known and unknown factors except for the experimental exposure (e.g. the treatment)

**Methods**
- random allocation of individuals into two or more treatment groups through a centralized concealed process
- method of assessment to reduce bias
  - **single-blind**: subject does not know group assignment (intervention or placebo)
  - **double-blind**: subject and observer both unaware of group assignment
  - **triple-blind**: subject, observer, and analyst unaware of group assignment (rarely done)
- one group receives placebo or standard therapy
- one or more groups receive(s) the intervention(s) under study
- the outcome is measured and the groups are compared
- all other conditions are kept the same between groups

**Advantages**
- “gold standard” of studies, upon which the practice of EBM is founded
- provides the strongest evidence for effectiveness of intervention
- with sufficient sample size and appropriate randomization, threats to validity are minimized
- allows prospective assessment of the effects of intervention while minimizing bias

**Disadvantages**
- some exposures are not amenable to randomization (e.g. cannot randomize subjects to poverty/wealth or to harmful exposures such as smoking) due to ethical or feasibility concerns
- difficult to randomly allocate groups (e.g. communities, neighbourhoods)
- difficult to study rare events, since RCTs would require extremely large sample sizes
- costly

Other Study Designs

1. META-ANALYSIS

**Definition**
- combines the results of independent (studies identified through a systematic review) that address a common research hypothesis into one large study

**Subjects**
- combination of all the subjects used in original studies

**Methods**
- selection of relevant studies from the published literature which meet quality criteria
- statistical models used to combine the results of each independent study
- provides a summary statistic of overall results as well as graphic representation of included studies

**Advantages**
- attempts to overcome the problem of reduced power due to small sample sizes of individual studies
- ability to control for inter-study variation

**Disadvantages**
- sources of bias may not be controlled for
- reliance on published studies may increase the potential conclusion of an effect as it can be difficult to publish studies that show no significant results (publication bias)
- the decision to include/reject a particular study is subjective
Methods of Analysis

Distributions

- distribution describes the probability of events
- normal (Gaussian) or non-normal (skewed, bimodal, etc.)
- characteristics of the normal distribution
  - mean = median = mode
  - 67% of observations fall within one standard deviation of the mean
  - 95% of observations fall within two standard deviations of the mean
- measures of central tendency
  - mean: sum of all observations divided by total number of variables
  - median: value at the 50th percentile, this is a better reflection of the central tendency for a skewed distribution
  - mode: most frequently observed value in a series
- measures of dispersion
  - range: the largest value minus the smallest value
  - variance: a measure of the spread of data
  - standard deviation: the average distance of data points from the mean (the positive square root of variance)
- given the mean and standard deviation of a normal or binomial distribution curve, a description of the entire distribution of data is obtained

Data Analysis

Statistical Hypotheses

- null (H₀)
  - no relationship exists between the two stated variables (i.e. no association between the hypothesized exposure and the outcome)
- alternative (H₁)
  - a relationship does exist between the two stated variables

Type I Error (α Error)

- the null hypothesis is falsely rejected (e.g. concluding an intervention X is effective when it is not, or declaring an observed difference to be real rather than by chance)
- the probability of this error is denoted by the p-value
- studies tend to be designed to minimize this type of error, since a type I error can have larger clinical significance than a type II error

Type II Error (β Error)

- the null hypothesis is falsely accepted (e.g. stating intervention X is not effective when it is, or declaring an observed difference/effect to have occurred by chance when it is present)
- higher level of error is acceptable for most studies
- can also be used to calculate statistical power

Power

- probability of correctly rejecting a null hypothesis when it is in fact false (i.e. the probability of finding a specified difference to be statistically significant at a given p-value)
- power increases with an increase in sample size
- power = 1 – β, and is therefore equal to the probability of a true positive result

Statistical Significance

- the probability that the statistical association found between the variables is due to random chance alone (i.e. that there is no association)
- the preset probability is set sufficiently low that one would act on the result; frequently p=0.05
- when statistical tests result in a probability less than the preset limit, the results are said to be statistically significant (i.e. p<0.05)

Clinical Significance

- measure of clinical usefulness (e.g. 1 mmHg BP reduction may be statistically significant, but may not be clinically significant)
- depends on factors such as cost, availability, patient compliance, and side effects in addition to statistical significance

Trend

- an observed directional relationship that does not meet criteria for statistical significance and thus should be interpreted with caution

Example Calculation

Data set: 17, 14, 17, 10, 7
Mean = (17 + 14 + 17 + 10 + 7) ÷ 5 = 13
Median (write the list in order, median is the number in the middle)
= 7, 10, 14, 17, 17 = 14
Mode (number repeated more often)
= 17
Range = 17 - 7 = 10
Variance = [(17 – 13)² + (14 – 13) ² + (17 – 13) ² + (10 – 13) ² + (7 – 13) ²] ÷ 5 = 19.5
Standard Deviation = √variance = √19.5 = 4.42
Confidence Interval (CI)
- provides a range of values within which the true population result (e.g. the mean) lies
- frequently reported as 95% CI (e.g. one can be 95% certain that the true value is within this data range)
- bounded by the upper and lower confidence limits

Data
- information collected from a sample of a population
- there are 2 overall classes of data listed with examples:
  - discrete
    - categorical (e.g. gender, marital status)
    - ordinal (e.g. low, medium, high)
  - continuous (e.g. serum cholesterol, hemoglobin, age)

Accuracy
- how closely a measurement approaches the true value

Reliability
- how consistent a measurement is when performed by different observers under the same conditions or by the same observer under different conditions

Validity
- extent to which a measurement approaches what it is designed to measure
- determined by the accuracy and reliability of a test

Internal Validity
- degree to which the findings of the sample truly represent the findings in the study population
- dependent on the precision and accuracy

External Validity
- degree to which the results of the study can be generalized to other situations or populations

Common Statistical Tests

<table>
<thead>
<tr>
<th>Table 7. Statistical Tests</th>
<th>2-Test (known as t-test for samples &lt; 30)</th>
<th>Analysis of Variance (ANOVA)</th>
<th>Chi-square Test ($\chi^2$)</th>
<th>Linear Regression</th>
<th>Logistic Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What are you trying to show?</strong></td>
<td>Compare the mean values of an outcome variable between two groups (e.g. difference in average BP between men and women)</td>
<td>Compare the mean values of an outcome variable between two or more groups (e.g. difference in average BP between persons in three towns)</td>
<td>Test the correspondence between a theoretical frequency distribution and an observed frequency distribution. (e.g. if one sample of 20 patients is 30% hypertensive and another comparison group of 25 patients is 60% hypertensive, a chi-squared test determines if this variation is more than expected due to chance alone)</td>
<td>Looks at associations between two or more continuous variables (e.g. age and blood pressure)</td>
<td>Show how a change in one explanatory variable affects the status (e.g. ill vs. non-ill) of the outcome variable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>What kind of data do you have in your study?</strong></th>
<th>Data on two groups</th>
<th>Mean of groups (one or more) Overall mean of an entire sample</th>
<th>Data on two or more populations and two or more outcome measures</th>
<th>Data on at least one population</th>
<th>Data on at least one population</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>What kind of variables do you measure?</strong></th>
<th>Dependent variable: Continuous data</th>
<th>Continuous data</th>
<th>Categorical (2 or more)</th>
<th>Continuous</th>
<th>Categorical (discrete outcomes usually dichotomous)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent variable: Categorical (2 only)</td>
<td>Categorical (2 or more)</td>
<td>Categorical (2 or more)</td>
<td>Continuous</td>
<td>Continous</td>
<td>Continous/categorical</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Assumptions</strong></th>
<th>“Normal” distribution</th>
<th>None</th>
<th>None</th>
<th>None</th>
</tr>
</thead>
</table>

A wider confidence interval implies more variance than a tighter confidence interval.
Causation

Criteria for Causation (Sir Bradford Hill)
1. strength of association: the frequency with which the factor is found in the disease and the frequency with which it occurs in the absence of disease
2. consistency: is it the same outcome with different populations or study design?
3. specificity: is the association particular to your intervention and measured outcome?
4. temporal relationship: did the exposure occur before the onset of the disease?
5. biological gradient: finding a quantitative relationship between the factor and the frequency (e.g. dose response relationship)
6. biological plausibility: does the association/causation make biological sense?
7. coherence: can the relationship be explained/accounted for based on what we know about the laws of science, logic, etc.?
8. experimental evidence: experiment that investigates what happens when the suspected offending agent is removed (e.g. is there improvement?)
9. analogy: do other established associations provide a model for this type of the relationship?

Note: not all criteria must be fulfilled to establish scientific causation, and the modern practice of EBM emphasizes ‘experimental evidence’ as superior to other criteria for experimental causation review. However many causation questions in health cannot be answered with experimental methods.

Assessing Evidence

• critical appraisal is the process of systematically examining research evidence to assess validity, results, and relevance before using it to inform a decision

Figure 12. Pyramid of pre-appraised evidence

VALIDITY
- The degree to which the outcome observed in the study can be attributed to the intervention
- Were all patients randomized?
- Were all patients analyzed in the groups to which they were randomized?
- Were all patients treated equally except for the intervention?
- Were all patients analyzed in the study? Were they followed up?
- Were all patients randomized? Were the groups similar (i.e. demographics, prognostic factors) at the start of the trial?
- Were outcome assessors aware of group allocation? Were ethical issues continuously upheld?

Analysis
- Per-Protocol Analysis (PP)
  Strategy of analysis in which only patients who complete the entire study are counted towards the results.
- Intention-to-Treat Analysis (ITT)
  When groups are analyzed exactly as they existed upon randomization (i.e. using data from all patients, including those who did not complete the study).
Health Services Research

Continuous Quality Improvement (CQI)

Quality Improvement
- method of evaluating and improving processes; focusing more on systems and systematic biases, which are thought to be the cause of variation in quality, as opposed to individuals
- taking measures to increase efficiency of action with the purpose of achieving optimal quality

Quality Assurance
- management system to assure the quality of health care provided by workers and received by patients
- constantly aims to improve standards and the frequency of attaining those standards
- five-stage process of quality assurance
  - establishment of functional goals
  - implementation of procedures to achieve those goals
  - regular assessment of performance relative to the goals
  - proposal of solutions to close the gap between performance and goals
  - documentation and reporting of this assessment activity

Quality Control
- method of maintaining standards by reviewing the quality of all factors involved in the process

Continuous Quality Improvement
- management approach to improve and maintain quality via continuous assessment of potential defects, followed by action to improve process, avoid decrease in quality or correcting process in early stages
- continuous feed-forward process

Quality Management
- encompasses quality assurance, quality control and quality improvement to achieve consistent quality

Total Quality Management
- management philosophy for improving quality while controlling costs
- focusing on the system rather than the individual, to ensure decisions are made to support quality and remove barriers to quality inherent in bureaucratic, hierarchical systems

Audit
- process of systematic examination of a quality system carried out by internal or external quality auditors
- to determine whether quality processes and results comply with goals, and whether processes have been implemented effectively

Systems Analyses Tools
1. 5 Whys: brainstorming to simplify the process of change; continue asking 'why' until the root of the problem is discovered
2. Ishikawa Diagrams (aka Fishbone Diagrams): identify generic categories of problems that have an overall contribution on the effect (see Figure 13)
3. **Defect check sheets:** consider all defects and tally up the number of times the defect occurs

4. **Pareto Chart:** x vs. y chart; x-axis = defect categories, y-axis = frequency; plot cumulative frequency on the right y-axis
   - Purpose is to highlight most important among large set of factors contributing to defects/poor quality

**Precede-Proceed Model**
- Tool for designing, implementing, and evaluating health interventions/programs

**Table 8. Precede-Proceed Model**

<table>
<thead>
<tr>
<th>PRECEDE Phase</th>
<th>PROCEED Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 – Identify the ultimate desired result</td>
<td>Phase 5 – Implementation (design and conduct the intervention)</td>
</tr>
<tr>
<td>Phase 2 – Identify and set priorities among health issues and</td>
<td>Phase 6 – Process Evaluation (determine if the program is implemented as planned)</td>
</tr>
<tr>
<td>their behavioural and environmental determinants</td>
<td>Phase 7 – Impact Evaluation (measure intermediate objectives – predisposing, enabling, and reinforcing factors)</td>
</tr>
<tr>
<td>Phase 3 – Identify the predisposing, enabling, and reinforcing</td>
<td>Phase 8 – Outcome Evaluation (measure desired result)</td>
</tr>
<tr>
<td>factors that affect the behaviours and environmental determinants</td>
<td></td>
</tr>
<tr>
<td>Phase 4 – Identify the administrative and policy factors that</td>
<td></td>
</tr>
<tr>
<td>influence what can be implemented</td>
<td></td>
</tr>
</tbody>
</table>

**Cost Analysis**

**Cost Benefit Analysis**
- A process of, either explicitly or implicitly, weighing the total expected costs against the total expected benefits of one or more actions in order to choose the best or most profitable option
- All costs are adjusted for the time value of money, so that costs that may change over time are expressed on a common basis in terms of their present value

**Cost Effectiveness Analysis (CEA)**
- A comparison of the relative expenditure (costs) and outcomes (effects) of two or more courses of action
- Cost effectiveness analysis is often used where a full cost benefit analysis is inappropriate
- A CEA is commonly expressed in terms of a ratio: the denominator is a gain in health from a measure (e.g. years of life, premature births averted, sight-years gained) and the numerator is the cost of the health gain
- The most commonly used outcome measure is quality-adjusted life years (QALY)

**Outbreak of Infectious Diseases**

**Definitions**

**Outbreak**
- Occurrence of new cases clearly in excess of the baseline frequency of the disease in a defined community or population over a given period of time
- Synonymous with epidemic, although generally considered to be an epidemic that is localized, has an acute onset, or is relatively short in duration
Epidemic
• any disease, infectious or chronic, occurring at a greater frequency than usually expected in a defined community or institutional population over a given time period (i.e. excessive rate of disease)

Endemic
• constant presence of disease or infectious agent in a given geographic area or population subgroup (i.e. usual rate of disease)

Pandemic
• epidemic over a wide area, crossing international boundaries, and affecting a large number of people

Attack Rate
• cumulative incidence of infection within a defined group observed during a specific period of time in an epidemic
• calculated by dividing the total number of people who develop clinical disease by the population at risk, usually expressed as a percentage

Secondary Attack Rate
• number of cases among contacts occurring within the incubation period following exposure to the primary case, in relation to the total exposed contacts
• infectiousness reflects the ease of disease transmission and is usually measured by the secondary attack rate

Pathogenicity Rate
• power of an organism to produce clinical disease in those that are affected

Virulence
• severity of the disease produced by the organism in a given host
• expressed as the ratio of the number of cases of severe and fatal infection to the total number of clinically affected

Case-Fatality Rate
• proportion of individuals contracting a disease who die as a result of that disease
• most frequently applied to a specific outbreak of acute disease in which all patients have been followed for an adequate period of time to include all attributable deaths
• must be clearly differentiated from the mortality rate

Mortality Rate/Crude Death Rate
• estimation of the portion of the population that dies during a specified period from all causes of death

All-Cause Mortality Rate by Age Group
• estimation of the portion of the population in a given age group that dies during a specified period from all causes of death for that age group

Morbidity Rate
• estimation of the portion of the population that suffers illness or ill health during a specified period

Steps to Control an Outbreak

1. Define the Problem
• is it an outbreak?

2. Appraise Existing Data and Institute a Surveillance System
• case definition: formulated from the most common symptoms or signs; definition includes the likely date of onset of illness of the first case (e.g. any person with onset of fever higher than 38.5°C and cough within past 28 d)
• active surveillance: identify those who may have been exposed to the infectious agent and who fit the case definition through active efforts, including:

3. Formulate Hypotheses and Implement Initial Control Measures
• track outbreak evolution to develop hypotheses about potential source and populations at risk
• case management depends on symptoms, suspected agent, population at risk, and location
• population management requires public health services in the community and infection control teams in hospitals to disseminate information about
  • risk reduction
  • personal preventative measures (e.g. post-exposure prophylaxis)
  • decreasing risk of propagation (e.g. quarantine)
4. Test the Hypothesis through Analysis of Surveillance Data or Special Studies

- analyze outbreak surveillance data
- generate epidemic curves
  - usually a frequency histogram, with the number of cases plotted on the vertical axis and dates or times of onset along the horizontal axis
  - curve can indicate whether the epidemic (outbreak) has a common source or whether it is propagated
  - point source epidemic: exposure is brief and essentially simultaneous (see Figure 15a)
  - extended source epidemic: exposure lasts for a period of days to weeks and may be continuous (no irregular peaks, see Figure 15b) or intermittent (irregularly spaced peaks)
  - propagated epidemic: begins with only a few exposed persons but is maintained by person-to-person transmission (e.g. measles/influenza); epidemic curve shows a series of peaks (see Figure 15c)
- use epidemic curves, cross-sectional studies, and/or case-control studies to evaluate hypotheses about cause of outbreak

5. Draw Conclusions and Re-Adjust Hypothesis and Control Measures

- establish cause of outbreak with further epidemiologic investigation and revise initial control measures accordingly

6. Plan for Long-Term Prevention and Control

- implement prevention measures to avoid similar future incidents
  - strengthen resistance of hosts (e.g. immunization)
  - interrupt modes of transmission in environment (e.g. improvements in food processing)
- communicate outbreak prevention and control strategies to the public


**Environmental Health**

**Definition**
- study of conditions in the natural and human-made environment that influence human health and well-being
- environmental exposures
  - four main reservoirs: air, food, water, and soil
  - three main routes: inhalation, ingestion, or absorption (skin)
  - usually divided into two main settings:
    - workplace (including schools): may see high level exposure in healthy individuals (see Occupational Health, PH23)
    - non-workplace: generally low level but chronic exposure; population at risk includes extremes of age, developing fetuses, and ill or immunocompromised individuals
- health impacts of the environment also include factors such as urban planning and how individuals interact with the built environment (e.g. safe pedestrian and bicycle paths are neighbourhood features that can facilitate more active lifestyles among residents)

**Environmental Health Jurisdiction**

<table>
<thead>
<tr>
<th>Public Health Unit</th>
<th>Enforcement of water and food safety regulations (including restaurant food safety)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sanitation</td>
</tr>
<tr>
<td></td>
<td>Assessment of local environmental risks</td>
</tr>
<tr>
<td></td>
<td>Monitoring and follow-up of reportable diseases</td>
</tr>
<tr>
<td>Municipal Government</td>
<td>Waste disposal</td>
</tr>
<tr>
<td></td>
<td>Recycling</td>
</tr>
<tr>
<td></td>
<td>Water and sewage treatment/collection/distribution</td>
</tr>
<tr>
<td>Provincial and Territorial Government</td>
<td>Water and air quality standards</td>
</tr>
<tr>
<td></td>
<td>Industrial emission regulation</td>
</tr>
<tr>
<td></td>
<td>Toxic waste disposal</td>
</tr>
<tr>
<td>Federal Government</td>
<td>Designating and regulating toxic substances</td>
</tr>
<tr>
<td></td>
<td>Regulating food products (e.g. Health Canada)</td>
</tr>
<tr>
<td></td>
<td>Setting policy for pollutants that can travel across provincial boundaries</td>
</tr>
<tr>
<td>International</td>
<td>Multilateral agreements (e.g. Kyoto Protocol, UN Convention on Climate Change,</td>
</tr>
<tr>
<td></td>
<td>International Joint Commission)</td>
</tr>
</tbody>
</table>
Risk Assessment

Hazard Identification
- what is the hazard involved?
- assess potential hazards by taking an environmental health history

Risk Characterization
- is the identified agent likely to elicit the patient's current symptoms?
- review known health impacts of the hazard and identify specific properties that contribute to or diminish adverse effects (e.g. some agents only become dangerous at threshold levels)

Exposure Assessment
- is the patient's exposure to the environmental agent sufficient to have caused the current symptoms?
- quantify exposure through direct measurement or by reviewing frequency and nature of contact with hazard

Air

Physical Contaminants
- sound waves
  - ionizing radiation
  - radon is naturally produced by soil containing uranium or radium, can contaminate indoor air and is associated with a small proportion of lung cancers
- ultraviolet radiation is increasing due to ozone layer destruction and increases risk of skin cancer
  - non-ionizing radiation
  - visible light, infrared, microwave

Chemical Contaminants
- ground-level ozone
  - main component of smog with levels increasing in major cities
  - worsens asthma, irritates upper airway
- carbon monoxide (fossil fuel related, common byproduct of combustion)
  - aggravates cardiac disease at low levels
  - headache, nausea, dizziness at moderate levels
  - fatal at high levels
- sulphur dioxide (fossil fuel related), nitrogen oxides
  - contribute to acid rain
  - exacerbate breathing difficulties
- organic compounds (e.g. benzene, methylene chloride, tetrachloroethylene)
  - variety of health effects at high levels (e.g. benzene is a known carcinogen)
  - tend to be fat-soluble, easily absorbed through skin and difficult to excrete
- heavy metals (e.g. nickel, cadmium, chromium)
  - present in industrial emissions
- variety of health effects: upper airway disease, asthma, decreased lung function
- second hand tobacco smoke
  - respiratory problems, increase risk of lung cancer

Biological Contaminants
- particulates
  - associated with decreased lung function, asthma, upper airway irritation
- moulds thrive in moist areas; 10-15% of the population allergic
- bacteria survive as spores and aerosols, can be distributed through ventilation systems (e.g. Legionella)
- dust mites (year-round) and pollens (seasonal) can trigger upper and lower-airway symptoms

Climate Change
- anthropogenic greenhouse gas emissions (e.g. carbon dioxide, methane) leading to adverse changes in the global environment
  - increased extreme weather conditions (e.g. floods, hurricanes, heat waves)
  - increased distribution of disease vectors (e.g. mosquitoes and malaria)
  - increased malnutrition from crop failures
  - increased diarrheal diseases

BPA, the Toxin Concern of 2009
Bisphenol A (BPA) is a chemical compound found in some hard, clear, lightweight plastics and resins. According to the NIH, animal studies suggest that ingested BPA may imitate estrogen and other hormones. In October 2008, Canada became the first country in the world to ban the import and sale of polycarbonate baby bottles containing BPA, stating that although exposure levels are below levels that cause negative effects, current safety margins need to be higher. The US FDA does not consider normal exposure to BPA to be a hazard, however the NIH has some concern that fetuses, infants, and children exposed to BPA may be at increased risk for early-onset puberty, prostate, and breast cancer.

Effects of Ionizing Radiation
- α-particles are larger and damage the skin and bronchial lining (airway irritation).
- β-particles are smaller and cause deeper damage (alveoli).
Water

Biological Contaminants
- mostly due to human and animal waste
- Aboriginal Canadians, rural Canadians at higher risk
- bacteria: *Escherichia coli* (e.g. Walkerton, ON), *Salmonella*, *Pseudomonas*, *Shigella*
- protozoa: *Giardia*, *Cryptosporidium* (e.g. North Battleford, SK)

Chemical/Industrial Contaminants
- chlorination by-products (e.g. chloriform can cause cancer at high levels)
- volatile organic compounds, heavy metals, pesticides, and other industrial waste products can be present in groundwater
- fluoride at high levels (greater than that of municipal fluoridation) can cause skeletal fluorosis

Soil

- contamination sources: rupture of underground storage tanks, use of pesticides and herbicides, percolation of contaminated water runoffs, leaching of wastes from landfills, dust from smelting and coal burning power plants, direct discharge of industrial wastes, lead deposition, leakage of transformers
- most common chemicals: petroleum hydrocarbons, solvents, lead, pesticides, motor oil, other industrial waste products
- health effects:
  - infants and toddlers at highest risk of exposure due to hand-mouth behaviours
  - dependent on contaminant: leukemia, kidney damage, liver toxicity, neuromuscular blockade, developmental damage to the brain and nervous system, skin rash, eye irritation, headache, nausea, fatigue
- biological contamination: tetanus, *Pseudomonas*

Food

<table>
<thead>
<tr>
<th>Source</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmonella</em></td>
<td>GI symptoms</td>
</tr>
<tr>
<td><em>Campylobacter</em></td>
<td>Joint pain, GI symptoms</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>Watery or bloody diarrhea, hemolytic uremic syndrome (esp. children)</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>Listeriosis: nausea, vomiting, fever, headache, rarely meningitis or encephalitis</td>
</tr>
<tr>
<td><em>Clostridium botulinum</em></td>
<td>Dizziness, weakness, respiratory failure, GI symptoms: thirst, nausea, constipation</td>
</tr>
</tbody>
</table>

Prion (BSE)
- Beef and beef products
- Creutzfeldt-Jakob disease

other biological food contaminants include:
- viruses
- mould toxins (e.g. aflatoxin → liver cancer)
- parasites (e.g. *Toxoplasmosis*, tapeworm)
- paralytic and shellfish poisoning (rare)
- genetically modified organisms (GMO) – controversial with respect to health and environmental risk/benefits

Chemical Contaminants
- many persistent organic pollutants are fat-soluble and undergo bioamplification
- drugs (antibiotics, hormones)
- inadequately prepared herbal medications
- food additives and preservatives
  - nitrites highest in cured meats; can be converted to carcinogenic nitrosamines
  - sulphites commonly used as preservatives; associated with sulphite allergy (hives, nausea, shock)
- pesticide residues
  - older pesticides (e.g. DDT) have considerable human health effects
  - debate over risks of DDT vs. risks of malaria in malaria-endemic countries

Table 10. Comparison of Select Biological Contaminants of Food and Effects on Human Health

- *Honey and Botulism*
  - Although exceedingly rare, infant botulism has been documented as a form of food poisoning from *C. botulinum* found in honey. When an infant swallows spores of this bacterium, they grow and produce a toxin in the baby’s intestine. By the time an infant is 1, its gut has a healthy colony of “good” bacteria that prevents this from occurring.

- *To Fluoridate or Not*
  - At the recommended concentration of 0.8-1.0 mg/L, fluoride reduces cavities by 18-40%, and there is little risk of fluorosis unless other exposures (e.g. toothpaste, rinses, mouthwash, etc.) are swallowed. Opposition raises concerns that the intake is not easily controlled, and that children, and others may be more susceptible to health problems. However, public health experts strongly support fluoridation as an effective measure to prevent dental caries at the community level and reduce dental health inequities.

- *The Walkerton Tragedy*
  - In May 2000, the drinking water system in the town of Walkerton, ON, became contaminated with *Escherichia coli* 0157:H7 and *Campylobacter* jejuni. Over 2,300 individuals became ill; 27 people developed hemolytic uremic syndrome and 7 individuals died in the outbreak.

- *Organic Foods*
  - Foods designated as “organic” in Canada must conform to the Organic Products Regulations enforced by the Canadian Food Inspection Agency
    - Organic foods are not free of synthetic pesticide residues but typically contain smaller amounts compared to conventionally grown foods
    - Currently, there has not been strong evidence to suggest that eating organic foods is safer or more nutritious compared to eating conventionally grown food

- *To Toronto Notes 2014*
  - To Toronto Notes 2014
  - To Toronto Notes 2014


• polychlorinated biphenyls (PCBs)
  § effects (severe acne, numbness, muscle spasm, bronchitis) much more likely to be seen in occupationally exposed individuals than in the general population
• dioxins and furans
  § levels highest in fish and marine mammals, also present in breast milk
  § can cause immunosuppression, liver disease, respiratory disease

### Heavy Metal Toxicity

**Mechanism**
• after exposure, superabundant metals bind to proteins, alter their enzymatic activity, and lead to diffuse disease manifestations

**Predisposing Factors in At-Risk Groups**
• children: hand-to-mouth, incomplete blood brain barrier
• pregnant women and developing fetus: heavy metals cross placenta; mothers release heavy metal stores at times of calcium stress
• adults: occupation, hobbies, environment (home, country)

**Etiology**
• iatrogenic (e.g. gold treatment for rheumatoid arthritis, lithium treatment for bipolar affective disorder)
• inhalation (e.g. zinc oxide, lead gasoline fumes)
• ingestion (e.g. lead paint, mercury in fish, folk remedies)
• industry (e.g. methyl mercury industrial spill caused Minamata disease)

**Treatment**
• generalized workup: symptoms are usually wide-ranging and non-specific
• chelation therapy (e.g. dimercaprol)

### Occupational Health

• occupational health is the maintenance and promotion of health in the work environment
• occupational health services include physicians, nurses, engineers, ergonomists, safety officers, physicists, technicians and others
• services encompass health promotion and protection (primary prevention), disease prevention (secondary prevention), and treatment and rehabilitation (tertiary prevention)
• general bias towards reporting occupational injuries versus occupational disease, as occupational disease is harder to identify

### Workplace Health Promotion and Protection

• take action in the workplace so the worker is protected from injury or illness
  § identifying workplace hazards [e.g. through material safety data sheets (MSDS)]
  § assessing risk
  § reducing exposure
    § source: substituting a less toxic chemical
    § path: enclosing a source of noise in a sound-proof room
    § worker: personal protection equipment (e.g. reflective vests, helmets)
    § worker education: emergency protocols, material safety education
    § rotation of workers: decrease exposure for each worker but more workers exposed

### Workplace Disease Prevention

• monitor workers’ health to prevent the development of disease
  § periodic examinations to facilitate pre-symptomatic diagnosis (e.g. screening for lead exposure); substance misuse screening where performance impairment is suspected

### Workplace Treatment and Rehabilitation

• treat injury or illness with safe return to the workplace
• may require rehabilitation, retraining, change in job duties, and/or workers’ compensation
**Workplace Legislation**

- universal across Canada for corporate responsibility in the workplace; due diligence, application of Workplace Hazardous Materials Information System (WHMIS), existence of joint health and safety committees in the workplace with representatives from workers and management
- jurisdiction in Canada is provincial (90% of Canadian workers), except for 16 federally regulated industries (e.g. airports, banks, highway transport) under the Canada Labour Code
- Ontario’s Occupational Health and Safety Act
  - sets out rights of workers and duties of employers, procedures for dealing with workplace hazards, and law enforcement
  - workers have the right to
    - participate (e.g. have representatives on joint health and safety committees)
    - know (e.g. be trained and have information about workplace hazards)
    - refuse work (e.g. workers can decline tasks they feel are overly dangerous)
    - stop work (e.g. ‘certified’ workers can halt work if they feel it is dangerous to other workers)
  - employers must take precautions to protect the health and safety of employees and investigate concerns
  - enforced by Ministry of Labour via inspectors
- Health Protection and Promotion Act (HPPA) (Ontario)
  - Medical Officer of Health has right to investigate and manage health hazards where workplace exposures may impact non-workers (e.g. community members living close to the work site)

**Taking an Occupational Health History**

- current and previous job duties
- exposures
  - identification: screen for chemical, metal, dust, biologic, psychologic and physical hazards; review relevant workplace material safety data sheets (MSDS)
  - assessment: duration, concentration, route, exposure controls (e.g. ventilation, personal protective equipment)
- temporal relationship: changes in symptoms in relationship to work environment
- presence of similar symptoms in co-workers
- non-work exposures: home, neighbourhood, hobbies

**Occupational Hazards**

<table>
<thead>
<tr>
<th>Physical</th>
<th>Chemical</th>
<th>Biological</th>
<th>Psychosocial</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Trauma (fractures, lacerations)</td>
<td>• Organic solvents (e.g. benzene, methyl alcohol; most toxic is carbon tetrachloride)</td>
<td>• Exposure to bacteria, viruses, fungi, protozoa, Rickettsia</td>
<td>• Workload, responsibility, fear of job loss, geographical isolation, shift work, harassment (sexual/non-sexual)</td>
</tr>
<tr>
<td>• Noise (hearing loss)</td>
<td>• Mineral dusts (e.g. silica leads to silicosis and predisposition to TB, asbestos leads to diffuse fibrosis and mesothelioma, coal leads to pneumoconiosis)</td>
<td>• Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)</td>
<td>• Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)</td>
</tr>
<tr>
<td>• Temperature (heat cramps, heat exhaustion, heat stroke)</td>
<td>• Heavy metals (e.g. nickel, cadmium, mercury, lead)</td>
<td>• Consider exposure to disease in endemic countries, travelers from endemic countries, or recent travel history in the setting of acute onset of symptoms (e.g. SARS, TB)</td>
<td></td>
</tr>
<tr>
<td>• Air pressure (barotrauma, decompression sickness)</td>
<td>• Lead is ubiquitous and can cause severe disability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ergonomic</td>
<td>• Gases (e.g. halogen gases, sulphur dioxide, carbon monoxide, nitrogen oxides)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Repetitive use/overuse injuries, excessive force, awkward postures, poorly designed physical work environment</td>
<td>• Second hand smoke (causal factor for lung cancer, lung disease, heart disease, asthma exacerbations; may be linked to miscarriage)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tendosynovitis, bursitis, carpal tunnel syndrome</td>
<td>• Exposure restricted in most municipal, provincial, and federal jurisdictions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Radiation</td>
<td>• Skin diseases (major portion of complications, e.g. contact dermatitis, occupational acne, pigmentation disorders)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Non-ionizing: visible light, infrared</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ionizing: UV, x-rays, γ rays</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Electricity</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix – Reportable Diseases

As an essential part of the health system, physicians in Canada are required by law to report certain diseases to public health for the following reasons:

1. to control the outbreak
   - if the disease presents an outbreak threat (e.g. measles, Salmonella, respiratory diseases in institutions)
2. to prevent spread
   - if the disease presents a significant threat to individuals or a subset of the population (e.g. Lassa Fever)
3. for surveillance
   - if the disease is preventable with immunization (e.g. polio, diphtheria, congenital rubella)
4. if infected individuals require education, treatment and/or partner notification (e.g. gonorrhea, TB)

Physicians should also report unlisted diseases that appear in clusters.

The following list is based on the reportable diseases in Ontario for 2011.
(Each province will have their own similar legislation)

**Source:** Health Protection and Promotion Act, O. Reg. 559/91, amended to O. Reg.49/07.

### Acquired Immunodeficiency Syndrome (AIDS)
### Amebiasis
### Anthrax
### Botulism
### Brucellosis
### Campylobacter enteritis
### Chancroid
### Chickenpox (Varicella)
### Chlamydia trachomatis infections
### Cholera
### Clostridium difficile associated disease (CDAD) outbreaks in public hospitals
### Cryptosporidiosis
### Cyclosporiasis
### Cytomegalovirus infection, congenital
### Diphtheria
### Encephalitis, including:
  i. Primary, viral
  ii. Post-infectious
  iii. Vaccine-related
  iv. Subacute sclerosing panencephalitis
  v. Unspecified
### Food poisoning, all causes
### Gastroenteritis, institutional outbreaks
### Giardiasis, except asymptomatic cases
### Gonorrhea
### Haemophilus influenzae b disease, invasive
### Hantavirus pulmonary syndrome
### Hemorrhagic fevers, including:
  i. Ebola virus disease
  ii. Marburg virus disease
  iii. Other viral causes
### Hepatitis, viral:
  i. Hepatitis A
  ii. Hepatitis B
  iii. Hepatitis C
  iv. Hepatitis D (Delta hepatitis)
### Herpes, neonatal
### HIV
### Influenza
### Lassa Fever
### Legionellosis
### Leprosy
### Lyme Disease
### Malaria
### Meningitis, acute:
  i. Bacterial
  ii. Viral
  iii. Other
### Meningococcal disease, invasive
### Mumps
### Ophthalmia neonatorum
### Paratyphoid fever
### Pertussis (whooping cough)
### Plague
### Poliomyelitis, acute
### Psittacosis/Ornithosis
### Q Fever
### Rabies
### Respiratory infection outbreaks in institutions
### Rubella
### Rubella, congenital syndrome
### Salmonellosis
### Severe Acute Respiratory Syndrome (SARS)
### Shigellosis
### Smallpox
### Streptococcal infections, Group A invasive
### Streptococcal infections, Group B neonatal
### Streptococcus pneumoniae, invasive syphilis
### Tetanus
### Transmissible spongiform encephalopathy, including:
  i. Creutzfeldt-Jakob disease, all types
  ii. Gerstmann-Sträussler-Scheinker syndrome
  iii. Fatal familial insomnia
  iv. Kuru
### Trichinosis
### Tuberculosis
### Tularemia
### Typhoid Fever
### Verotoxin-producing E. coli infection indicator conditions, including
### Hemolytic Uremic Syndrome (HUS)
### West Nile Virus illness, including:
  i. West Nile fever
  ii. West Nile neurological manifestations
### Yellow Fever
### Yersiniosis
References

Journals

Government Resources

Textbooks

Websites
Canadian Institute for Health Information. Available from: http://www.cihi.ca.

Evidence-Based Medicine Resources
Acronyms ................................................. 2
Psychiatric Assessment ............................. 2
Psychiatric Assessment ............................. 2
History
Mental Status Exam
Summary of Axes

Suicide .................................................. 4

Psychotic Disorders ................................. 6
Differential Diagnosis of Psychosis
Schizophrenia
Schizotypal Disorder
Brief Psychotic Disorder
Schizoaffective Disorder
Delusional Disorder
Shared Psychotic Disorder (Folie à Deux)

Mood Disorders .............................. 9
Mood Episodes
Depressive Disorders
Postpartum Mood Disorders
Bipolar Disorders

Anxiety Disorders................................. 13
Panic Disorder
Generalized Anxiety Disorder (GAD)
Phobic Disorders
Obsessive-Compulsive Disorder (OCD)
Post-Traumatic Stress Disorder (PTSD)

Adjustment Disorder ............................. 18

Bereavement ........................................... 18

Cognitive Disorders ............................... 19
Delirium
Dementia

Substance-Related Disorders .................. 21
Nicotine
Alcohol
Opioids
Cocaine
Amphetamines
Marijuana
“Club Drugs”

Somatoform Disorders ............................... 26
Body Dysmorphic Disorder
Conversion Disorder
Hypochondriasis
Pain Disorder
Somatization Disorder

Dissociative Disorders ............................. 27

Sleep Disorders ................................. 28
Nocturnal Myoclonus
Narcolepsy
Primary Insomnia
Sleep Apnea

Sexuality and Gender ............................. 28
Gender Dysphoria
Paraphilias

Eating Disorders ................................. 29
Anorexia Nervosa
Bulimia Nervosa

Personality Disorders ............................. 31

Child Psychiatry ................................. 33
The Child Psychiatric Interview
Developmental Concepts
Mood Disorders
Anxiety Disorders
Childhood Schizophrenia
Pervasive Developmental Disorders (PDD)
Attention Deficit Hyperactivity Disorder (ADHD)
Oppositional Defiant Disorder (ODD)
Conduct Disorder (CD)

Psychotherapy ....................................... 39
Behavior Mechanisms
Behavior Therapy
Cognitive Therapy
Cognitive Behavioural Therapy
Dialectical Behavioural Therapy
Other Therapies

Pharmacotherapy ................................. 41
Antipsychotics
Antidepressants
Mood Stabilizers
Anxiolytics
Electroconvulsive Therapy
Experimental Therapies

Canadian Legal Issues .............................. 50
Common Forms
Consent
Community Treatment Order (CTO)
Duty to Inform/Warn

References ............................................. 52
Diagnostic Criteria reprinted with permission from the
Diagnostic and Statistical Manual of Mental Disorders,
Association.
Psychiatric Assessment

History

Identifying Data
- name, sex, age, ethnicity, marital status, religion, occupation, education, type of residence, with whom they are living, referral source

Reliability of Patient as a Historian
- may need collateral source (e.g. parent, teacher) if patient unable/unwilling to co-operate

Chief Complaint
- in patient's own words, duration

History of Present Illness
- reason for seeking help (that day), current symptoms (onset, duration and course), stressors, supports, functional status, relevant associated symptoms (pertinent positives and negatives)
- safety screen: is the patient endangering self or others? dependents at home (e.g. children, pets), ability to drive safely, ability to care for self (e.g. eating, hygiene, taking medications)

Psychiatric Functional Inquiry
- mood: depressed, manic
- anxiety: worries, obsessions, compulsions, panic attacks, phobias, history of trauma
- psychotic: hallucinations, delusions, thought form disorders
- suicide/homicide: ideation, plan, intent, history of attempts
- organic: EtOH/drug use or withdrawal, illness, dementia

Past Psychiatric History
- all previous psychiatric diagnoses, psychiatric contacts, treatments (pharmacological and non-pharmacological) and hospitalizations
- also include past suicide attempts, substance use/abuse, and legal problems

Past Medical/Surgical History
- all medical, surgical, neurological (e.g. head trauma, seizures), and psychosomatic illnesses
- medications, allergies

Family Psychiatric/Medical History
- family members: ages, occupations, personalities, medical or genetic illnesses and treatments, relationships with parents/siblings
- family psychiatric history: any past or current psychiatric illnesses and hospitalizations, suicide, substance abuse

Past Personal History
- prenatal and perinatal history (desired vs. unwanted pregnancy, maternal and fetal health, domestic violence, maternal substance use, complications of pregnancy/delivery)
- early childhood to age 3 (developmental milestones, activity/attention level, family stability, attachment figures)
- middle childhood to age 11 (school performance, peer relationships, fire-setting, stealing, incontinence)
- late childhood to adolescence (drug/alcohol, legal problems, peer and family relationships)
- physical or sexual abuse in childhood/adolescence
- adulthood (education, occupations, relationships)
- psychosexual history (paraphilias, gender roles, sexual abuse, sexual dysfunction)
- personality before current illness, recent changes in personality

N.B. The content in this chapter does not reflect the changes made to diagnostic criteria in the DSM-V
### Mental Status Exam (MSE)

#### General Appearance and Behaviour
- dress, grooming, posture, gait, physical characteristics, body habitus, apparent vs. chronological age, facial expression (e.g. sad, suspicious)
- psychomotor activity (agitation, retardation), abnormal movements or lack thereof (tremors, akathisia, tardive dyskinesia, paralysis), attention level and eye contact, attitude toward examiner (ability to interact, level of co-operation)

#### Speech
- rate (e.g. pressured, slowed), rhythm/fluency, volume, tone, articulation, quantity, spontaneity

#### Mood and Affect
- mood: subjective emotional state (in patient's own words)
- affect: objective emotional state inferred from emotional responses to stimuli. Described in terms of:
  - quality (euthymic, depressed, elevated, anxious)
  - range (full, restricted, flat, blunted)
  - stability (fixed, labile)
- mood congruence (inferred by reader by comparing mood and affect descriptions)
- appropriateness to thought content

#### Thought Process
- coherence (coherent, incoherent)
- logic (logical, illogical)
- stream
  - goal-directed
  - circumstantial: speech that is indirect and delayed in reaching its goal; eventually comes back to the point
  - tangential: speech is oblique or irrelevant; does not come back to the original point
  - loosening of associations: illogical shifting between topics
  - flight of ideas: quickly skipping from one idea to another where the ideas are marginally connected, associated with mania
- word salad: jumble of words lacking meaning or logical coherence
- perseveration: repetition of the same verbal or motor response to stimuli
- echolalia: repetition of phrases or words spoken by someone else
- thought blocking: sudden cessation of flow of thought and speech
- clang associations: speech based on sound such as rhyming or punning
- neologism: use of novel words or of existing words in a novel fashion

#### Thought Content
- suicidal ideation/homicidal ideation
  - frequency and perversiveness of thoughts, formulation of plan, means to plan, intent, active vs. passive, protective factors
- pre-occupations, ruminations: reflections/thoughts at length, not fixed or false
- obsession: recurrent and persistent thought, impulse or image which is intrusive or inappropriate
  - cannot be stopped by logic or reason
  - causes marked anxiety and distress
- common themes: contamination, orderliness, sexual, pathological doubt/worry/guilt
- magical thinking: belief that thinking something will make it happen; normal in children
- ideas of reference: similar to delusion (fixed false belief), but the reality of the belief is questioned
- overvalued ideas: unusual/odd beliefs that are not of delusional proportions
- first rank symptoms of schizophrenia: thought insertion/withdrawal/broadcasting
- delusion: a fixed false belief that is out of keeping with a person's cultural or religious background and is firmly held despite incontrovertible proof to the contrary

#### Perception
- hallucination: sensory perception in the absence of external stimuli that is similar in quality to a true perception
  - auditory (most common), visual, gustatory, olfactory, tactile
- illusion: misperception of a real external stimulus
- depersonalization: change in self-awareness such that the person feels unreal, detached from his or her body, and/or unable to feel emotion
- derealization: feeling that the world/outer environment is unreal

---

**Spectrum of Affect**

<table>
<thead>
<tr>
<th>Full</th>
<th>Restricted</th>
<th>Blunted</th>
<th>Flat</th>
</tr>
</thead>
</table>

There is poor correlation between clinical impression of suicide risk and frequency of attempts.

**Delusions**

- Persecutory: belief that others are trying to cause harm to you
- Reference: interpreting publicly known events/celebrities as having direct reference to you
- Erotomania: belief that another is in love with you
- Grandiose: an inflated sense of self-worth or power
- Religious: belief of receiving instructions/powers from a higher being; of being a higher being
- Somatic: belief that you have a physical disorder/defect
- Nihilistic: belief that things do not exist; a sense that everything is unreal

**Cognitive Assessment**

Use MMSE to assess:

- Orientation (time and place)
- Memory (immediate and delayed recall)
- Attention and concentration
- Language (comprehension, reading, writing, repetition, naming)
- Spatial ability (intersecting pentagons)

Gross screen for cognitive dysfunction:

Total score is out of 30: <24 abnormal, 20-24 mild, 10-19 moderate, <10 severe
Cognition
- level of consciousness
- orientation: time, place, person
- memory: immediate, recent, remote
- global evaluation of intellect (below average, average, above average)
- intellectual functions: attention, concentration, calculation, abstraction (proverb interpretation, similarities test), language, communication

Insight
- patient’s ability to realize that he or she has a physical or mental illness and to understand its implications

Judgement
- patient’s ability to understand relationships between facts and draw conclusions that determine one’s actions

Summary of Axes

Multiaxial Assessment
- Axis I
  - differential diagnosis of DSM-IV clinical disorders
- Axis II
  - personality disorders, developmental disability
- Axis III
  - general medical conditions that are potentially relevant to the understanding or management of the mental disorder
- Axis IV
  - psychosocial and environmental issues
- Axis V
  - Global Assessment of Functioning (GAF, 0 to 100) incorporating effects of axes I to IV

Formulation
- summary outlining current issues and interrelations between an individual’s biological, psychological, and social factors
- for each category: predisposing, precipitating, perpetuating, and protecting factors

Approach to Management
- biological (e.g. pharmacotherapy), psychological [e.g. cognitive behavioural therapy (CBT)], social (e.g. support group)

Suicide

Epidemiology
- attempted:completed = 20:1
- M:F = 1:4 for attempts, 3:1 for completed

Risk Factors
- epidemiologic factors
  - age: increases after age 14, second most common cause of death for ages 15-24, highest rates in persons >65 yr
  - sex: male
  - race/ethnic background: white or native Canadians on reserves
  - marital status: widowed/divorced
  - living situation: alone; no children <18 yr old in the household
  - other: stressful life events, access to firearms
- psychiatric disorders
  - mood disorders (15% lifetime risk in depression; higher in bipolar)
  - anxiety disorders (especially panic disorder)
  - schizophrenia (10-15% risk)
  - substance abuse (especially alcohol – 15% lifetime risk)
  - eating disorders (5% lifetime risk)
  - adjustment disorder
  - conduct disorder
  - personality disorders (borderline, antisocial)
- past history
  - prior suicide attempt
  - family history of suicide attempt/completion

Assessing Insight and Judgement
Insight
- Do you think that you have a mental illness?
- Why are you taking this medication?
- Why are you in the hospital?

Judgement
Can be observed from collected history and patient’s appearance and actions.
- Is he/she dressed appropriately for the weather?
- Is he/she acting appropriately in the given situation?
- Is he/she taking care of self and/or dependents?

Axis V: Global Assessment of Functioning
The description of each 10-point range in the GAF scale has two components: the first part covers symptom severity, and the second part covers functioning. It should be noted that in situations where the individual’s symptom severity and functioning are discordant, the final GAF rating always reflects the worse of the two.
91-100 Superior functioning in a wide range of activities
81-90 Absent or minimal symptoms
71-80 If symptoms are present, they are transient and expected reactions to psychosocial stressors
61-70 Some mild symptoms or some difficulty but generally functioning well
51-60 Moderate symptoms or difficulty
41-50 Serious symptoms or difficulty
31-40 Some impairment in reality testing/communication, impairment in several areas
21-30 Behaviour is influenced by delusions/hallucinations or serious impairment in communication/judgment
11-20 Some danger of hurting self or others or occasionally fails to maintain minimal hygiene or gross impairment in communication
1-10 Persistent danger of severely hurting self or others or persistent inability to maintain minimal personal hygiene or serious suicidal act
0 Inadequate information

Suicide Risk Factors
SAD PERSONS
Sex (male)
Age >60 yr old
Depression
Previous attempts
Ethanol abuse
Rational thinking loss (delusions, hallucinations, hopelessness)
Suicide in family
Organized plan
No spouse (no support systems)
Serious illness, intractable pain
Clinical Presentation
- symptoms associated with suicide:
  - hopelessness
  - anhedonia
  - insomnia
  - severe anxiety
  - impaired concentration
  - psychomotor agitation
  - panic attacks

Approach
Every Patient: “Have you had any thoughts of wanting to hurt or kill yourself?”
- passive ideation: would rather not be alive but has no active plan for suicide
  - e.g. “I’d rather not wake up” or “I would not mind if a car hit me”
- active ideation
  - e.g. “I think about killing myself”
- plan: “Do you have a plan as to how you would end your life?”
- intent: “You talk about wanting to die, but are you planning to do this?” or “What has stopped you from ending your life?”
- past attempts: highest risk if previous attempt in past year
  - ask about lethality, outcome, medical intervention

Assessment of Suicidal Ideation
- onset and frequency of thoughts: “When did this start?” or “How often do you have these thoughts?”
- control over suicidal ideation: “Can you stop the thoughts or call someone for help?”
- lethality: “Do you want to end your life?” or “What do you think would happen if you actually took those pills?”
- access to means: “How will you get a gun?” or “Which bridge do you think you would go to?”
- time and place: “Have you picked a date and place? Is it in an isolated location?”
- provocative factors: “What makes you feel worse (e.g. being alone)?”
- protective factors: “What keeps you alive (e.g. friends, family, pets, faith, therapist)?”
- final arrangements: “Have you written a suicide note? Made a will? Given away your belongings?”
- practiced suicide or aborted attempts: “Have you put the gun to your head?” “Held the medications in your hand?” “Stood at the bridge?”
- ambivalence: “There must be a part of you that wants to live, after all you came here for help”

Assessment of Suicide Attempt
- setting (isolated vs. others present, chance of discovery)
- planned vs. impulsive attempt, triggers/stressors
- intoxication
- medical attention (brought in by another person vs. brought in by self to ER)
- time lag from suicide attempt to ER arrival
- expectation of lethality, dying
- reaction to survival (guilt/remorse vs. disappointment/self-blame)

Management
- proper documentation of the clinical encounter and rationale for management is essential
- higher risk (hospitalization needs to be strongly considered)
  - patients with a plan, access to lethal means, recent social stressors, and symptoms suggestive of a psychiatric disorder
  - do not leave patient alone; remove potentially dangerous objects from room
  - if patient refuses to be hospitalized, complete form for involuntary admission (Form 1)
- lower risk
  - patients who are not actively suicidal, with no plan or access to lethal means
  - discuss protective factors and supports in their life, remind them of what they live for, promote survival skills that helped them through previous suicide attempts
  - make a safety plan: an agreement that they will:
    - not harm themselves
    - avoid alcohol, drugs, and situations that may trigger suicidal thoughts
    - follow-up with you at a designated time
    - contact a health care worker, call a crisis line or go to an emergency department if they feel unsafe or if their suicidal feelings return or intensify
  - depression: consider hospitalization if symptoms severe or if psychotic features are present; otherwise outpatient treatment with good supports and SSRIs/SNRIs
  - alcohol-related: usually resolves with abstinence for a few days; if not, suspect depression
  - personality disorders: crisis intervention/confrontation, may or may not hospitalize
  - schizophrenia/psychosis: hospitalization might be necessary
  - parasuicide/self-mutilation: long-term psychotherapy with brief crisis intervention when necessary

Pharmacotherapy and Suicide Risk
Once antidepressant therapy is initiated, patients should be followed frequently as there is a “suicide window” in which the patient may still be depressed, but now has enough energy to carry out suicide. Avoid tricyclic antidepressants (TCAs) because of high lethality in overdose!
**Psychotic Disorders**

**Definition**
- characterized by a significant impairment in reality testing
  - delusions or hallucinations (with/without insight into their pathological nature)
  - behaviour so disorganized that it is reasonable to infer that reality testing is disturbed

**Table 1. Differentiating Psychotic Disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Psychotic Symptoms</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief psychotic disorder</td>
<td>≥1 positive symptoms of criterion A</td>
<td>&lt; 1 mo</td>
</tr>
<tr>
<td>Schizophreniform disorder</td>
<td>Criterion A</td>
<td>1-6 mo</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Criterion A</td>
<td>&gt; 6 mo</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>≥2 wk (with no mood symptoms)</td>
<td>&gt; 1 mo</td>
</tr>
<tr>
<td>Delusional disorder</td>
<td>Non-bizarre delusions, hallucinations</td>
<td>&gt; 1 mo</td>
</tr>
<tr>
<td>2º to substance intoxication/withdrawal</td>
<td>Criterion A</td>
<td>During intoxication or ≤1 mo after withdrawal</td>
</tr>
<tr>
<td>2º to mood disorder</td>
<td>Delusions/hallucinations (mood congruent)</td>
<td>Unspecified</td>
</tr>
</tbody>
</table>

**Differential Diagnosis of Psychosis**
- primary psychotic disorders: schizophrenia, schizophreniform, brief psychotic, schizoaffective, shared psychotic, delusional disorder
- mood disorders: depression with psychotic features, bipolar disorder (mania or depression with psychotic features)
- personality disorders: schizotypal, schizoid, borderline, paranoid, obsessive-compulsive
- general medical conditions: tumour, head trauma, dementia, delirium, metabolic, infection, stroke, temporal lobe epilepsy
- substance-induced psychosis: intoxication or withdrawal, prescribed medications, toxins

**Schizophrenia**

**DSM-IV-TR Diagnostic Criteria for Schizophrenia**

A. characteristic symptoms (active phase): ≥2 of the following, each present for a significant portion of time during a 1-mo period (or less if successfully treated)
- delusions
- hallucinations
- disorganized speech (e.g. frequent derailment or incoherence)
- grossly disorganized or catatonic behaviour
- negative symptoms [e.g. affective flattening, alogia (inability to speak), or avolition (inability to initiate and persist in goal-directed activities)]

Note: only 1 "A" symptom is required if delusions are bizarre or hallucinations consist of a voice keeping a running commentary on the person's behaviour or thoughts, or 2 or more voices conversing with each other

B. social/occupational dysfunction: ≥1 major areas of functioning (work, interpersonal relations, self-care) markedly below the level achieved prior to the onset of symptoms

C. continuous signs of disturbance for ≥6 mo, including ≥1 mo of active phase symptoms; may include prodromal or residual phases

D. schizoaffective and mood disorders excluded

E. the disturbance is not due to the direct physiological effects of a substance or a GMC

F. if history of pervasive developmental disorder, additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 mo

**Subtypes**
- paranoid
  - preoccupation with delusions (typically persecutory or grandiose) or frequent auditory hallucinations
  - relative preservation of cognitive functioning and affect; onset tends to be later in life; believed to have the best prognosis
• catatonic
  ▪ at least two of: motor immobility (catalepsy or stupor); excessive motor activity (purposeless); extreme negativism (resistance to instructions/Attempts to be moved) or mutism; peculiar voluntary movement (posturing, stereotyped movements, prominent mannerisms); echolalia or echopraxia (copying another’s speech or movements)
• disorganized
  ▪ disorganized speech and behaviour; flat or inappropriate affect
  ▪ poor premorbid personality, early and insidious onset, and continuous course without significant remissions
• undifferentiated
  ▪ meets criteria for schizophrenia, but does not fall into the 3 previous subtypes
  ▪ residual
  ▪ no longer have prominent delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour
  ▪ continuing evidence of residual illness such as negative symptoms or attenuated symptoms of criteria A

Epidemiology
• prevalence: 0.5%-1%; M:F = 1:1
• mean age of onset: females ~27; males ~21

Etiology
• multifactorial: disorder is a result of interaction between both biological and environmental factors
  ▪ genetic: 40% concordance in monozygotic (MZ) twins; 46% if both parents have schizophrenia; 10% of dizygotic (DZ) twins, siblings, children affected
  ▪ neurochemistry (“dopamine hypothesis” theory): excess activity in the mesolimbic dopamine pathway may mediate the positive symptoms of psychosis while decreased dopamine in the prefrontal cortex may mediate negative and cognitive symptoms. GABA, glutamate and ACh dysfunction are also thought to be involved
  ▪ neuroanatomy: decreased frontal lobe function; asymmetric temporal/limbic function; decreased basal ganglia function; subtle changes in thalamus, cortex, corpus callosum, and ventricles; cytoarchitectural abnormalities
  ▪ neuroendocrinology: abnormal growth hormone, prolactin, cortisol, and ACTH
  ▪ neuropsychology: global defects seen in attention, language, and memory suggest lack of connectivity of neural networks
  ▪ environmental: indirect evidence of cannabis use, geographical variance, winter season of birth, obstetrical complications, and prenatal viral exposure

Pathophysiology
• neurodegenerative theory
  ▪ natural history may be a rapid or gradual decline in function and ability to communicate
  ▪ glutamate system may mediate progressive degeneration by excitotoxic mechanism which leads to production of free radicals
• neurodevelopmental theory: abnormal development of the brain from prenatal life
  ▪ neurons fail to migrate correctly, make inappropriate connections, and break down in later life
  ▪ inappropriate apoptosis during neurodevelopment resulting in faulty connections between neurons

Management of Schizophrenia
• biological
  ▪ acute treatment and maintenance with antipsychotics ± anticonvulsants ± anxiolytics
• psychosocial
  ▪ psychotherapy (individual, family, group): supportive, CBT (see CBT, PS41)
  ▪ assertive community treatment (ACT): mobile mental health teams that provide individualized treatment in the community and help patients with medication adherence, basic living skills, social support, job placements, and community resources
  ▪ social skills training, employment programs, disability benefits
  ▪ housing (group home, boarding home, transitional home)

Course and Prognosis
• the majority of individuals display some type of prodromal phase
• course is variable: some individuals have exacerbations and remissions and others remain chronically ill; accurate prediction of the long term outcome is not possible
• early in the illness, negative symptoms may be prominent; positive symptoms appear and typically diminish with treatment; negative symptoms may become more prominent and more disabling
• over time: 1/3 improve, 1/3 remain the same, 1/3 worsen
Schizophreniform Disorder

- **diagnosis**: criteria A, D and E of schizophrenia are met; an episode of the disorder lasts from 1-6 mo. If the symptoms have extended past 6 mo the diagnosis becomes schizophrenia
- **treatment**: similar to acute schizophrenia
- **prognosis**: better than schizophrenia; begins and ends more abruptly; good pre- and post-morbid function

Brief Psychotic Disorder

- **diagnosis**: acute psychosis (presence of 1 or more positive symptoms in criteria A 1-4 of schizophrenia) lasting from 1 day to 1 mo, with eventual full return to premorbid level of functioning
- can occur after a stressful event or postpartum (see Postpartum Mood Disorders, PS12)
- **treatment**: secure environment, antipsychotics, anxiolytics
- **prognosis**: good, self-limiting, should return to pre-morbid function in about 1 mo

Schizoaffective Disorder

**DSM-IV-TR Diagnostic Criteria for Schizoaffective Disorder**


A. **uninterrupted period of illness during which there is either a MDE, manic episode, or a mixed episode concurrent with symptoms meeting criteria A for schizophrenia**

B. **in the same period, delusions or hallucinations for ≥2 wk in the absence of prominent mood symptoms**

C. **symptoms that meet criteria for a mood episode are present for a substantial portion of total duration of active and residual periods of the illness**

D. **the disturbance is not due to the direct physiological effects of a substance or GMC**

- **treatment**: antipsychotics, mood stabilizers, antidepressants
- **prognosis**: between that of schizophrenia and of mood disorder

Delusional Disorder

**DSM-IV-TR Diagnostic Criteria for Delusional Disorder**


A. **non-bizarre delusions for ≥1 mo**

B. **criterion A for schizophrenia has never been met (though patient may have tactile or olfactory hallucinations if they are related to the delusional theme)**

C. **functioning not markedly impaired; behaviour not obviously odd or bizarre**

D. **if mood episodes occur concurrently with delusions, total duration has been brief relative to duration of the delusional periods**

E. **the disturbance is not due to the direct physiological effects of a substance or GMC**

- **subtypes**: erotomanic, grandiose, jealous, persecutory, somatic, mixed, unspecified
- **treatment**: psychotherapy, antipsychotics, antidepressants
- **prognosis**: chronic, unremitting course but high level of functioning

Shared Psychotic Disorder (Folie à Deux)

- **diagnosis**: delusion that develops in an individual who is in a close relationship with another person who already has a psychotic disorder with prominent delusions; the delusion is similar in content to that of the other person
- **treatment**: separation of the two people results in the disappearance of the delusion in the healthier member; antipsychotics may play a role
- **prognosis**: good
Mood Disorders

Definitions
- Mood disorders are defined by the presence of mood episodes
- Mood episodes represent a combination of symptoms comprising a predominant mood state that is abnormal in quality or duration (e.g., major depressive, manic, mixed, hypomanic)
- Types of mood disorders include:
  - Depressive (major depressive disorder, dysthymia)
  - Bipolar (bipolar I/II disorder, cyclothymia)
  - Secondary to GMC, substances, medications

Table 2. Secondary Causes of Mood Disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>V Vascular</td>
<td>Cardiomyopathy, CHF, MI, CVA</td>
</tr>
<tr>
<td>I Infectious</td>
<td>Encephalitis/meningitis, hepatitis, TB, syphilis, HIV/AIDS</td>
</tr>
<tr>
<td>N Neoplastic</td>
<td>Pancreatic cancer, carcinoid, pheochromocytoma, CNS tumour</td>
</tr>
<tr>
<td>D Degenerative</td>
<td>Huntington's disease, multiple sclerosis, tuberous sclerosis, degenerative (vascular, Alzheimer's dementia)</td>
</tr>
<tr>
<td>I Intoxication/Drugs/Deficiencies</td>
<td>Antihypertensives, antiparkinsonian, hormones, steroids, antituberculous, interferon, antineoplastic medications, vitamin deficiencies (Wernicke's encephalopathy, beriberi, pellagra, pernicious anemia)</td>
</tr>
<tr>
<td>C Congenital</td>
<td>—</td>
</tr>
<tr>
<td>A Autoimmune</td>
<td>SLE, polyarteritis nodosa</td>
</tr>
<tr>
<td>T Traumatic</td>
<td>—</td>
</tr>
<tr>
<td>E Endocrine/Metabolic</td>
<td>Hypothyroidism, hyperthyroidism, hypopituitarism, SIADH, porphyria, Wilson's disease, diabetes</td>
</tr>
</tbody>
</table>

Medical Workup of Mood Disorder
- Routine screening: physical examination, CBC, thyroid function test, electrolytes, extended electrolytes, urinalysis, drug screen
- Additional screening: neurological consultation, chest x-ray, ECG, CT

Mood Episodes

DSM-IV-TR Criteria for Major Depressive Episode
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition (Copyright 2000), American Psychiatric Association.

A. ≥ 5 of the following symptoms have been present during the same 2-wk period and represent a change from previous functioning; at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure (anhedonia)

Note: Do not include symptoms that are clearly due to a GMC, mood-incongruent delusions or hallucinations
- Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others
- Markedly diminished interest or pleasure in all or almost all activities most of the day, nearly every day
- Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a mixed episode (see PS10)

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

D. The symptoms are not due to the direct physiological effects of a substance or a GMC

E. The symptoms are not better accounted for by bereavement; the symptoms persist for longer than 2 mo; symptoms are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation
DSM-IV-TR Criteria for Manic Episode


A. a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting ≥1 wk (or any duration if hospitalization is necessary) (note: in DSM-5, “persistently increased goal-directed activity or energy” has been added to criteria A)

B. during the period of mood disturbance, ≥3 of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree:

- inflated self-esteem or grandiosity
- decreased need for sleep (e.g. feels rested after only 3 h of sleep)
- more talkative than usual or pressure to keep talking
- flight of ideas or subjective experience that thoughts are racing
- distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli)
- increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
- excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g. engaging in unrestrained shopping sprees, sexual indiscretions, or foolish business investments)

C. the symptoms do not meet criteria for a mixed episode (see below)

D. the mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features

E. the symptoms are not due to the direct physiological effects of a substance (e.g. drug of abuse, medication, or other treatment) or a GMC (e.g. hyperthyroidism).

Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g. medication, ECT therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder (this has been removed in DSM-5)

Mixed Episode
- criterion met for both manic episode and MDE nearly every day for 1 wk
- criteria D and E of manic episodes are met

Note: in DSM-5, mixed episode is no longer a separate mood diagnosis; instead, depressed episodes and manic episodes can have a “with mixed features” specifier

Hypomanic Episode
- criterion A of a manic episode is met, but duration is ≥4 d
- criteria B and E of manic episodes are met
- episode associated with an uncharacteristic decline in functioning that is observable by others
- change in function is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization
- absence of psychotic features

Depressive Disorders

MAJOR DEPRESSIVE DISORDER

DSM-IV-TR Diagnostic Criteria for Major Depressive Disorder (MDD), Single Episode (vs. Recurrent)


A. presence of a single MDE (vs. recurrent, which requires presence of two or more MDEs; to be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a MDE)

B. the MDE is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder NOS

C. there has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode

Note: This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment-induced or are due to the direct physiological effects of a GMC

Features/Specifiers
- psychotic: with hallucinations or delusions
- chronic: lasting 2 yr or more
- catatonic: at least two of: motor immobility, excessive motor activity, extreme negativism or mutism, peculiarities of voluntary movement, echolalia or echopraxia
- melancholic: quality of mood is distinctly depressed, mood is worse in the morning, early morning awakening, marked weight loss, excessive guilt, psychomotor retardation
- atypical: increased sleep, weight gain, leaden paralysis, rejection hypersensitivity
- postpartum: (see Postpartum Mood Disorders, PS12)
- seasonal: pattern of onset at the same time each year (most often in the fall or winter)

Note: in DSM-5 the specifiers have changed to include: with anxious distress, with mixed features, with melancholic features, with atypical features, with mood-congruent psychotic features, with mood-incongruent psychotic features, with catatonia, with peripartum onset, with seasonal pattern
Epidemiology
- prevalence: 12.2%
  - lifetime prevalence: male 2.9%, female 5%
  - annual prevalence: peak prevalence age 15-25 yr (M:F = 1:2)

Etiology
- biological
  - genetic: 65-75% MZ twins; 14-19% DZ twins
  - neurotransmitter dysfunction: decreased activity of 5HT, NE and DA at the level of the synapse; changes in GABA and glutamate; changes in brain circuitry
  - neuroendocrine dysfunction: increased production of corticotropin causing excessive HPA axis activity
  - neuroanatomy: smaller frontal lobes and hippocampal volume; increased ventricle sizes
  - neurophysiologic: decreased REM latency and slow-wave sleep; increased REM length
  - secondary to GMC
- psychosocial
  - psychodynamic (e.g. low self-esteem)
  - cognitive (e.g. negative thinking)
  - environmental factors (e.g. job loss, bereavement, history of abuse, early life adversity)
  - co-morbid psychiatric diagnoses (e.g. anxiety, substance abuse, developmental disability, dementia, eating disorder)

Risk Factors
- sex: female > male
- age: onset between 25-50 yr of age
- family history: depression, alcohol abuse, sociopathy
- childhood experiences: loss of parent before age 11, negative home environment (abuse, neglect)
- personality: insecure, dependent, obsessional
- recent stressors: illness, financial, legal
- postpartum <6 mo
- lack of intimate, confiding relationships or social isolation

Depression in the Elderly
- affects about 15% of community residents >65 yr old; up to 50% in nursing homes
- high suicide risk due to social isolation, chronic medical illness
- suicide peak: males aged 80-90; females aged 50-65
- dysphoria may not be a reliable indicator of depression in those >85 yr
- often present with somatic complaints (e.g. changes in weight, sleep, energy) or anxiety symptoms
- may have prominent cognitive changes after onset of mood symptoms (dementia syndrome of depression)
- refer to Table 4 (see Dementia, PS21) to compare with delirium and dementia

Treatment
- biological: antidepressants primarily; could also consider lithium, antipsychotics, anxiolytics, light therapy, ECT, repetitive transcranial magnetic stimulation (rTMS)
- psychological
  - individual therapy (psychodynamic, interpersonal, CBT), family therapy, group therapy
  - social: vocational rehabilitation, social skills training
  - experimental: magnetic stimulation therapy (MST), deep brain stimulation, vagal nerve stimulation
- studies suggest CBT with pharmacotherapy results in better outcomes

Prognosis
- one year after diagnosis of a MDE without treatment: 40% of individuals still have symptoms that are sufficiently severe to meet criteria for a full MDE, 20% continue to have some symptoms that no longer meet criteria for a MDE, 40% have no mood disorder

DYSTHYMIA

DSM-IV-TR Diagnostic Criteria for Dysthymic Disorder
Note: in DSM-5 this has been changed to Persistent Depressive Disorder

A. depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for ≥2 yr
- Note: In children and adolescents, mood can be irritable and duration must be at least 1 yr
B. presence, while depressed, of ≥2 of the following
  - poor appetite or overeating
  - insomnia or hypersomnia
  - low energy or fatigue
- low self-esteem
- poor concentration or difficulty making decisions
- feelings of hopelessness

C. during the 2-yr period (1 yr for children or adolescents) of the disturbance, the person has never been without the symptoms in criteria A and B for more than 2 mo at a time

D. no MDE has been present during the first 2 yr of the disturbance (1 yr for children and adolescents); i.e. the disturbance is not better accounted for by chronic MDD, or MDD in partial remission

E. there has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode, and criteria have never been met for Cyclothymic Disorder

F. the disturbance does not occur exclusively during the course of a chronic psychotic disorder, such as Schizophrenia or Delusional Disorder

G. the symptoms are not due to the direct physiological effects of a substance or a GMC

H. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

**Epidemiology**
- point prevalence: 3%; life prevalence: 6%; M:F = 1:2-3

**Treatment**
- psychological
  - principal treatment for dysthymia
  - individual, group, and family therapy
- biological
  - antidepressant therapy (SSRIs/SNRIs) as an outpatient

---

### Postpartum Mood Disorders

**Postpartum “Blues”**
- transient period of mild depression, mood instability, anxiety, decreased concentration, increased concern over own health and health of baby – considered to be normal emotional changes related to the puerperium
- occurs in 50-80% of mothers; begins 2-4 d postpartum, usually lasts 48 h, can last up to 10 d
- does not require psychotropic medication
- patient at increased risk of developing postpartum depression

**Postpartum Depression (PPD)**
- diagnosis: MDE, onset within 4 wk postpartum
- clinical presentation:
  - typically lasts 2 to 6 mo; residual symptoms can last up to 1 yr
  - may present with psychosis – rare (0.2%), usually associated with mania, but also with MDE
  - severe symptoms include extreme disinterest in baby, suicidal and infanticidal ideation
- epidemiology: occurs in 10% of mothers, risk of recurrence 50%
- risk factors:
  - previous history of a mood disorder (postpartum or otherwise)
  - psychosocial factors: stressful life events, unemployment, marital conflict, lack of social support, unwanted pregnancy, colicky or sick infant
- treatment:
  - psychotherapy (CBT or IPT)
  - short-term safety of maternal SSRIs for breastfeeding infants established; long-term effects unknown
  - if depression severe, consider ECT
- prognosis:
  - impact on child development: increased risk of cognitive delay, insecure attachment, behavioural disorders
  - treatment of mother improves outcome for child at 8 mo through increased mother-child interaction

---

### Bipolar Disorders

**BIPOLAR I / BIPOLAR II DISORDER**

**Definition**
- Bipolar I Disorder
  - disorder in which at least one manic or mixed episode has occurred
  - commonly accompanied by at least 1 MDE but not required for diagnosis
- Bipolar II Disorder
  - disorder in which there is at least 1 MDE and at least 1 hypomanic episode
  - no past manic or mixed episodes
**Epidemiology**
- prevalence: 0.6-0.9%; M:F = 1:1
- age of onset: teens to 20's

**Risk Factors**
- high SES
- genetic: 60-65% of bipolar patients have family history of major mood disorders

**Classification**
- classification of bipolar disorder involves describing the current or most recent mood episode as either manic, hypomanic, mixed or depressed
- the current or most recent episode can be further classified as without psychotic features, with psychotic features, with catatonic features, with postpartum onset, with seasonal pattern, with rapid cycling (at least 4 episodes of a mood disturbance in the previous 12 mo that meet criteria for a major depressive, manic, mixed, or hypomanic episode)

**Treatment**
- biological: lithium, anticonvulsants, antipsychotics, antidepressants, ECT
- psychological: supportive or psychodynamic psychotherapy, CBT, ITP or interpersonal social rhythm therapy
- social: vocational rehabilitation, consider leave of absence from school/work, consider substitute decision maker for finances, drug and EtOH cessation, sleep hygiene, social skills training, education for family members

**Course and Prognosis**
- high suicide rate (15% mortality from suicide)
- relapsing and remitting course with alternating manic and depressive episodes; depressive symptoms tend to occur more frequently and last longer than manic episodes
- patients spend almost half of their lives symptomatic
- may switch rapidly between depression and mania without any period of euthymia in between
- high recurrence rate for mania – 90% will have a subsequent episode in the next 5 yr

**CYCLOTHYMIA**

**Diagnosis**
- presence of numerous periods of hypomanic and depressive symptoms (not meeting criteria for MDE) for ≥2 yr; never without symptoms for >2 mo
- no MDE, manic or mixed episodes, no evidence of psychosis
- symptoms are not due to the direct physiological effects of a substance or GMC
- symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

**Treatment**
- similar to Bipolar I: anticonvulsants ± psychotherapy

---

**Anxiety Disorders**

**Definition**
- anxiety is a universal human characteristic involving tension, apprehension, or even terror
- serves as an adaptive mechanism to warn about an external threat by activating the sympathetic nervous system (fight or flight)
- manifestations of anxiety can be described through:
  - physiology: main brain structure involved is the amygdala (fear conditioning); neurotransmitters involved include 5-HT, cholecystokinin, epinephrine, norepinephrine, DA
  - psychology: one's perception of a given situation is distorted which causes one to believe it is threatening in some way
  - behaviour: once feeling threatened, one responds by escaping or facing the situation, thereby causing a disruption in daily functioning
- anxiety becomes pathological when:
  - fear is greatly out of proportion to risk/severity of threat
  - response continues beyond existence of threat or becomes generalized to other similar or dissimilar situations
  - social or occupational functioning is impaired
Differential Diagnosis

Table 3. Differential Diagnosis of Anxiety Disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Post-MI, arrhythmia, congestive heart failure, pulmonary embolus, mitral valve prolapse</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Asthma, COPD, pneumonia, hyperventilation</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hyperthyroidism, pheochromocytoma, hypoglycemia, hyperadrenalism, hyperparathyroidism</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Vitamin B12 deficiency, porphyria</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Neoplasm, vestibular dysfunction, encephalitis</td>
</tr>
<tr>
<td>Substance-Induced</td>
<td>Intoxication (caffeine, amphetamines, cocaine, thyroid preparations, OTC for colds/ decongestants), withdrawal (benzodiazepines, alcohol)</td>
</tr>
<tr>
<td>Other Psychiatric Disorders</td>
<td>Psychotic disorders, mood disorders, personality disorders (OCPD), somatoform disorders</td>
</tr>
</tbody>
</table>

Medical Workup of Anxiety Disorder
- routine screening: physical examination, CBC, thyroid function test, electrolytes, urinalysis, urine drug screening
- additional screening: neurological consultation, chest x-ray, ECG, CT

Panic Disorder

DSM-IV-TR Diagnostic Criteria for Panic Disorder without Agoraphobia

A. both (1) and (2)
- (1) recurrent unexpected panic attacks: a discrete period of intense fear or discomfort, in which ≥4 of the following symptoms develop abruptly and reach a peak within 10 min
  - palpitations, pounding heart, or accelerated heart rate
  - sweating
  - trembling or shaking
  - sensations of shortness of breath or smothering
  - feeling of choking
  - chest pain or discomfort
  - nausea or abdominal distress
  - feeling dizzy, unsteady, lightheaded, or faint
  - derealization (feelings of unreality) or depersonalization (being detached from oneself)
  - fear of losing control or going crazy
  - fear of dying
  - paresthesias (numbness or tingling sensations), chills or hot flushes
- (2) at least one of the attacks has been followed by 1 mo (or more) of ≥1 of the following
  - persistent concern about having additional attacks
  - worry about the implications of the attack or its consequences (e.g. losing control, having a heart attack, “going crazy”)
  - a significant change in behaviour related to the attacks

B. absence of agoraphobia
C. the panic attacks are not due to the direct physiological effects of a substance or GMC
D. the panic attacks are not better accounted for by another mental disorder, such as social phobia, specific phobia, obsessive-compulsive disorder, post-traumatic stress disorder, separation anxiety disorder

Epidemiology
- prevalence: 1.5-5% (one of the top five most common reasons to see a family doctor); M:F = 1.2-3
- onset: average late 20’s, familial pattern

Treatment
- psychological
  - CBT: interoceptive exposure (eliciting symptoms of a panic attack and learning to tolerate the symptoms without coping strategies); cognitive restructuring (addressing underlying beliefs regarding the panic attacks), relaxation techniques (visualization, box-breathing)
- pharmacological
  - SSRIs: fluoxetine, citalopram, paroxetine, fluvoxamine, sertraline
  - SNRIs: venlafaxine
  - with SSRIs/SNRIs start with low doses, titrate up slowly
  - anxiety disorders often require treatment at higher doses for a longer period of time (i.e. up to 8-12 wk than used for depression)
  - to prevent non-compliance due to physical side effects, explain symptoms to expect prior to initiation of therapy
  - other antidepressants (TCAs, mirtazapine, MAOIs)
    - consider avoiding bupropion due to stimulating effects
  - benzodiazepines (short term, low dose, regular schedule, long half-life, avoid prn use)
Prognosis
- 6-10 yr post-treatment: 30% well, 40-50% improved, 20-30% no change or worse
- clinical course: chronic, but episodic with psychosocial stressors

Panic Disorder with Agoraphobia
- agoraphobia
  - anxiety about being in places or situations from which escape might be difficult (or embarrassing) or where help may not be available in the event of having an unexpected panic attack
  - fears commonly involve situations such as being out alone, being in a crowd, standing in a line, or travelling on a bus
- situations are avoided, endured with anxiety or panic, or require companion
- treatment: as per panic disorder

Generalized Anxiety Disorder (GAD)

DSM-IV-TR Diagnostic Criteria for Generalized Anxiety Disorder

A. excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 mo, about a number of events or activities (such as work or school performance)
B. the person finds it difficult to control the worry
C. the anxiety and worry are associated with ≥3 of the following 6 symptoms (with at least some symptoms present for more days than not for the past 6 mo)
  - restlessness or feeling keyed up or on edge
  - being easily fatigued
  - difficulty concentrating or mind going blank
  - irritability
  - muscle tension
  - sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)
D. the focus of the anxiety and worry is not confined to features of an Axis I disorder, such as panic disorder, social phobia, etc.
E. the anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
F. the disturbance is not due to the direct physiological effects of a substance or a GMC and does not occur exclusively during a Mood Disorder, a Psychotic Disorder, or a Pervasive Developmental Disorder

Epidemiology
- 1-yr prevalence: 3-8%; M:F = 1:2
  - if considering only those receiving inpatient treatment, ratio is 1:1
- most commonly presents in early adulthood

Treatment
- lifestyle: caffeine and EtOH avoidance, sleep hygiene
- psychological: CBT including relaxation techniques, mindfulness
- biological
  - SSRIs and SNRIs are 1st line (paroxetine, escitalopram, sertraline, venlafaxine XL)
  - 2nd line: bupropion (caution due to stimulating effects ), buspirone (tid dosing)
  - add-on benzodiazepines (short term, low dose, regular schedule, long half-life, avoid prn)
  - β-blockers not recommended

Prognosis
- chronically anxious adults become less so with age
- depends on pre-morbid personality functioning, stability of relationships, work, and severity of environmental stress
- difficult to treat

Phobic Disorders

Specific Phobia
- definition: marked and persistent fear that is excessive or unreasonable, cued by presence or anticipation of a specific object or situation
- lifetime prevalence 12-16%; M:F ratio variable
- types: animal/insect, environment (heights, storms), blood/injection/injury, situational (airplane, closed spaces), other (loud noise, clowns)
Social Phobia (Social Anxiety Disorder)
- definition: marked and persistent fear of social or performance situations in which one is exposed to unfamiliar people or to possible scrutiny by others; fearing he/she will act in a way that may be humiliating or embarrassing (e.g. public speaking, initiating or maintaining conversation, dating, eating in public)
- lifetime prevalence may be as high as 13-16%; F>M

Diagnostic Criteria for Phobic Disorders
- exposure to stimulus almost invariably provokes an immediate anxiety response; may present as a panic attack
- person recognizes fear as excessive or unreasonable
- situations are avoided or endured with anxiety/distress
- significant interference with daily routine, occupational/social functioning, and/or marked distress
- if person is <18 yr, duration is at least 6 mo

Treatment
- psychological
  - cognitive behaviour therapy (focusing on both in vivo and virtual exposure therapy – gradually facing feared situations)
  - behavioural therapy is more efficacious than medication
- biological
  - β-blockers or benzodiazepines in acute situations (e.g. public speaking)

Prognosis
- chronic

Obsessive-Compulsive Disorder (OCD)

DSM-IV-TR Diagnostic Criteria for Obsessive Compulsive Disorder
A. either obsessions or compulsions:
  - obsessions as defined by (1), (2), (3), and (4)
    1. recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress
    2. the thoughts, impulses, or images are not simply excessive worries about real-life problems
    3. the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action
    4. the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed)
  - compulsions as defined by (1) and (2)
    1. repetitive behaviours or mental acts that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly
    2. the behaviours or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviours or mental acts either are not connected in a realistic way with what they are designed to neutralize/prevent or are clearly excessive
B. at some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable (ego-dystonic)
Note: This does not apply to children
C. the obsessions or compulsions cause marked distress, are time-consuming (take ≥1 h a day), or significantly interfere with the person’s normal routine, occupational (or academic) functioning, or usual social activities or relationships
D. if another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g. preoccupation with food in the presence of an Eating Disorder)
E. the disturbance is not due to the direct physiological effects of a substance or a GMC

Epidemiology
- lifetime prevalence rates 2-3%; M=F
- rate of OCD in first-degree relatives is higher than in the general population

Treatment
- CBT: exposure with response prevention (ERP) – involves exposure to feared situations with the addition of preventing the compulsive behaviours; cognitive strategies include challenging underlying beliefs
- pharmacotherapy: SSRIs/SNRIs, clomipramine; adjunctive risperidone

Prognosis
- tends to be refractory and chronic
Post-Traumatic Stress Disorder (PTSD)

DSM-IV-TR Diagnostic Criteria for Post-Traumatic Stress Disorder

A. the person has been exposed to a traumatic event in which both of the following were present
   (1) the person experienced, witnessed, or was confronted with an event or events that
      involved actual or threatened death or serious injury, or a threat to the physical integrity
      of self or others
   (2) the person's response involved intense fear, helplessness, or horror
      Note: in children, this may be expressed instead by disorganized or agitated behaviour
B. the traumatic event is persistently re-experienced in one (or more) of the following ways:
   (1) recurrent and intrusive distressing recollections of the event, including images, thoughts,
      or perceptions
      Note: in children, repetitive play may occur in which themes or aspects of the trauma are
      expressed
   (2) recurrent distressing dreams of the event
      Note: in children, there may be frightening dreams without recognizable content
   (3) acting or feeling as if the traumatic event were recurring (includes a sense of reliving the
      experience, illusions, hallucinations, and dissociative flashback episodes, including those
      that occur on awakening or when intoxicated)
      Note: in children, trauma-specific reenactment may occur
   (4) intense psychological distress at exposure to internal or external cues that symbolize or
      resemble an aspect of the traumatic event
   (5) physiological reactivity on exposure to internal or external cues that symbolize or
      resemble an aspect of the traumatic event
C. persistent avoidance of stimuli associated with the trauma and numbing of general
   responsiveness (not present before the trauma), as indicated by ≥3 of the following:
   (1) efforts to avoid thoughts, feelings, or conversations associated with the trauma
   (2) efforts to avoid activities, places, or people that arouse recollections of the trauma
   (3) inability to recall an important aspect of the trauma
   (4) markedly diminished interest or participation in significant activities
   (5) feeling of detachment or estrangement from others
   (6) restricted range of affect (e.g. unable to have loving feelings)
   (7) sense of a foreshortened future (e.g. does not expect to have a career, marriage, children,
      or a normal life span)
D. persistent symptoms of increased arousal (not present before the trauma), as indicated by ≥2 of
   the following:
   (1) difficulty falling or staying asleep
   (2) irritability or outbursts of anger
   (3) difficulty concentrating
   (4) hypervigilance
   (5) exaggerated startle response
E. duration of the disturbance (symptoms in Criteria B, C, and D) is ≥1 mo
F. the disturbance causes clinically significant distress or impairment in social, occupational, or
   other important areas of functioning

Epidemiology
• prevalence in general population: 7%
• men's trauma is most commonly combat experience/physical assault; women's trauma is usually
  physical or sexual assault

Treatment
• CBT: exposure therapy, challenge dysfunctional beliefs, emotional regulation techniques (e.g.
  breathing, relaxation)
• biological
  • SSRIs
  • benzodiazepines (for acute anxiety)
  • adjunctive atypical antipsychotics (risperidone, olanzapine)
• Eye Movement Desensitization and Reprocessing (EMDR); an experimental method of
  reprocessing memories of distressing events by recounting them while using a form of dual
  attention stimulation such as eye movements, bilateral sound, or bilateral tactile stimulation (its
  use is controversial because of limited evidence)

Complications
• substance abuse, relationship difficulties, depression, impaired social and occupational
  functioning disorders, Axis II disorders
Adjustment Disorder

DSM-IV-TR Diagnostic Criteria for Adjustment Disorder

A. the development of emotional or behavioural symptoms in response to an identifiable stressor(s) occurring within 3 mo of the onset of the stressor(s)

B. these symptoms or behaviours are clinically significant as evidenced by either of the following
   (1) marked distress that is in excess of what would be expected from exposure to the stressor
   (2) significant impairment in social or occupational (academic) functioning

C. the stress-related disturbance does not meet criteria for another Axis I disorder and is not merely an exacerbation of a pre-existing Axis I or Axis II disorder

D. the symptoms do not represent bereavement

E. once the stressor (or its consequences) has terminated, the symptoms do not persist for more than an additional 6 mo
   • specify if
     * acute: if the disturbance lasts less than 6 mo
     * chronic: if the disturbance lasts for 6 mo or longer

Adjustment disorders are coded based on the subtype, which is selected according to the predominant symptoms

Classification
• types of stressors
  ▪ single (e.g. termination of romantic relationship)
  ▪ multiple (e.g. marked business difficulties and marital problems)
  ▪ recurrent (e.g. seasonal business crises)
  ▪ continuous (e.g. living in a crime-ridden neighbourhood)
  ▪ developmental events (e.g. going to school, leaving parental home, getting married, becoming a parent, failing to attain occupational goals, retirement)
  ▪ Note: the specific stressor is specified on Axis IV

• subtypes, adjustment disorder with:
  ▪ depressed mood
  ▪ anxiety
  ▪ mixed anxiety and depressed mood
  ▪ disturbance of conduct
  ▪ mixed disturbance of emotions and conduct
  ▪ unspecified

Epidemiology
• M=F

Treatment
• brief psychotherapy (group, individual), crisis intervention
• biological
  ▪ benzodiazepines may be used for those with anxiety symptoms (short-term, low-dose, regular schedule)
  ▪ SSRIs for both depression and anxiety symptoms

Bereavement

Clinical Presentation
• length and characteristics of “normal” bereavement are variable between individuals/cultures
• may present with symptoms of MDE/MDD but individual regards depressed mood as normal
• diagnosis of MDD only given if symptoms persist >2 mo after loss (note – this stipulation has been removed in DSM-5; it is now possible to diagnose MDD regardless of how close it comes to loss)
• presence of following symptoms may indicate abnormal grief/presence of MDD
  ▪ guilt about things other than actions taken or not taken by the survivor at the time of death
  ▪ thoughts of death other than the survivor feeling that they would be better off dead or should have died with the deceased person; morbid preoccupation with worthlessness
  ▪ marked psychomotor retardation; prolonged and marked functional impairment
  ▪ hallucinatory experiences other than thinking that the survivor hears the voice of or transiently sees the image of the deceased person
• prolonged or complicated grief may occur if unable to “move on” or re-engage in life

Risk Factors for Poor Bereavement Outcome:
• Poor social supports
• Unanticipated death or lack of preparation for death
• Highly dependent relationship with deceased
• High initial distress
• Other concurrent stresses and losses
• Death of a child
• Pre-existing psychiatric disorders, especially depression and separation anxiety
Delirium

- see Neurology, N17 and Geriatric Medicine, GM3

DSM-IV-TR Diagnostic Criteria for Delirium due to a GMC

A. disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention
B. a change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia
C. the disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day
D. there is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a GMC

Clinical Presentation and Assessment

- common symptoms
  - wandering attention
  - distractibility
  - disorientation (time, place, rarely person)
  - misinterpretations, illusions, hallucinations
  - speech/language disturbances (dysarthria, dysnomia, dysgraphia)
  - affective symptoms (anxiety, fear, depression, irritability, anger, euphoria, apathy)
  - shifts in psychomotor activity (gropping/picking at clothes, attempts to get out of bed when unsafe, sudden movements, sluggishness, lethargy)
- Folstein Mini Mental Status Exam (see sidebar, PS3) is helpful to assess baseline of altered mental state (i.e. score will improve as symptoms resolve)

Risk Factors

- hospitalization (incidence 10-40%)
- nursing home residents (incidence 60%)
- childhood (e.g. febrile illness, anticholinergic use)
- old age (especially males)
- severe illness (e.g. cancer, AIDS)
- pre-existing cognitive impairment or brain pathology
- recent anesthesia
- substance abuse

Etiology

- Infectious (encephalitis, meningitis, UTI, pneumonia)
- Withdrawal (alcohol, barbiturates, benzodiazepines)
- Acute metabolic disorder (electrolyte imbalance, hepatic or renal failure)
- Trauma (head injury, postoperative)
- CNS pathology (stroke, hemorrhage, tumour, seizure disorder, Parkinson's)
- Hypoxia (anemia, cardiac failure, pulmonary embolus)
- Deficiencies (vitamin B₁₂, folic acid, thiamine)
- Endocrinopathies (thyroid, glucose, parathyroid, adrenal)
- Acute vascular (shock, vasculitis, hypertensive encephalopathy)
- Toxins: substance use, sedatives, opioids (especially morphine), anesthetics, anticholinergics, anticonvulsants, dopaminergic agents, steroids, insulin, glyburide, antibiotics (especially quinolones), NSAIDs
- Heavy metals (arsenic, lead, mercury)

Investigations

- standard: CBC and differential, electrolytes, Ca²⁺, PO₄³⁻, Mg²⁺, glucose, ESR, LFTs, Cr, BUN, TSH, vitamin B₁₂, folic acid, albumin, urine C&S, R&M
- as indicated: ECG, CXR, CT head, toxicology/heavy metal screen, VDRH, HIV, LP, EEG (typically abnormal: generalized slowing or fast activity), blood cultures
- indications for CT head: focal neurological deficit, acute change in status, anticoagulant use, acute incontinence, gait abnormality, history of cancer
Management

• intrinsic
  - identify and treat underlying cause immediately
  - stop all non-essential medications
  - maintain nutrition, hydration, electrolyte balance and monitor vitals

• extrinsic
  - environment should be quiet and well lit
  - optimize hearing and vision
  - room near nursing station for closer observation; constant care if patient jumping out of bed, pulling out lines
  - family member present for reassurance and re-orientation
  - calendar, clock for orientation cues

• biological
  - low dose antipsychotics
  - haloperidol has the most evidence; reasonable alternatives include risperidone, olanzapine or quetiapine
  - benzodiazepines only to be used in alcohol withdrawal delirium; otherwise, can worsen delirium

• physical restraints if patient becomes violent

Prognosis

• up to 50% 1 yr mortality rate after episode of delirium

Dementia

• see Neurology, N17

DSM-IV-TR Diagnostic Criteria for Dementia (Alzheimer’s Type)


A. the development of multiple cognitive deficits manifested by both
  1. memory impairment (impaired ability to learn new information or to recall previously learned information)
  2. ≥1 of the following cognitive disturbances:
     * aphasia (language disturbance)
     * apraxia (impaired ability to carry out motor activities despite intact motor function)
     * agnosia (failure to recognize or identify objects despite intact sensory function)
  3. disturbance in executive functioning (i.e. planning, organizing, sequencing, abstracting)
B. the cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning
C. the course is characterized by gradual onset and continuing cognitive decline
D. the cognitive deficits in Criteria A1 and A2 are not due to any of the following:
  1. other central nervous system conditions that cause progressive deficits in memory and cognition
  2. systemic conditions that are known to cause dementia
  3. substance-induced conditions
E. the deficits do not occur exclusively during the course of a delirium
F. the disturbance is not better accounted for by another Axis I disorder

Epidemiology

• prevalence increases with age: 10% in patients >65 yr of age; 25% in patients over 85 yr of age
• prevalence is increased in people with Down’s syndrome and head trauma
• Alzheimer’s dementia comprises >50% of cases; vascular causes comprise approximately 15% of cases (other causes of dementia – see Neurology, N18)
• average duration of illness from onset of symptoms to death is 8-10 yr

Subtypes

• with or without behavioural disturbance (e.g. wandering, agitation)
• early onset: age of onset <65 yr
• late onset: age of onset >65 yr

Investigations (rule out reversible causes)

• standard: see Delirium, PS19
• as indicated: VDRL, HIV, SPECT, CT head in dementia
• indications for CT head: same as for delirium, plus: age <60, rapid onset (unexplained decline in cognition or function over 1-2 mo), dementia of relatively short duration (<2 yr), recent significant head trauma, unexplained neurological symptoms (new onset of severe headache/seizures)
Management

- see Neurology, N20 for further management
- treat underlying medical problems and prevent others
- provide orientation cues for patient (e.g. clock, calendar)
- provide education and support for patient and family (e.g. day programs, respite care, support groups, home care)
- consider long-term care plan (nursing home) and power of attorney/living will
- inform Ministry of Transportation about patient’s inability to drive safely
- consider pharmacological therapy
  - cholinesterase inhibitors [e.g. donepezil (Aricept®)] for mild to severe disease
  - NMDA receptor antagonist (e.g. memantine) for moderate to severe disease
  - low-dose neuroleptics (e.g. risperidone, quetiapine), antidepressants or trazodone if behavioural or emotional symptoms prominent – start low and go slow
- reassess pharmacological therapy every 3 mo

Table 4. Comparison of Dementia, Delirium and Pseudodementia of Depression

<table>
<thead>
<tr>
<th></th>
<th>Dementia</th>
<th>Delirium</th>
<th>Pseudodementia of Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Gradual/step-wise decline</td>
<td>Acute (h-d)</td>
<td>Subacute</td>
</tr>
<tr>
<td>Duration</td>
<td>Months-years</td>
<td>Days-weeks</td>
<td>Variable</td>
</tr>
<tr>
<td>Natural History</td>
<td>Progressive</td>
<td>Fluctuating, reversible</td>
<td>Recurrent</td>
</tr>
<tr>
<td></td>
<td>Usually irreversible</td>
<td>High morbidity/mortality in very old</td>
<td>Usually reversible</td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td>Normal</td>
<td>Fluctuating (over 24 h)</td>
<td>Normal</td>
</tr>
<tr>
<td>Attention</td>
<td>Not initially affected</td>
<td>Decreased (wandering, easy distraction)</td>
<td>Difficulty concentrating</td>
</tr>
<tr>
<td>Orientation</td>
<td>Intact initially</td>
<td>Impaired (usually to time and place), fluctuates</td>
<td>Intact</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Disinhibition, impairment in ADL/ADL, personality change, loss of social graces</td>
<td>Severe agitation/retardation</td>
<td>Importuning, self-harm/suicide</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>Normal</td>
<td>Fluctuates between extremes</td>
<td>Slowing</td>
</tr>
<tr>
<td>Sleep Wake Cycle</td>
<td>Fragmented sleep at night</td>
<td>Reversed sleep wake cycle</td>
<td>Early morning awakening</td>
</tr>
<tr>
<td>Mood and Affect</td>
<td>Labile but not usually anxious</td>
<td>Anxious, irritable, fluctuating</td>
<td>Depressed, stable</td>
</tr>
<tr>
<td>Cognition</td>
<td>Decreased executive functioning, paucity of thought</td>
<td>Fluctuating preceded by mood changes</td>
<td>Fluctuating</td>
</tr>
<tr>
<td>Memory Loss</td>
<td>Recent, eventually remote</td>
<td>Marked recent</td>
<td>Recent</td>
</tr>
<tr>
<td>Language</td>
<td>Agnosia, aphasia, decreased comprehension, repetition, speech (echolalia, palilalia)</td>
<td>Dysnomia, dysgraphia, speech rambling, irrelevant, incoherent, subject changes</td>
<td>Not affected</td>
</tr>
<tr>
<td>Delusions</td>
<td>Compensatory</td>
<td>Nightmarish and poorly formed</td>
<td>Nihilistic, somatic</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Variable</td>
<td>Visual common</td>
<td>Less common, auditory predominates</td>
</tr>
<tr>
<td>Quality of Hallucinations</td>
<td>Vacuous/bland</td>
<td>Frightening/bizarre</td>
<td>Self-deprecatory</td>
</tr>
<tr>
<td>Medical Status</td>
<td>Variable</td>
<td>Acute illness, drug toxicity</td>
<td>R/O systemic illness, medications</td>
</tr>
</tbody>
</table>

Substance-Related Disorders

Epidemiology

- 47% of those with substance abuse have mental health problems
- 29% of those with a mental health disorder have a substance use disorder
- 47% of those with schizophrenia and 25% of those with an anxiety disorder have a substance use disorder

Types of Substance Use Disorders

1. *Substance abuse*: maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by ≥1 of the following occurring within a 12 mo period
   - recurrent use in situations in which it is physically hazardous (e.g. driving)
   - recurrent use resulting in failure to fulfill major role obligation
   - recurrent substance-related legal problems
   - continued use despite interference with social or interpersonal function

Substance Abuse

HELP
- Hazardous
- Education/work/home consequences
- Legal problems
- Personal/social consequences
2. **substance dependence**: maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by ≥3 occurring at any time in the same 12 mo period

- tolerance (need for increased amount to achieve intoxication or diminished effect with same amount of substance)
- withdrawal/usage to avoid withdrawal
- taken in larger amount or over longer period than intended
- persistent desire or unsuccessful efforts to cut down
- excessive time to procure, use substance, or recover from its effects
- important interests/activities given up or reduced
- continued use despite physical/psychological problem caused/exacerbated by substance

**Note**: in DSM-5 "Substance Use Disorders" will take the place of distinguishing substance abuse from substance dependence

### Classification of Substances

<table>
<thead>
<tr>
<th>Category</th>
<th>Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressants</td>
<td>Alcohol, Opioids, Barbiturates, Benzodiazepines, GHB</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Amphetamines, Methylphenidate, Cocaine</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>Cannabis, LSD, PCP, Ketamine, Psilocybin</td>
</tr>
</tbody>
</table>

### Nicotine

- see [Family Medicine, Smoking Cessation, FM10](#)

### Alcohol

- see [Family Medicine, Alcohol, FM12](#) and [Emergency Medicine, ER48](#)

#### History

- CAGE: validated screening questionnaire
  - C ever felt the need to Cut down on drinking?
  - A ever felt Annoyed at criticism of your drinking?
  - G ever feel Guilty about your drinking?
  - E ever need a drink first thing in morning (Eye opener)?
  - for men, a score of ≥2 is a positive screen; for women, a score of ≥1 is a positive screen
  - if positive CAGE, then assess further to distinguish between problem drinking and alcohol dependence

#### General Assessment

- When was your last drink?
- Do you have to drink more to get the same effect?
- Do you get shaky or nauseous when you stop drinking?
- Have you ever had a withdrawal seizure?
- How much time and effort do you put into obtaining alcohol?
- Has your drinking affected your ability to work, go to school, or have relationships?
- Have you suffered any legal consequences?
- Has your drinking caused any medical problems?

#### Table 5. Canada’s Low-Risk Alcohol Drinking Guidelines

<table>
<thead>
<tr>
<th>Moderate Drinking</th>
<th>Men: 3 or less/d (&lt;15/wk)</th>
<th>Women: 2 or less/d (&lt;10/wk)</th>
<th>Elderly: 1 or less/d</th>
</tr>
</thead>
</table>

#### Alcohol Intoxication

- legal limit for impaired driving is 10.6 mmol/L (50 mg/dL) reached by 2-3 drinks/h for men and 1-2 drinks/h for women
- coma can occur with >60 mmol/L (non-tolerant drinkers) and 90-120 mmol/L (tolerant drinkers)

#### Alcohol Withdrawal

- occurs within 12 to 48 h after prolonged heavy drinking and can be life-threatening
- alcohol withdrawal can be described as having 4 stages, however not all stages may be experienced
  - stage 1 (onset 12-18 h after last drink): "the shakes" tremor, sweating, agitation, anorexia, cramps, diarrhea, sleep disturbance
  - stage 2 (onset 7-38 h): alcohol withdrawal seizures, usually tonic-clonic, nonfocal and brief
  - stage 3 (onset 48 h): visual, auditory, olfactory or tactile hallucinations
  - stage 4 (onset 3-5 d): delirium tremens, confusion, delusions, hallucinations, agitation, tremors, autonomic hyperactivity (fever, tachycardia, hypertension)

- course: in young almost completely reversible; elderly often left with cognitive deficits
- mortality rate 20% if untreated

- **MCAT**
  - More drug needed to achieve intoxication
  - Cutting down unsuccessful
  - Activities given up or reduced
  - Time to procure, use substance, or recover from effects is excessive

- **A “Standard Drink”**
  - Spirit (40%): 1.5 oz. or 43 mL
  - Table Wine (12%): 5 oz. or 142 mL
  - Fortified Wine (18%): 3 oz. or 85 mL
  - Regular Beer (5%): 12 oz. or 341 mL
  - OR
  - 1 pint of beer = 1.5 SD
  - 1 bottle of wine = 5 SD
  - 1 “mickey” = 8 SD
  - “26-er” = 17 SD
  - “40 oz.” = 27 SD

- **Delirium Tremens**
  - (alcohol withdrawal delirium)
  - Autonomic hyperactivity (diaphoresis, tachycardia, increased respiration)
  - Hand tremor
  - Insomnia
  - Psychomotor agitation
  - Anxiety
  - Nausea or vomiting
  - Tonic-clonic seizures
  - Visual/tactile/auditory hallucinations
  - Persecutory delusions

- Make sure to ask about other alcohols: mouthwash, rubbing alcohol, methanol, ethylene glycol, aftershave (may be used as a cheaper alternative)
Management of Alcohol Withdrawal

- monitor using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) scoring system
  - areas of assessment include
    - nausea and vomiting
    - tactile disturbances
    - tremor
    - auditory disturbances
    - agitation
    - all categories are scored from 0-7 (except: orientation/sensorium 0-4), maximum score of 67
    - mild <10
    - moderate 10-20
    - severe >20

Table 6. CIWA-A Scale Treatment Protocol for Alcohol Withdrawal

| Basic Protocol | Diazepam 20 mg PO q1-2h prn until CIWA-A < 10 points |
| History of Withdrawal Seizures | Dexamphetamine 20 mg PO q1h for minimum of three doses regardless of subsequent CIWA scores |
| If age > 65 or patient has severe liver disease, severe asthma or respiratory failure | Lorazepam PO/SI/IM 1-4 mg q1-2h |
| If hallucinations are present | Haloperidol 2-5 mg IM/PO q1-4h – max 5 doses/d or atypical antipsychotics (olanzapine, risperidone) Diazepam 20 mg x 3 doses as seizure prophylaxis (haloperidol lowers seizure threshold) |
| Admit to Hospital if | Still in withdrawal after > 80 mg of diazepam Delirium tremens, recurrent arrhythmias, or multiple seizures Medically ill or unsafe to discharge home |

Wernicke-Korsakoff Syndrome

- alcohol-induced amnestic disorders due to thiamine deficiency
- necrotic lesions: mammillary bodies, thalamus, brainstem
- Wernicke’s encephalopathy (acute and reversible): triad of nystagmus (CN VI palsy), ataxia and confusion
- Korsakoff’s syndrome (chronic and only 20% reversible with treatment): anterograde amnesia and confabulations; cannot occur during an acute delirium or dementia and must persist beyond usual duration of intoxication/withdrawal
- management
  - Wernicke’s: thiamine 100 mg PO OD x 1-2 wk
  - Korsakoff’s: thiamine 100 mg PO bid/tid x 3-12 mo

Treatment of Alcohol Dependence

- non-pharmacological
  - psychotherapy: motivational enhancement therapy (MET, increasing motivation to change), CBT (assertiveness training, increasing social support, planning leisure activities), marital and family therapy
  - behaviour therapy: contingency management, community reinforcement approach (CRA)
  - supportive services: counseling, detoxification centres, Alcoholics Anonymous
  - inpatient programs (e.g. 28-day programs)
    - individual readiness for change must always be considered with non-pharmacological interventions (refer to Prochaska’s Stages of Change Model, Population Health and Epidemiology, PH6)

- pharmacological
  - naltrexone: opioid antagonist, shown to be successful in reducing the “high” associated with alcohol, moderately effective in reducing cravings, frequency or intensity of alcohol binges
  - disulfiram (Antabuse®): blocks oxidation of alcohol (blocks acetaldehyde dehydrogenase);
    - with alcohol consumption, acetaldehyde accumulates to cause a toxic reaction (vomiting, tachycardia, death); if patient relapses, must wait 48 h before restarting Antabuse®
  - acamprosate (Campral): NMDA glutamate receptor antagonist; useful in maintaining abstinence and decreasing cravings

Opioids

- types of opioids: heroin, morphine, oxycodone, Tylenol #3® (codeine), hydromorphone
- major risks associated with the use of contaminated needles: increased risk of hepatitis B and C, bacterial endocarditis, HIV/AIDS

Acute Intoxication

- direct effect on receptors in CNS resulting in decreased pain perception, sedation, decreased sex drive, nausea/vomiting, decreased GI motility (constipation and anorexia), and respiratory depression
Toxic Reaction
- typical syndrome includes shallow respirations, miosis, bradycardia, hypothermia, decreased level of consciousness
- management
  - ABGs
  - IV glucose
  - naloxone hydrochloride (Narcan®): 0.4 mg up to 2 mg IV for diagnosis
  - treatment: intubation and mechanical ventilation, ± naloxone drip, until patient alert without naloxone (up to 48+ h with long-acting opioids)
  - caution with longer half-life; may need to observe for toxic reaction for at least 24 h

Withdrawal
- symptoms: depression, insomnia, drug-craving, myalgias, nausea, chills, autonomic instability (lacrimation, rhinorrhea, piloerection)
- onset: 6-12 h; duration: 5-10 d
- complications: loss of tolerance (overdose on relapse), miscarriage, premature labour
- management: long-acting oral opioids (methadone, buprenorphine), α-adrenergic agonists (clonidine)

Treatment of Chronic Abuse
- psychosocial treatment (e.g. Narcotics Anonymous) usually emphasize total abstinence
- naltrexone or naloxone (opioid antagonists) may also be used to extinguish drug-seeking behaviour
- long-term treatment may include withdrawal maintenance treatment with methadone or buprenorphine

Suboxone® formulation includes naloxone in addition to buprenorphine, in an effort to prevent injection of the drug. When naloxone is injected, it will precipitate opiate withdrawl and block the opiate effect of buprenorphine; however it will not have this antagonist action when taken sublingually.

Table 7. Comparison of Methadone and Suboxone® (buprenorphine and naloxone)

<table>
<thead>
<tr>
<th></th>
<th>Suboxone®</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Combined formulation of partial opiate agonist and opiate antagonist (which is only active when injected)</td>
<td>Full opiate agonist</td>
</tr>
<tr>
<td>Ceiling effect</td>
<td>Yes. This limits the risk of overdose and abuse potential</td>
<td>No. Higher risk of overdose and abuse potential</td>
</tr>
<tr>
<td>Half life</td>
<td>36-48 h, dosing can be daily or alternate days</td>
<td>24-36 h, daily dosing</td>
</tr>
<tr>
<td>Withdrawal symptoms</td>
<td>Mild</td>
<td>Moderate/severe</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>Limited to mild/moderate opioid dependence</td>
<td>More effective for severe opioid dependence</td>
</tr>
<tr>
<td>Cost</td>
<td>Expensive</td>
<td>Inexpensive</td>
</tr>
<tr>
<td>FDA approval</td>
<td>2002</td>
<td>1947</td>
</tr>
</tbody>
</table>

Cocaine
- street names: blow, C, coke, crack, flake, freebase, rock, snow
- alkaloid extracted from leaves of the coca plant; blocks presynaptic uptake of dopamine (causing euphoria), norepinephrine and epinephrine (causing vasospasm, hypertension)
- self-administered by inhalation or intravenous route

Intoxication
- elation, euphoria, pressured speech, restlessness, sympathetic stimulation (e.g. tachycardia, mydriasis, sweating)
- prolonged use may result in paranoia and psychosis

Overdose
- medical emergency: hypertension, tachycardia, tonic-clonic seizures, dyspnea, and ventricular arrhythmias
- treatment with IV diazepam to control seizures and propranolol or labetalol to manage hypertension and arrhythmias

Withdrawal
- initial "crash" (1-48 h): increased sleep, increased appetite
- withdrawal (1-10 wk): dysphoric mood plus fatigue, irritability, vivid unpleasant dreams, insomnia or hypersomnia, psychomotor agitation or retardation
- complications: relapse, suicide (significant increase in suicide during withdrawal period)
- management: supportive management

OxyNEO vs. OxyContin
As of 2012, OxyContin was no longer available in Canada and was replaced by a new formulation of oxycodone called OxyNEO. OxyNEO is reported to be more tamper-resistant than OxyContin as the tablet is more difficult to crush. Furthermore, if OxyNEO is crushed, and added to water, it forms a thick gel-like substance that cannot be easily injected.

Common Presentations of Drug Use

<table>
<thead>
<tr>
<th>System</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Weight loss (especially cocaine, heroin)</td>
</tr>
<tr>
<td></td>
<td>Injected conjunctiva (cannabis)</td>
</tr>
<tr>
<td></td>
<td>Pinpoint pupils (opioids)</td>
</tr>
<tr>
<td></td>
<td>Track marks (injection drugs)</td>
</tr>
<tr>
<td>MSK</td>
<td>Trauma</td>
</tr>
<tr>
<td>GI</td>
<td>Viral hepatitis (injection drugs)</td>
</tr>
<tr>
<td></td>
<td>Unexplained elevations in ALT (injection drugs)</td>
</tr>
<tr>
<td>Behavioural</td>
<td>Missed appointments</td>
</tr>
<tr>
<td></td>
<td>Non-compliance</td>
</tr>
<tr>
<td></td>
<td>Drug-seeking (especially benzodiazepines, opioids)</td>
</tr>
<tr>
<td>Psychological</td>
<td>Insomnia</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Flat affect (benzodiazepines, barbiturates)</td>
</tr>
<tr>
<td></td>
<td>Paranoia (cannabis)</td>
</tr>
<tr>
<td></td>
<td>Psychosis (cocaine, cannabis, hallucinogens)</td>
</tr>
<tr>
<td>Social</td>
<td>Marital discord</td>
</tr>
<tr>
<td></td>
<td>Family violence</td>
</tr>
<tr>
<td></td>
<td>Absenteeism and poor performance</td>
</tr>
</tbody>
</table>
**Treatment of Chronic Abuse**
- psychotherapy, group therapy, NA (narcotics anonymous) and behaviour modification useful in maintaining abstinence

**Complications**
- cardiovascular: arrhythmias, MI, CVA, ruptured AAA
- neurologic: seizures
- psychiatric: psychosis, paranoia, delirium, suicidal ideation

**Amphetamines**
- intoxication characterized by euphoria, improved concentration, sympathetic and behavioural hyperactivity and at high doses can cause coma
- chronic use can produce a paranoid psychosis which can resemble schizophrenia with agitation, paranoia, delusions and hallucinations
- withdrawal symptoms include dysphoria, fatigue, and restlessness
- treatment of stimulant psychosis: antipsychotics

**Cannabis**
- cannabis (marijuana) is the most commonly used illicit drug
- psychoactive substance: delta-9-tetrahydrocannabinol (A9-THC)
- intoxication characterized by tachycardia, conjunctival vascular engorgement, dry mouth, altered sensorium, increased appetite, increased sense of well-being, euphoria/laffughter, muscle relaxation, impaired performance on psychomotor tasks including driving
- high doses can cause depersonalization, paranoia, anxiety and may trigger psychosis and schizophrenia if predisposed
- chronic use associated with tolerance and an apathetic, amotivational state
- cessation does produce a significant withdrawal phenomenon
- treatment of dependence: behavioural and psychological interventions to maintain an abstinent state

**Hallucinogens**
- types of hallucinogens: LSD, mescaline, psilocybin mushrooms, PCP, salvia
- LSD is a highly potent drug: intoxication characterized by tachycardia, HTN, mydriasis, tremor, hyperpyrexia, and a variety of perceptual and mood changes
- high doses can cause depersonalization, paranoia, and anxiety
- no specific withdrawal syndrome characterized
- treatment of agitation and psychosis: support, reassurance, diminished stimulation; benzodiazepines or high potency antipsychotics seldom required

**“Club Drugs”**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Effect</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDMA (Ecstasy, “X”, “E”)</td>
<td>Acts on serotonergic and dopaminergic pathways, properties of a hallucinogen and stimulant</td>
<td>Enhanced sensorium; feelings of well-being, empathy</td>
<td>Sweating, tachycardia fatigue, muscle spasms (especially jaw clenching), ataxia, hyperthermia, arrhythmias, DIC, rhabdomyolysis, renal failure, seizures, death</td>
</tr>
<tr>
<td>Gamma Hydroxybutyrate (GHB, “G”, “Liquid Ecstasy”)</td>
<td>Biphasic dopamine response (inhibition then release) and releases opiate-like substance</td>
<td>Euphoric effects, increased aggression, impaired judgment</td>
<td>Sweating, tachycardia, fatigue, muscle spasms (especially jaw clenching), ataxia, severe withdrawal from abrupt cessation of high doses: tremor, seizures, psychosis</td>
</tr>
<tr>
<td>Flunitrazepam (Rohypnol®, “Roofies”, “Rope”, “The Forget Pill”)</td>
<td>Potent benzodiazepine, rapid oral absorption</td>
<td>Sedation, psychomotor impairment, amnesic effects, decreased sexual inhibition</td>
<td>CNS depression with E0DH</td>
</tr>
<tr>
<td>Ketamine (Special K, “K-Kat”)</td>
<td>NMDA receptor antagonist, rapid-acting general anesthetic used in pediatrics and by veterinarians</td>
<td>“Dissociative” state, profound amnesia/analgesia; hallucinations and sympathomimetic effects</td>
<td>Psychological distress, accidents due to intensity of experience and lack of bodily control, in overdose, decreased LOC, respiratory depression, catatonia</td>
</tr>
</tbody>
</table>

**Medical Uses of Marijuana**
- Anorexia-cachexia (AIDS, cancer)
- Spasticity, muscle spasms (multiple sclerosis, spinal cord injury)
- Levodopa-induced dyskinesia (Parkinson’s Disease)
- Controlling tics and obsessive-compulsive behaviour (Tourette’s syndrome)
- Reducing intra-ocular pressure (glaucoma)

**Cannabis Use and Risk of Psychotic or Affective Mental Health Outcomes: A Systematic Review**

**Date Rape Drugs**
- GHB
- Flunitrazepam (Rohypnol®)
- Ketamine

**Formication**
Tactile hallucination that insects or snakes are crawling over or under the skin. Especially associated with crystal meth use.

**Pharm Party**
An increasing trend among teenagers where assorted prescription medications are brought to a party and ingested at random.
Table 8. The Mechanism and Effects of Common “Club Drugs” (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Effect</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methamphetamine</td>
<td>Amphetamine stimulant, induces norepinephrine, dopamine and serotonin release</td>
<td>Rush begins in min, effects last 6-8 h, increased activity, decreased appetite, general sense of well-being, tolerance occurs quickly, users often binge and crash</td>
<td>Short term use: high agitation, rage, violent behaviour, occasionally hyperthermia and convulsions Long term use: addiction, anxiety, confusion, insomnia, paranoia, auditory and tactile hallucinations (esp. formication), delusions, mood disturbance, suicidal and homicidal thoughts, stroke, may be contaminated with lead, and IV users may present with acute lead poisoning</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>Not understood, used by veterinarians to immobilize large animals</td>
<td>Amnestic, euphoric, hallucinatory state</td>
<td>Horizontal/vertical nystagmus, myoclonus, ataxia, autonomic instability (treat with diazepam IV), prolonged agitated psychosis (treat with haloperidol); high risk for suicide; violence towards others High dose can cause coma</td>
</tr>
</tbody>
</table>

**Somatoform Disorders**

**General Characteristics**
- physical signs and symptoms lacking a known medical basis in the presence of psychological factors that are judged to be important in the initiation, exacerbation, or maintenance of the disturbance
- cause significant distress or impairment in functioning
- symptoms are produced unconsciously and are not the result of malingering or factitious disorder
- primary gain: somatic symptom represents a symbolic resolution of an unconscious psychological conflict; serves to reduce anxiety and conflict; no external incentive
- secondary gain: the sick role; external benefits obtained or unpleasant duties avoided (e.g. work)

**Management of Somatoform Disorders**
- brief frequent visits
- limit number of physicians involved in care
- focus on psychosocial not physical symptoms
- minimize medical investigations; coordinate necessary investigations
- psychotherapy: CBT, biofeedback, conflict resolution
- minimize psychotropic drugs: anxiolytics in short term only, antidepressants for depressive symptoms

**Body Dysmorphic Disorder**
- preoccupation with imagined defect in appearance or excess concern around a slight anomaly
- usually related to the face
- M=F; prevalence 1-2.2% in the community; 6-15% in dermatology/cosmetic surgery clinics
- may lead to avoidance of work or social situations

**Conversion Disorder**
- one or more symptoms or deficits affecting voluntary motor or sensory function that mimic a neurological or GMC (e.g. impaired co-ordination, local paralysis, double vision, seizures or convulsions)
- psychological factors thought to be etiologically related to the symptoms as the initiation of symptoms is preceded by conflicts or other stressors
- 11-300/100,000 in general population; focus of treatment in 1-3% of outpatient referrals to mental health clinics
- more common in rural populations and in individuals with little medical knowledge
- spontaneous remission in 95% of acute cases, 50% of chronic cases (>6 mo)
**Hypochondriasis**
- preoccupation with fear of having, or the idea that one has, a serious disease based on a misinterpretation of one or more bodily signs or symptoms
- evidence does not support diagnosis of a physical disorder
- fear of having a disease despite medical reassurance
- belief is not of delusional intensity (as in delusional disorder, somatic type) as person acknowledges unrealistic interpretation
- duration is ≥6 mo; onset in 3rd-4th decade of life
- community prevalence 1.1-4.5%; prevalence in general medical practice 4-9%; higher in psychiatric settings

**Pain Disorder**
- pain is primary symptom and is of sufficient severity to warrant medical attention
- usually no organic pathology but when it exists, reaction is excessive
- lifetime prevalence 12%
- psychiatric disorders (mood, anxiety, substance) may precede, co-exist or result from pain disorder

**Somatization Disorder**
- recurring, multiple, clinically significant physical complaints which result in patient seeking treatment or having impaired functioning
- ≥8 physical symptoms that have no organic pathology including each of:
  - four pain symptoms related to at least four different sites or functions
  - two gastrointestinal symptoms, not including pain
  - one sexual symptom, not including pain
  - one pseudo-neurological symptom, not including pain (e.g. numbness, paresthesia)
- onset before age 30; extends over a period of years
- lifetime prevalence 0.2-2% among women and 0.2% among men
- cultural factors may influence sex ratio
- complications: anxiety, depression, unnecessary medications or surgery
- often a misdiagnosis for an insidious illness so rule out all organic illnesses (e.g. multiple sclerosis)

**Dissociative Disorders**

**Definition**
- dissociation so severe that the usually integrated functions of consciousness and perception of self break down
- sudden or gradual onset, transient or chronic course
- symptoms cause distress or impaired functioning
- differential diagnosis: PTSD, acute stress disorder, somatization disorder, substance abuse, GMC (e.g. complex/partial seizures)

Table 9. Dissociative Disorders

<table>
<thead>
<tr>
<th>Amnesia</th>
<th>Fugue</th>
<th>Identity Disorder</th>
<th>Depersonalization Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Inability to recall important personal information, usually of a traumatic or stressful nature; may be localized, selective or generalized</td>
<td>Sudden, unexpected travel away from home or workplace with inability to recall some or all of one’s past; may assume new identity</td>
<td>Two or more distinct personalities that take control of an individual’s behaviour; amnesia regarding personal history (aka Multiple Personality Disorder)</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>6% prevalence</td>
<td>Increased in survivors of trauma (war, abuse)</td>
<td>0.2% prevalence</td>
</tr>
<tr>
<td>Treatment</td>
<td>Psychotherapy, hypnosis</td>
<td>Usually spontaneous recovery</td>
<td>Three stages: symptom stabilization, attention to trauma, reintegration</td>
</tr>
<tr>
<td>Pharmacotherapy: clonazepam, fluoxetine, clomipramine</td>
<td>Psychotherapy, hypnosis</td>
<td>Ensure stability and safety</td>
<td>Psychotherapy, hypnosis</td>
</tr>
</tbody>
</table>
**Sleep Disorders**

- see [Neurology, N42](#)

**Criteria for Diagnosis**

- causes significant distress or impairment in functioning
- not due to medications, drugs, or a GMC

---

**Nocturnal Myoclonus**

- middle-aged and elderly
- myoclonic jerks every 20-40 s
- bed partner complaints
- treatment: benzodiazepines (clonazepam, nitrazepam)

---

**Narcolepsy**

- see [Neurology, N42](#)

---

**Primary Insomnia**

- see [Family Medicine, FM48](#)

---

**Sleep Apnea**

- see [Respirology, R31](#)

---

**Sexuality and Gender**

---

**Gender Dysphoria**

- gender identity is set at approximately 3 yr of age

**typical presentation**

- strong and persistent cross-gender identification
- repeated stated desire or insistence that one is of the opposite sex
- preference for cross-dressing, cross-gender roles in make-believe play
- intense desire to participate in the stereotypical games and pastimes of the opposite sex
- strong preference for playmates of the opposite sex
- significant distress or impairment in functioning and persistent discomfort with his or her sex or gender role

**treatment**

- psychotherapy
- hormonal therapy
- sexual reassignment surgery

---

**Paraphilias**

- **definition**: recurrent, intense sexual arousal, fantasies, sexual urges or behaviour involving non-human objects, suffering or humiliation of oneself or one's partner, children or other non-consenting person causing significant distress or impairment in social, occupational or other areas of functioning

- **subtypes**: exhibitionism, fetishism, frotteurism, voyerism, pedophilia, sexual masochism, sexual sadism, transvestite fetishism, paraphilia NOS

- rarely self-referred; come to medical attention through interpersonal or legal conflict

- person usually has more than one paraphilia; 5% of paraphilias attributed to women

**typical presentation**

- begins in childhood or early adolescence; increasing in complexity and stability with age
- chronic, decreases with advancing age but may increase with stress

**treatment**

- anti-androgen drugs
- behaviour modification
- psychotherapy

---

**SEXUAL DYSFUNCTION**

- see [Gynecology, GY31](#) and [Urology, U30](#)
Eating Disorders

Epidemiology
- anorexia nervosa (AN): 1% of adolescent and young adult females; onset 13-20 yr old
- bulimia nervosa (BN): 2-4% of adolescent and young adult females; onset 16-18 yr old
- F:M=10:1; mortality 5-10%

Etiology
- multifactorial: psychological, sociological and biological associations
- individual: perfectionism, lack of control in other life areas, history of sexual abuse
- personality: obsessive-compulsive, histrionic, borderline
- familial: maintenance of equilibrium in dysfunctional family
- cultural factors: prevalent in industrialized societies, idealization of thinness in the media
- genetic factors
  - AN: 6% prevalence in siblings, with one study of twin pairs finding concordance in 9 of 12 monozygotic pairs versus concordance in 1 of 14 dizygotic pairs
  - BN: higher familial incidence of affective disorders than the general population

Risk Factors
- physical factors: obesity, chronic medical illness (e.g. diabetes mellitus)
- psychological factors: individuals who by career choice are expected to be thin, family history (mood disorders, eating disorders, substance abuse), history of sexual abuse, homosexual males, competitive athletes, concurrent associated mental illness [depression, OCD, anxiety disorder (especially panic and agoraphobia), substance abuse (specifically for BN)]

Anorexia Nervosa

DSM-IV-TR Diagnostic Criteria for Anorexia Nervosa

A. refusal to maintain body weight at or above a minimally normal weight for age and height (e.g. weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected)

B. intense fear of gaining weight or becoming fat, even though underweight

C. disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight

D. in postmenarcheal females, amenorrhea, i.e. the absence of at least three consecutive menstrual cycles (note: this criterion has has been removed in DSM-5)

Specific Type
- restricting: during the current episode of AN, the person has not regularly engaged in binge-eating or purging behaviour
- binge-eating/purging: during the current episode of AN, the person has regularly engaged in binge-eating or purging behavior

Management
- outpatient programs and inpatient programs are available
- inpatient hospitalization for treatment of eating disorders is rarely on an acute basis (unless there is a concurrent psychiatric reason for emergent admission e.g. suicide risk)
- admit to a medical ward for hospitalization: <65% of standard body weight (<85% of standard body weight for adolescents), hypovolemia requiring intravenous fluid, heart rate <40 bpm, abnormal serum chemistry or if actively suicidal
- agree on target body weight on admission and reassure this weight will not be surpassed
- psychotherapy (individual/group/family): addressing food and body perception, coping mechanisms, health effects
- monitor for complications of AN (see Table 10)
- monitor for refeeding syndrome:
  - a potentially life-threatening metabolic response to refeeding in severely malnourished patients resulting in severe shifts in fluid and electrolyte levels
  - complications include hypophosphatemia, congestive heart failure, cardiac arrhythmias, delirium and death
  - prevention: slow refeeding, gradual increase in nutrition, supplemental phosphorus, close monitoring of electrolytes and cardiac status

Athletic Triad
- Disordered eating
- Amenorrhea
- Osteoporosis

Screening Question for Purging Behaviours
“To lose weight, some people will use laxatives or vomit, have you ever tried that or used other ways to lose weight?”

Some diabetics may use insulin to lose weight, be aware of this in Type 1 DM.
Prognosis
- early intervention much more effective
- with treatment, 70% resume a weight of at least 85% of expected levels and about 50% resume normal menstrual function
- eating peculiarities and associated psychiatric symptoms are common and persistent
- long-term mortality: 10% to 20% of patients hospitalized will die in next 10 to 30 yr (secondary to severe and chronic starvation, metabolic or cardiac catastrophes, with a significant proportion committing suicide)

Bulimia Nervosa

DSM-IV-TR Diagnostic Criteria for Bulimia Nervosa

A. recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following
   1. eating, in a discrete period of time, an amount of food that is larger than most people would eat during a similar period of time and under similar circumstances
   2. a sense of lack of control over eating during the episode (e.g. a feeling that one cannot stop eating or control what or how much one is eating)
B. recurrent inappropriate compensatory behaviour in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, enemas, or other medications, fasting, or excessive exercise
C. the binge eating and inappropriate compensatory behaviours both occur, on average, at least twice a week for 3 mo
D. self-evaluation is unduly influenced by body shape and weight
E. the disturbance does not occur exclusively during episodes of AN

Specific Type
- purging: during the current episode of BN, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas
- non-purging: during the current episode of BM, the person has used other inappropriate compensatory behaviours, such as fasting or excessive exercise, but has not regularly engaged in purging behaviours

Associated Features
- fatigue and muscle weakness due to repetitive vomiting and fluid/electrolyte imbalance
- tooth decay
- swollen appearance around angle of jaw and puffiness of eye sockets due to fluid retention
- reddened knuckles, Russell’s sign (knuckle callus from self-induced vomiting)
- trouble concentrating
- weight fluctuation over time

Management
- admission for significant electrolyte abnormalities
- biological: treatment of starvation effects, SSRIs
- psychological: develop trusting relationship with therapist to explore personal etiology and triggers, CBT, family therapy, recognition of health risks
- social: challenge destructive societal views of women, use of hospital environment to provide external patterning for normative eating behaviour

Prognosis
- few recover without recurrence
- good prognostic factors: onset before age 15, achieving a healthy weight within 2 yr of treatment
- poor prognostic factors: later age of onset, previous hospitalizations, individual and familial disturbance

Table 10. Physiologic Complications of Eating Disorders

<table>
<thead>
<tr>
<th>System</th>
<th>Starvation/Restriction</th>
<th>Binge-Purge</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Low BP, low HR, significant orthostatic changes, syncopal episodes, low temperature, vitamin deficiencies</td>
<td>Russell’s sign (knuckle callos), Parotid gland enlargement, Perioral skin irritation, Periorbital and palatal petechiae, Loss of dental enamel and caries, Aspiration pneumonia, Metabolic alkalosis secondary to hypokalemia and loss of acid</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Primary or secondary amenorrhea, decreased T_3/T_4</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Grand mal seizure (decreased Ca^{2+}, Mg^{2+}, PO_{4}^{3-})</td>
<td></td>
</tr>
</tbody>
</table>
Table 10. Physiologic Complications of Eating Disorders (continued)

<table>
<thead>
<tr>
<th>System</th>
<th>Starvation/Restriction</th>
<th>Binge-Purge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td>Dry skin, lanugo hair, hair loss or thinning, brittle nails, yellow skin from high carotene</td>
<td>Acute gastric dilation/rupture, pancreatitis, GERD, hematemesis secondary to Mallory-Weiss tear</td>
</tr>
<tr>
<td>GI</td>
<td>Constipation, GERD, delayed gastric emptying</td>
<td>Acute gastric dilation/rupture, pancreatitis, GERD, hematemesis secondary to Mallory-Weiss tear</td>
</tr>
<tr>
<td>CVS</td>
<td>Arhythmias, CHF</td>
<td>Arhythmias, cardiomyopathy (from use of ipecac), sudden cardiac death (decreased K+), sudden cardiac death (decreased K+), sudden cardiac death (decreased K+), sudden cardiac death (decreased K+)</td>
</tr>
<tr>
<td>MSK</td>
<td>Osteoporosis secondary to hypogonadism</td>
<td>Muscle wasting</td>
</tr>
<tr>
<td>Renal</td>
<td>Pre-renal failure (hypovolemia), renal calculi</td>
<td>Renal failure (electrolyte disturbances)</td>
</tr>
<tr>
<td>Extremities</td>
<td>Pedal edema (decreased albumin)</td>
<td>Pedal edema (decreased albumin)</td>
</tr>
<tr>
<td>Lab Values</td>
<td>Starvation: decreased RBCs, decreased WBCs, decreased LH, decreased FSH, decreased estrogen, decreased testosterone, increased growth hormone, increased cholesterol, Dehydration: increased BUN</td>
<td>Vomiting: decreased Na+, decreased K+, decreased Cl–, decreased H+, increased amylase, hypokalemia with metabolic alkalosis, Laxatives: decreased Na+, decreased K+, decreased Cl–, increased H+, metabolic acidosis</td>
</tr>
</tbody>
</table>

Personality Disorders

General Diagnostic Criteria
- an enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the individual's culture; manifested in two or more of: cognition, affect, interpersonal functioning, impulse control
- inflexible and pervasive across a range of situations
- causes distress or impaired functioning not necessarily for the person with the personality disorder (PD), but for those around him/her
- pattern is stable and well established by adolescence or early adulthood
- associated with many complications, such as depression, suicide, violence, brief psychotic episodes, multiple drug use and treatment resistance
- each PD is present in 1% of the population and are lifelong and chronic
- the mainstay of treatment is psychotherapy with the addition of pharmacotherapy to treat associated axis I disorders (i.e. depression, anxiety, substance abuse)
- main treatment for borderline personality disorder is dialectical behavioural therapy (consists of validating rather than blaming the patient, and replacing maladaptive behaviour with adaptive behaviour)

Table 11. Classification and Diagnosis of Personality Disorders

Note: For each personality disorder, the most recognizable feature is indicated in italics.

<table>
<thead>
<tr>
<th>Diagnostic Cluster</th>
<th>Diagnosis</th>
<th>Paranoid Personality Disorder (0.5-3%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster A “Mad”</td>
<td></td>
<td>Pervasive distrust and suspiciousness of others, interpret motives as malevolent</td>
</tr>
<tr>
<td>Patients seem odd, eccentric, withdrawn</td>
<td>Blame problems on others and seem angry and hostile</td>
<td></td>
</tr>
<tr>
<td>Familial association with psychotic disorders Common defense mechanisms: intellectualization, projection, magical thinking</td>
<td>Diagnosis requires 4 of:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Suspicious that others are exploiting or deceiving them</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Pre-occupied with trustworthiness of acquaintances</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Reluctant to confide in others</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Interpret benign remarks as threatening, demeaning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Holds grudges</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Perceives attacks on character and is quick to counterattack</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Questions fidelity of partner without justification</td>
</tr>
</tbody>
</table>

| Schizoid Personality Disorder* | Neither desires or enjoys close relationships including being a part of a family; prefers to be alone. |
|                               | Lifelong pattern of social withdrawal |
|                               | Seen as eccentric and reclusive with restricted affect |
|                               | Diagnosis requires 4 of: |
|                               | 1. Does not enjoy or desire close relationships |
|                               | 2. Chooses solitary activities |
|                               | 3. Little to no interest in sexual activity with others |
|                               | 4. Takes pleasure in few (if any) activities |
|                               | 5. Few or no close friends |
|                               | 6. Indifference to praise or criticism |
|                               | 7. Emotionally cold, detached, or has flattened affect |

<table>
<thead>
<tr>
<th>Schizotypal Personality Disorder (3-5.6%)</th>
<th>Pattern of eccentric behaviours, peculiar thought patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis requires 5 of:</td>
<td></td>
</tr>
<tr>
<td>1. Ideas of reference</td>
<td></td>
</tr>
<tr>
<td>2. Odd beliefs, magical thinking (inconsistent with cultural norms e.g. belief in telepathy, superstitions)</td>
<td></td>
</tr>
<tr>
<td>3. Unusual perceptual experiences (e.g. bodily illusions)</td>
<td></td>
</tr>
<tr>
<td>4. Suspiciousness</td>
<td></td>
</tr>
<tr>
<td>5. Inappropriate or restricted affect</td>
<td></td>
</tr>
<tr>
<td>6. Odd, eccentric appearance or behaviour (e.g. involved in cults, strange religious practices)</td>
<td></td>
</tr>
<tr>
<td>7. Few close friends</td>
<td></td>
</tr>
<tr>
<td>8. Odd thinking, odd speech (e.g. vague, stereotyped)</td>
<td></td>
</tr>
<tr>
<td>9. Excessive social anxiety</td>
<td></td>
</tr>
</tbody>
</table>

Borderline Personality Disorder
- DESPAIRER
- Disturbance of identity
- Emotionally labile
- Suicidal behavior
- Paranoia or dissociation
- Abandonment (fear of)
- Impulsive
- Relationships unstable
- Emptiness (feelings of)
- Rage (inappropriate)

Antisocial Personality Disorder
- CORRUPT
- Cannot conform to law
- Obligations ignored
- Reckless disregard for safety
- Remorselessness
- Underhanded (deceitful)
- Planning insufficient (impulsive)
- Temper (irritable and aggressive)
### Table 11. Classification and Diagnosis of Personality Disorders (continued)

<table>
<thead>
<tr>
<th>Diagnostic Cluster</th>
<th>Borderline Personality Disorder (2-4%)</th>
<th>Narcissistic Personality Disorder (2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unstable moods and behaviour; feel alone in the world, problems with self image</td>
<td>Sense of superiority; needs constant admiration, lacks empathy, but with fragile sense of self</td>
</tr>
<tr>
<td></td>
<td>History of repeated suicide attempts, self-harm behaviours <strong>10% suicide rate</strong></td>
<td>Consider themselves &quot;special&quot; and will exploit others for personal gain</td>
</tr>
<tr>
<td></td>
<td>Diagnosis requires 5 of:</td>
<td>Diagnosis requires 5 of:</td>
</tr>
<tr>
<td></td>
<td>1. Frantic efforts to avoid real or imagined abandonment</td>
<td>1. Exaggerated sense of self-importance (grandiosity)</td>
</tr>
<tr>
<td></td>
<td>2. Unstable and intense relationships</td>
<td>2. Preoccupied with fantasies of unlimited success, power, beauty, love</td>
</tr>
<tr>
<td></td>
<td>3. Unstable sense of self</td>
<td>3. Believes he/she is &quot;special&quot; and should associate with other &quot;special&quot; people</td>
</tr>
<tr>
<td></td>
<td>4. Impulsivity in two potentially harmful ways (sexual, drugs, spending)</td>
<td>4. Requires excessive admiration</td>
</tr>
<tr>
<td></td>
<td>5. Recurrent suicidal behaviour/self-harm</td>
<td>5. Sense of entitlement</td>
</tr>
<tr>
<td></td>
<td>6. Unstable mood/affect</td>
<td>6. Takes advantage of others</td>
</tr>
<tr>
<td></td>
<td>7. General feelings of emptiness</td>
<td>7. Lacks empathy</td>
</tr>
<tr>
<td></td>
<td>8. Difficulty controlling anger</td>
<td>8. Envious of others or believes that others are envious of him/her</td>
</tr>
<tr>
<td></td>
<td>9. Transient dissociative symptoms or paranoid ideation associated with stress</td>
<td>9. Arrogant attitudes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Cluster</th>
<th>Obsessive-Compulsive Personality Disorder (3-10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoccupation with orderliness, perfectionism, and mental and interpersonal control</td>
</tr>
<tr>
<td></td>
<td>Is inflexible, closed-off, and inefficient</td>
</tr>
<tr>
<td></td>
<td>Diagnosis requires 4 of:</td>
</tr>
<tr>
<td></td>
<td>1. Preoccupation with details, rules, lists, order, organization, or schedules to the extent that the point of an activity is lost</td>
</tr>
<tr>
<td></td>
<td>2. Perfectionism interferes with task completion</td>
</tr>
<tr>
<td></td>
<td>3. Excessively devoted to work to the exclusion of leisure activities and friendships</td>
</tr>
<tr>
<td></td>
<td>4. Inflexible about morality/ethics/values</td>
</tr>
<tr>
<td></td>
<td>5. Unable to discard worthless objects of no sentimental value</td>
</tr>
<tr>
<td></td>
<td>6. Rigid and stubborn</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Cluster</th>
<th>Avoidant Personality Disorder (0.5-1.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Timid and socially awkward with a pervasive sense of inadequacy and fear of criticism</td>
</tr>
<tr>
<td></td>
<td>Fear of embarrassing or humiliating themselves in social situations so remain withdrawn and socially inhibited</td>
</tr>
<tr>
<td></td>
<td>Diagnosis requires 4 of:</td>
</tr>
<tr>
<td></td>
<td>1. Avoids occupational activities that involve significant interpersonal contact for fear of criticism or rejection</td>
</tr>
<tr>
<td></td>
<td>2. Unwilling to get involved with people unless certain of being liked</td>
</tr>
<tr>
<td></td>
<td>3. Restrained in intimate relationships for fear of being shamed or ridiculed</td>
</tr>
<tr>
<td></td>
<td>4. Preoccupied with being rejected or criticized in social situations</td>
</tr>
<tr>
<td></td>
<td>5. Inhibited in new interpersonal situations due to fear of inadequacy</td>
</tr>
<tr>
<td></td>
<td>6. Views him or herself as inferior, socially inept or personally unappealing</td>
</tr>
<tr>
<td></td>
<td>7. Reluctant to engage in new activities for fear of embarrassment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Cluster</th>
<th>Histrionic Personality Disorder (1.3-3%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Attention-seeking behaviour and excessively emotional. Are dramatic, flamboyant and extroverted. Cannot form meaningful relationships. Often sexually inappropriate</td>
</tr>
<tr>
<td></td>
<td>Diagnosis requires 5 of:</td>
</tr>
<tr>
<td></td>
<td>1. Not comfortable unless centre of attention</td>
</tr>
<tr>
<td></td>
<td>2. Inappropriately sexually seductive</td>
</tr>
<tr>
<td></td>
<td>3. Uses physical appearance to attract attention</td>
</tr>
<tr>
<td></td>
<td>4. Speech is impressionistic, lacks detail</td>
</tr>
<tr>
<td></td>
<td>5. Theatrical and exaggerated expression of emotion</td>
</tr>
<tr>
<td></td>
<td>6. Easily influenced by others</td>
</tr>
<tr>
<td></td>
<td>7. Perceives relationships as more intimate than they actually are</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Cluster</th>
<th>Obsessive-Compulsive Personality Disorder (3-10%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoccupation with orderliness, perfectionism, and mental and interpersonal control</td>
</tr>
<tr>
<td></td>
<td>Is inflexible, closed-off, and inefficient</td>
</tr>
<tr>
<td></td>
<td>Diagnosis requires 4 of:</td>
</tr>
<tr>
<td></td>
<td>1. Preoccupation with details, rules, lists, order, organization, or schedules to the extent that the point of an activity is lost</td>
</tr>
<tr>
<td></td>
<td>2. Perfectionism interferes with task completion</td>
</tr>
<tr>
<td></td>
<td>3. Excessively devoted to work to the exclusion of leisure activities and friendships</td>
</tr>
<tr>
<td></td>
<td>4. Inflexible about morality/ethics/values</td>
</tr>
<tr>
<td></td>
<td>5. Unable to discard worthless objects of no sentimental value</td>
</tr>
<tr>
<td></td>
<td>6. Rigid and stubborn</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Cluster</th>
<th>Antisocial Personality Disorder (M: 3%, F: 1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lack of remorse for actions, manipulative and deceitful, often violate the law. May appear charming on first impression</td>
</tr>
<tr>
<td></td>
<td>Pattern of disregard for others and violation of rights of others must be present before the age of 15, however, for the diagnosis of ASPD patients must be at least 18</td>
</tr>
<tr>
<td></td>
<td>Diagnosis requires 3 of the following:</td>
</tr>
<tr>
<td></td>
<td>1. Failure to conform to social norms by committing unlawful acts</td>
</tr>
<tr>
<td></td>
<td>2. Deceitfulness, lying, manipulating others for personal gain</td>
</tr>
<tr>
<td></td>
<td>3. Impulsive, fails to plan ahead</td>
</tr>
<tr>
<td></td>
<td>4. Irresponsible, cannot sustain work</td>
</tr>
<tr>
<td></td>
<td>5. Lack of remorse for actions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Cluster</th>
<th>Dependent Personality Disorder (1.6-6.7%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pervasive and excessive need to be taken care of, excessive fear of separation, clinging and submissive behaviours</td>
</tr>
<tr>
<td></td>
<td>Difficulty making everyday decisions</td>
</tr>
<tr>
<td></td>
<td>Diagnosis requires 5 of:</td>
</tr>
<tr>
<td></td>
<td>1. Difficulty making everyday decisions without advice and reassurance from others</td>
</tr>
<tr>
<td></td>
<td>2. Needs others to assume responsibility for most major areas of his/her life</td>
</tr>
<tr>
<td></td>
<td>3. Difficulty expressing disagreement</td>
</tr>
<tr>
<td></td>
<td>4. Difficulty initiating projects due to lack of self-confidence</td>
</tr>
<tr>
<td></td>
<td>5. Goes to excessive lengths to obtain support</td>
</tr>
<tr>
<td></td>
<td>6. Uncomfortable or helpless when alone because of fear of being unable to take care of him/herself</td>
</tr>
<tr>
<td></td>
<td>7. Urgently seeks another relationship as a source of care and support when a close relationship ends</td>
</tr>
<tr>
<td></td>
<td>8. Unrealistically preoccupied with fears of being left to take care of him/herself</td>
</tr>
</tbody>
</table>

*DSM-V has proposed changes to these personality disorders*
Table 12. Key Differences between Schizoid, Schizotypal and Schizophrenia

<table>
<thead>
<tr>
<th>Thought form</th>
<th>Schizoid</th>
<th>Schizotypal</th>
<th>Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thought content</td>
<td>Organized</td>
<td>Organized, but vague and circumstantial</td>
<td>Disorganized, tangential, loosening of associations</td>
</tr>
<tr>
<td>Relationships</td>
<td>Solitary, NO desire for social relationships</td>
<td>Lacks close relationships, INTERESTED in relationships but socially inept</td>
<td>Socially marginalized, but not by choice</td>
</tr>
</tbody>
</table>

The Child Psychiatric Interview

- **ID**
  - name, age, school grade, living situation, family situation (all family members, age and occupation of parents), demographics
- **Chief Complaint**
  - onset, time course, stressors, impact on child's and family's functioning, supports
  - child's functioning and behaviour at home, at school, and with peers
  - mental status (see MSE, PS3)
- **History of Present Illness**
  - symptoms and features of most likely diagnostic area [e.g. disruptive behaviour disorders (ADHD, CD, ODD), developmental disorders, learning disorders, abuse, mood disorders, and anxiety disorders]
  - in adolescents, consider psychotic disorders, eating disorders, and substance abuse disorders
  - screen for comorbid conditions
  - what was the child like before and after the symptoms? what has changed? what is happening now?
- **Additional History**
  - past history: pregnancy, neonatal, developmental, temperamental, medical, surgical
  - psych history: past assessments (e.g. psychiatric, psychological, educational), treatments
  - family history: similar symptoms, medical, developmental, and psychosocial issues
- **Risk Assessment**
  - physical/sexual abuse, suicidality, aggression/homicidality, firesetting, risky behaviour
  - past risk issues (past suicide attempts, past aggression), previous contact with child protection services
  - brief developmental history: pregnancy, birth, milestones, general behaviour, parents' method of discipline, school functioning, peer relationships

Developmental Concepts

- **temperament**: innate psycho-physiological and behavioural characteristics of a child (e.g. emotionality, activity, and sociability); spectrum from "difficult" to "slow-to-warm-up" to "easy temperament", plotted on nine parameters:
  - activity level, adaptation, attention span and persistence, distractibility, intensity of reaction, quality of mood, response to a new stimulus, rhythmicity, threshold of responsiveness
- **parental fit**: the congruence between parenting style (authoritative, authoritarian, permissive) and child's temperament
- **attachment**: special relationship between child and primary caretaker(s); develops during first year, best predictor of a child's attachment style is their parent's attachment style (see Table 13)
- **stranger anxiety** (8 mo): infants cry at approach of stranger
- **separation anxiety** (10-18 mo): separation from attachment figure results in distress

Table 13. Attachment Models

<table>
<thead>
<tr>
<th>Parent/Caregiver</th>
<th>Attachment Type</th>
<th>Features in Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loving, consistently available, sensitive, and receptive</td>
<td>Secure</td>
<td>Able to use caregiver to calm self</td>
</tr>
<tr>
<td>Rejecting, unavailable psychologically, insensitive responses</td>
<td>Insecure (avoidant)</td>
<td>Not reliant on caregiver for soothing</td>
</tr>
<tr>
<td>Inconsistent, insensitive responses, role reversal</td>
<td>Insecure (ambivalent/resistant)</td>
<td></td>
</tr>
<tr>
<td>Frightening, dissociated, sexualized, or atypical</td>
<td>Disorganized</td>
<td></td>
</tr>
</tbody>
</table>
Mood Disorders

MAJOR DEPRESSIVE DISORDER (MDD)

Epidemiology
- pre-pubertal 1-2% (no gender differences); post-pubertal 4-18% (F:M = 2:1)

Clinical Presentation
- see Adult Mood Disorders, PS9
- physical factors: insomnia (children), hypersomnia (adolescents), somatic complaints, substance abuse
- psychological factors: irritability, boredom, anhedonia, low self-esteem, deterioration in academic performance, social withdrawal, lack of motivation
- comorbid diagnoses of anxiety, ADHD, conduct disorder, and eating disorders

Treatment
- majority never seek treatment
- individual (CBT, IPT)/family therapy and education, modified school program
- SSRIs (strongest evidence for fluoxetine)
- ECT: only in adolescents
- light therapy, self-help books

Prognosis
- prolonged episodes, up to 1-2 yr
- adolescent onset predicts chronic mood disorder; up to 2/3 will have another depressive episode within 5 yr
- complications
  - negative impact on family and peer relationships
  - school failure
  - significantly increased risk of suicide attempt (10%) or completion
  - substance abuse

BIPOLAR DISORDER

Clinical Presentation
- see Adult Bipolar Disorder/Mania, PS12
- mixed presentation and and psychotic symptoms (hallucinations and delusions) more common in adolescent population than adult population
- unipolar depression may be an early sign of adult bipolar disorder
  - ~30% of psychotic depressed adolescents receive a bipolar diagnosis within 2 yr of presentation
  - associated with rapid onset of depression, psychomotor retardation, mood-congruent psychosis, affective illness in family, pharmacologically induced mania

Treatment
- 1st line: mood stabilizers and/or antipsychotics
- 2nd line: antidepressants, benzodiazepines (careful of disinhibiting effect)

Anxiety Disorders

- prevalence 2-15%; F:M = 2:1

Diagnosis
- school problems, recurrent physical symptoms (abdominal pain, headaches) especially in mornings, social and relationship problems, social withdrawal and isolation, family conflict, irritability and mood symptoms, alcohol and drug use in adolescent

Treatment
- family psychotherapy, predictive and supportive environment
- CBT: child and parental education, relaxation techniques (e.g. deep breathing), exposure/desensitization, recognizing and correcting anxious thoughts
- pharmacotherapy: SSRIs (e.g. fluoxetine), benzodiazepines (e.g. clonazepam – use with caution, may have disinhibiting effect)
  - fluvoxamine and sertraline also have good evidence, particularly for OCD

Fluoxetine, Cognitive-Behavioral Therapy and Their Combination for Adolescents with Depression: Treatment for Adolescents with Depression Study (TADS) Randomized Controlled Trial

JAMA 2004;292:807-820

Study: Randomized controlled trial at 13 US academic and community clinics between spring 2000-summer 2003.

Patients: 439 patients ages 12-17 with a primary DSM IV diagnosis of major depressive disorder.

Outcomes: Children’s Depression Rating Scale-Revised (CDRS-R) total score.

Interventions: 12 wk of (1) fluoxetine (10-40 mg/d), (2) CBT, (3) CBT + fluoxetine (10-40 mg/d), or (4) placebo.

Results: Fluoxetine with CBT had a statistically significant CDRS-R score as compared to placebo (P<0.001) with a 71% response rate. This combo was greater than fluoxetine alone (P<0.02), and CBT alone (P<0.01). Fluoxetine alone was greater than CBT alone (P<0.01).
SEPARATION ANXIETY DISORDER

Epidemiology
- prevalence: 4% of children/adolescents
- on average 7.5 yr old at onset, 10 yr old at presentation
- common for mother to have an anxiety or depressive disorder

Differential Diagnosis
- simple or social phobia, depression, learning disorder, truancy, conduct disorder, school-related problems (e.g. bullying)

Clinical Presentation
- excessive and developmentally inappropriate anxiety on separation from primary caregiver with physical or emotional distress for at least 4 wk
- school refusal (75%)
- persistent worry, refusal to sleep, clinging, nightmares, somatic symptoms
- comorbid major depression common (2/3)
- worry about something happening to parent or themselves if separated

Prognosis
- if inadequately treated early on, may present later in a more severe form
- may develop into panic disorder with/without agoraphobia

SOCIAL PHOBIA (SOCIAL ANXIETY DISORDER)
- must distinguish between shy child and child with social anxiety
  - diagnosis only if anxiety interferes significantly with daily routine, social life, academic functioning, or if markedly distressed
  - features: temper tantrums, freezing, clinging behaviour, mutism, excessively timid, stays on periphery, refuses to be involved in group play
  - must be capable of developing social relationships
  - must occur in settings with peers, not just adults
  - selective mutism:
    - does not speak in front of others; no problems speaking at home
    - must rule out language or communication problems
    - severe form of social anxiety

POST-TRAUMATIC STRESS DISORDER
- diagnostic criteria same as adults (see PTSD, PS17)
  - in children, reliving of the trauma may occur through repetitive play which simulates the event, nightmares of the trauma which may progress to generalized nightmares (e.g. monsters), psychosomatic symptoms, omen formation (belief that there were predictors of the trauma which can be avoided in the future to escape future trauma)
  - common examples include: sexual/physical abuse, witnessing family violence, natural disasters
  - can also be associated with onset of sexual activity

OBSESSIVE-COMPULSIVE DISORDER
- diagnostic criteria same as adults, except it is not necessary for child to recognize thoughts or actions as excessive or unreasonable (see OCD, PS16)
  - 0.3–1% of children/adolescents; tends to begin earlier in boys than girls
    - tend to engage in rituals at home rather than in front of others
    - associated with Tourette’s disorder, tics, and ADHD
    - small subset associated with Group A Strep infections; has prepubertal onset and neurologic symptoms

PANIC DISORDER
- diagnostic criteria same as adults (see Panic Disorder, PS14)
- genetic/parental modeling/identification hypothesized as cause
- often parent with panic or depressive disorder

GENERALIZED ANXIETY DISORDER
- diagnostic criteria same as adults (see GAD, PS15)
  - Note: Only 1 item is required in children for Criteria C
  - often redo tasks, show dissatisfaction with their work and tend to be perfectionistic
  - often require reassurance and support to take on new tasks

SPECIFIC PHOBIA
- common phobias in childhood include a fear of heights, small animals, doctors, dentists, darkness, loud noises, thunder and lightning

Newer Generation Antidepressants for Depressive Disorders in Children and Adolescents
Cochrane DB Syst Rev 2012:11:CD004851
Study: Meta-analysis of 19 trials containing 3335 participants (including RCTs, cross-over trials and cluster trials).
Population: Children and adolescents aged 6-18 yr with diagnosed depressive disorder.
Interventions: Antidepressants, placebo.
Main Outcome Measure: Depression severity score.
Results: Children treated with an antidepressant had lower depression severity score and higher rates of response/remission. Children on antidepressants were also found to be at increased risk (59%) of suicide-related outcome (RR 1.58; 95% CI 1.02 to 2.45).
Conclusions: In children and adolescents, antidepressants are effective at treating depression, yet may cause a higher chance of suicide-related outcomes.

The shy child is quiet and reluctant to participate but slowly ‘warms up’.
**Childhood Schizophrenia**

**Epidemiology**
- 1/2,000 in childhood; increases after puberty to adult rates (1%) in late adolescence
- diagnostic criteria same as in adults (see Schizophrenia, PS6)
- less elaborate delusions than adults and visual hallucinations are more common
- <6 yr old may present in similar fashion to autism prior to onset of core symptoms
- prognosis poor as cognitive, language, social and personality development are disrupted

**Treatment**
- psychotherapy, family education
- low dose antipsychotics for psychotic symptoms (e.g. hallucinations) and target behaviours (e.g. aggression, hyperactivity, impulsiveness)
- hospitalization or residential placement, if severe

**Pervasive Developmental Disorders**

- include autism, Asperger’s, childhood disintegrative disorder, Rett’s disorder, and PDD NOS
- M:F = 3-4:1 (except for Rett’s with female predominance)

**Differential Diagnosis**
- developmental disability, childhood schizophrenia, social phobia, OCD, communication disorder, non-verbal learning disorder, ADHD, abuse, hearing or visual impairment, seizure disorder, motor impairment

**Management**
- hearing test to rule out impairment
- psychological testing to assess intellectual functioning and learning
- chromosomal analysis to rule out abnormalities (e.g. trisomy 21, fragile X syndrome)
- rule out psychotic disorders, social problems, depression, anxiety, abuse

**Treatment**
- team-based: school, psychologist, occupational therapist, physiotherapist, speech and language therapy, audiology, pediatrics, psychiatry
- family education and support
- treat concomitant disorders such as tics, OCD, anxiety, depression, and seizure disorder
- behaviour management, school programming
- pharmacotherapy: atypical antipsychotics (for aggression, agitation, self-mutilation, tics), SSRIs (for anxiety, depression), stimulants (for associated inattention and hyperactivity)

**Prognosis**
- variable, but improves with early intervention
- better if IQ >60 and able to communicate

**Note:** DSM-V has resulted in significant changes to these diagnoses. Autism, Asperger’s disorder, childhood disintegrative disorder and PDD NOS will be subsumed by the diagnosis of autism spectrum disorder

**AUTISTIC DISORDER**
- prevalence 1/1,000
- abnormalities in three areas:
  - **social interaction:** impaired non-verbal behaviours (eye contact, facial expression, hand gestures); failure to develop appropriate peer relationships; lack of seeking to share enjoyment/interests; lack of social/emotional reciprocity
  - **communication:** delay or lack of development of spoken language; impaired ability to start or sustain conversation with others; stereotyped/repetitive or idiosyncratic use of language; lack of make-believe play
  - **restricted and repetitive behaviours, interests, and activities:** stereotyped or restricted patterns of interest with abnormal intensity or focus; inflexible adherence to specific, non-functional routines; stereotyped hand or body movements (e.g. rocking); preoccupation with parts of objects (e.g. spinning wheels on toy cars only)
- at least 6 features before 3 yr old (at least 2 from social interaction and 1 from other 2 categories)

**ASPERGER’S DISORDER**
- prevalence 3/1,000
- no early speech and language delay, no cognitive deficits (express normal curiosity in environment and develop age-appropriate learning skills, self-help and adaptive behaviours), normal to high intelligence
- at least 2 items from social interaction and 1 from repetitive behaviours categories of autistic disorder criteria

Disorganized speech and behaviour is associated with many childhood disorders which must be differentiated from schizophrenia (e.g. Communication Disorders, Pervasive Developmental Disorders, ADHD, Stereotypic Movement Disorders)

Asperger’s vs. Autism
Children with Asperger’s have no delay or abnormality in language or cognition. Autism must have age of onset by 3 years whereas Asperger’s may not be diagnosed until later in life.
CHILDHOOD DISINTEGRATIVE DISORDER (CDD)
- similar to autism, but there must be a period of at least 2 yr (and up to 10 yr) of normal development followed by regression in multiple areas of functioning
- associated with developmental disability
- rule out degenerative brain disease, schizophrenia, general medical conditions

RETT’S DISORDER
- X-linked dominant disorder, therefore predominantly in girls
- restriction of brain growth beginning in first year of life
- normal development between 6 mo to 4 yr, then regression (loss of purposeful hand movements, developmental disability, seizures, neurological, respiratory and motor deficits)

**Attention Deficit Hyperactivity Disorder**

- prevalence: 5-12% of school-aged children; M:F = 4:1, although girls may be under-diagnosed
- girls tend to have inattentive/distractible symptoms; boys have impulsive/hyperactive symptoms

**Etiology**
- genetic: dopamine candidate genes, catecholamine/neuroanatomical hypothesis
- cognitive: developmental disability, inhibitory control and other errors of executive function
- arousal: alterations in the sensory system filters

**Diagnosis**
- differential: learning disorders, hearing/visual defects, thyroid, atopic conditions, congenital problems (fetal alcohol syndrome, Fragile X), lead poisoning, history of head injury, traumatic life events (abuse)
- diagnosis (3 subtypes):
  - **Combined Type**: 6 or more symptoms of inattention and 6 or more symptoms of hyperactivity-impulsivity
  - **Predominantly Inattentive Type**: 6 or more symptoms of inattention
  - **Predominantly Hyperactive-Impulsive Type**: 6 or more symptoms of hyperactivity-impulsivity
- symptoms persist for >6 mo
- onset before age 7
- symptoms present in at least two settings (i.e. home, school, work)
- interferes with academic, family, and social functioning
- does not occur exclusively during the course of another psychiatric disorder

**Table 14. Core Symptoms of ADHD (DSM-IV)**

<table>
<thead>
<tr>
<th>Inattention</th>
<th>Hyperactivity</th>
<th>Impulsivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Careless mistakes</td>
<td>Fidgets, squirms in seat</td>
<td>Blurs out answers before questions completed</td>
</tr>
<tr>
<td>Cannot sustain attention in tasks or play</td>
<td>Leaves seat when expected to remain seated</td>
<td>Difficulty awaiting turn</td>
</tr>
<tr>
<td>Does not listen when spoken to directly</td>
<td>Runs and climbs excessively</td>
<td>Interrupts/intrudes on others</td>
</tr>
<tr>
<td>Fails to complete tasks</td>
<td>Cannot play quietly</td>
<td></td>
</tr>
<tr>
<td>Disorganized</td>
<td>On the “go”, driven by a motor</td>
<td></td>
</tr>
<tr>
<td>Avoids, dislikes tasks that require sustained mental effort</td>
<td>Talks excessively</td>
<td></td>
</tr>
<tr>
<td>Loses things necessary for tasks or activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distractible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forgetful</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Features**
- average onset 3 yr old
- identification upon school entry
- rule out developmental delay, genetic syndromes, encephalopathies or toxins (alcohol, lead)
- risk of substance abuse, particularly cannabis and cocaine, depression, anxiety, academic failure, poor social skills, risk of comorbid CD and/or ODD, risk of adult ASPD
- associated with family history of ADHD, difficult temperamental characteristics
Treatment
- non-pharmacological: parent management, anger control strategies, positive reinforcement, social skills training, individual/family therapy, resource room, tutors, classroom intervention, exercise routines, extracurricular activities
- pharmacological
  - standard treatment:
    - stimulants: methylphenidates (Ritalin®, Concerta® (long-acting)), Biphetin®,
    - amphetamines: dextroampheta mine, mixed amphetamine salts (Adderall®), lisdexamfetamine (Vyvanse®)
    - SNRI: atomoxetine (Strattera®)
  - for comorbid symptoms: antidepressants, antipsychotics

Prognosis
- 65% continue into adulthood; secondary personality disorders and compensatory anxiety disorders are identifiable
- 70-80% continue into adolescence, but hyperactive symptoms usually abate

Oppositional Defiant Disorder
- prevalence: 2-16%

Diagnosis
- pattern of negativistic/hostile and defiant behaviour for ≥6 mo with ≥4 of:
  - loses temper, argues with adults, defies adult rules, deliberately annoys, blames others, touchy/easily annoyed, angry and resentful, spiteful or vindictive
  - behaviour causes significant impairment in social, academic or occupational functioning
  - behaviours do not occur exclusively during the course of a psychotic or mood disorder
  - criteria not met for conduct disorder (CD); if 18 yr or older, criteria not met for ASPD
  - features that typically differentiate ODD from transient developmental stage: onset <8 yr, chronic duration (≥6 mo), frequent intrusive behaviour
  - impact of ODD: poor school performance, few friends, strained parent/child relationships
  - may progress to CD

Treatment
- establish boundaries
- parent management training and psychoeducation
- individual/family therapy
- pharmacotherapy for comorbid disorders
- school/day care interventions to help with behaviour management

Conduct Disorder
- prevalence: 1.5-3.4% (M:F = 4-12:1)

Etiology
- parental/familial factors: parental psychopathology (e.g. ASPD, substance abuse), child rearing practices (e.g. child abuse, discipline), low socio-economic status (SES), family violence
- child factors: difficult temperament, ODD, learning problems, neurobiology

Diagnosis
- differential: ADHD, depression, head injury, substance abuse
- diagnostic: use multiple sources (Achenbach Child Behavioural Checklist, Teacher’s Report Form)
  - pattern of behaviour that violates rights of others and age appropriate social norms with ≥3 criteria noted in past 12 mo and ≥1 in past 6 mo:
    - aggression to people and animals (bullying, physical fights, use of weapons, forced sex)
    - destruction of property, firesetting with intent to damage
    - deceitfulness or theft (breaking and entering, car theft)
    - violation of rules (out all night before age 13, runaway ≥2 times or for long periods of time, often truant from school before age 13)
    - disturbance causes clinically significant impairment in social, academic or occupational functioning
    - if individual is 18 yr or older, criteria not met for ASPD

- diagnostic types
  - childhood onset: at least one criterion prior to age 10
  - adolescent onset: absence of any criteria until age 10
  - more aggressive, gang-related delinquency
  - mild, moderate, severe
Treatment
• early intervention necessary and more effective; long-term follow-up required
• parent management training, anger replacement training, CBT, family therapy, education/employment programs, social skills training, medications for aggressiveness or comorbid disorders
• pharmacotherapy is insufficient; mainly used for treatment of comorbid disorders

Prognosis
• poor prognostic indicators include early-age onset, high frequency and variety of behaviours, pervasiveness (i.e. in home, school, community), comorbid ADHD, early sexual activity, substance abuse
• 50% of CD children become adult ASPD

Psychosocial Treatment
• see Pediatrics:
  ▪ Child Abuse, Pediatrics P14
  ▪ Chronic Recurrent Abdominal Pain, Pediatrics P39
  ▪ Developmental Delay, Pediatrics P22
  ▪ Intellectual Disability, Pediatrics P23
  ▪ Learning Disability, Pediatrics P25
  ▪ Elimination Disorders, Pediatrics P9
  ▪ Sleep Disturbances, Pediatrics P12

Psychotherapy
• theory: one’s present outlook is shaped by one's past and unconscious psychological forces
• insight allows change in personality and behaviour
• conflict – three stages
  ▪ non-resolvable conflict
  ▪ attempt to repress
  ▪ return of conflict in disguised form (symptom or character trait)
• emphasis on early interaction with caregiver
• sources of information
  ▪ past and present experiences and relationships
  ▪ relationship with therapist
    ▪ transference: unconscious reenactment of early interpersonal patterns in relationship with therapist
    ▪ countertransference: therapist's transference to patient
    ▪ resistance: elements in the patient which oppose treatment
• techniques
  ▪ free association: patient says whatever comes to mind
  ▪ dream analysis
  ▪ Prochaska’s stages of change model is important for all conflict resolutions

Defense Mechanisms
• defense mechanisms are unconsciously activated by the patient in response to anxiety provoking events and feelings

<table>
<thead>
<tr>
<th>Table 15. Defense Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1: Psychotic Defenses</strong></td>
</tr>
<tr>
<td>Common in psychosis; normally seen throughout childhood and in dreams</td>
</tr>
<tr>
<td>• Denial: replacing external reality with wishful fantasy</td>
</tr>
<tr>
<td>• Distortion: reshaping of reality to meet inner beliefs</td>
</tr>
<tr>
<td>• Projection: interpreting internal impulses as though they are outside oneself; in psychosis seen as frank delusion about reality (e.g. persecutory delusions)</td>
</tr>
<tr>
<td><strong>Level 2: Immature Defenses</strong></td>
</tr>
<tr>
<td>Common in personality disorders, severe depression. Normally seen throughout adolescence</td>
</tr>
<tr>
<td>• Acting out: express unconscious wish through impulsive action</td>
</tr>
<tr>
<td>• Blocking: of thinking, affect, or impulse</td>
</tr>
<tr>
<td>• Hypochondriasis: exaggeration of illness</td>
</tr>
<tr>
<td>• Introjection: internalizing qualities of an object (i.e. victim identifying with aggressor)</td>
</tr>
<tr>
<td>• Passive-aggressive behaviour</td>
</tr>
<tr>
<td>• Regression: returning to an earlier stage of development to avoid present stressors</td>
</tr>
<tr>
<td>• Somatization: unconscious expression of psychic pain/tension as physical symptoms</td>
</tr>
</tbody>
</table>
### Table 15. Defense Mechanisms (continued)

<table>
<thead>
<tr>
<th>Level 3: Neurotic Defenses</th>
<th>Common in adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controlling</strong></td>
<td>shifting emotional response to an object/idea resembling that which is anxiety provoking</td>
</tr>
<tr>
<td><strong>Displacement</strong>:</td>
<td>attributing moods/attitudes/conflicts to external world or objects</td>
</tr>
<tr>
<td><strong>Externalization</strong>:</td>
<td>limiting function to avoid anxiety producing internal conflicts</td>
</tr>
<tr>
<td><strong>Intellectualization</strong>:</td>
<td>using intellectual processing to avoid experiencing affect</td>
</tr>
<tr>
<td><strong>Isolation</strong></td>
<td>limiting function to avoid anxiety producing internal conflicts</td>
</tr>
<tr>
<td><strong>Rationalization</strong>:</td>
<td>using rational explanations to justify behaviours that are unacceptable</td>
</tr>
<tr>
<td><strong>Dissociation</strong>:</td>
<td>temporary modification of sense of self to avoid emotional distress</td>
</tr>
<tr>
<td><strong>Reaction formation</strong>:</td>
<td>transforming an unacceptable impulse into its opposite</td>
</tr>
<tr>
<td><strong>Repression</strong>:</td>
<td>withholding or removing from consciousness an idea/feeling</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 4: Mature Defenses</th>
<th>Common in emotionally healthy adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Altruism</strong></td>
<td>planning for future discomfort</td>
</tr>
<tr>
<td><strong>Asceticism</strong></td>
<td>denying pleasurable effects of an experience</td>
</tr>
<tr>
<td><strong>Humour</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Suppression</strong></td>
<td>postpone attention to impulse or conflict</td>
</tr>
</tbody>
</table>

### Psychodynamic Therapy

- **psychoanalysis** (exploratory psychotherapy)
  - original therapy developed by Freud, goal is self-revelation and insight
  - the exploration of the meaning of early experiences and how they affect emotions and patterns of behaviour presently
  - time intensive (e.g. 4-5 times/wk for 3-7 yr)
  - for individuals who can tolerate ambiguity in explorations of feelings and treatment
- **supportive psychotherapy**
  - goal is not insight but reduction of anxiety
  - strengthen healthy defense mechanisms to assist day-to-day functioning
  - techniques include: enhancing self-esteem, clarification, confrontation, rationalization, reframing, encouragement, rehearsal/anticipation, de-catastrophizing, allowing “venting” of frustrations
- **short term/brief psychotherapy**
  - resolution of particular emotional problems, or acute crisis
  - number of sessions agreed on at outset (6-20)
- **interpersonal psychotherapy**
  - short-term treatment looking at relationship patterns and teaching coping mechanisms
  - focus on personal social roles and relationships to help deal with problems in current functioning

### Behaviour Therapy

- modification of internal or external events which precipitate or maintain emotional distress; useful in the treatment of anxiety disorders, substance abuse, paraphilias
- **systematic desensitization**: mastering anxiety-provoking situations by approaching them gradually and in a relaxed state that limits anxiety
- **flooding**: confronting feared stimulus for prolonged periods until it is no longer frightening
- **positive reinforcement**: strengthening behaviour and causing it to occur more frequently by rewarding it
- **negative reinforcement**: causing behaviour to occur more frequently by removing a noxious stimulus when desired behaviour occurs
- **extinction**: causing a behaviour to diminish by not rewarding it
- **punishment** (aversion therapy): causing a behaviour to diminish by applying a noxious stimulus

### Cognitive Therapy

- theory: moods/emotions are influenced by one's thoughts
- psychiatric disturbances are frequently caused by habitual errors in thinking
- goal is to help patient become aware of inaccurate automatic thoughts and correct assumptions with a more balanced perspective
- useful for depression, anxiety disorders, self-esteem problems
- use of this therapy presupposes a significant level of functioning of the patient
- patients asked to keep thought records (often in chart form, with column headings “situation”, “feeling”, “thought” and “cognitive distortion”) to monitor their thoughts, when/where they think these thoughts, how the thoughts make them feel and what their underlying error in thinking might be
Cognitive Behavioural Therapy (CBT)

- combines cognitive and behaviour therapies to teach the patient to weaken connections between thinking patterns, habitual behaviours and mood/anxiety problems
- good for treatment of mild/moderate depression/anxiety

Dialectical Behavioural Therapy (DBT)

- therapy that combines CBT techniques with approaches derived from Buddhist meditation practices
- originally developed for borderline patients but has since been found to be effective for the treatment of several other disorders
- focuses on four types of skills: mindfulness, emotion regulation, interpersonal effectiveness, and distress tolerance
- individual and group therapy settings

Other Therapies

- group psychotherapy
  - goals: self-understanding, acceptance, social skills
- family therapy
  - family system considered more influential than individual especially for children
  - focus on here and now, re-establishing parental authority, strengthening normal boundaries, and rearranging alliances
- hypnosis: mixed evidence for the treatment of pain, phobias, anxiety, and smoking cessation
- mindfulness-based cognitive therapy: derived from Buddhist meditative practices; aims to help people attend to thoughts, behaviours and emotions non-judgmentally and in the moment using guided breathing exercises

Pharmacotherapy

Antipsychotics

- “antipsychotics” and “neuroleptics” are terms used interchangeably
- indications: schizophrenia and other psychotic disorders, mood disorders with or without psychosis, violent behaviour, autism, Tourette’s, somatoform disorders, dementia, OCD
- onset: immediate calming effect and decrease in agitation; thought disorder responds in 2-4 wk
- rational use:
  - no reason to combine antipsychotics
  - choosing an antipsychotic:
    - all antipsychotics are equally effective, except for clozapine
    - atypical antipsychotics are as effective as typical or first generation antipsychotics but are thought to have better side effect profiles
    - choose a drug that the patient has responded to in the past or that was used successfully in a family member
  - route: PO, short-acting or long-acting depot IM injections, sublingual
  - duration: minimum 6 mo, usually for life

Long-Acting Preparations

- antipsychotics formulated in oil for IM injection (see Table 17)
- received on an outpatient basis
- indications: individuals with schizophrenia or other chronic psychosis who relapse because of non-adherence
- dosing: start at low dosages, and then titrate every 2 to 4 wk to maximize safety and minimize side effects
- should be exposed to oral form prior to first injection
- side effects: risk of EPS, parkinsonism, increased risk of neuroleptic malignant syndrome

Canadian Guidelines for the Treatment of Acute Psychosis in the Emergency Setting

- haloperidol 5 mg IM ± lorazepam 2 mg IM
- olanzapine 2.5-10 mg (PO, IM, quick dissolve)
- risperidone 2 mg (M-tab, liquid)

Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia

- NEJM 2005;353:1209-23
- Study: Randomized, double-blind, active-control trial with median follow-up of 6 mo.
- Patients: 1432 patients with a diagnosis of schizophrenia (as per DSM-IV criteria) and able to take antipsychotic medications (as determined by study doctors). Mean age 41, 74% male, 26% female.
- Intervention: 1 to 4 capsules daily of olanzapine (20.1 mg), quetiapine (514.3 mg), risperidone (3.9 mg), perphenazine (20.8 mg), or ziprasidone (112.8 mg), with dosage at the discretion of the study doctor. Mean modal doses in parentheses.
- Main Outcome: Discontinuation of treatment for any cause
- Results: Olanzapine group had statistically significant lower rate of discontinuation for any cause (84%) compared to other antipsychotics (70-76%). Quetiapine was associated with a significantly higher rate of metabolic side effects.

Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia

- NEJM 2005;353:1209-23
- Study: Randomized, double-blind, active-control trial with median follow-up of 6 mo.
- Patients: 1432 patients with a diagnosis of schizophrenia (as per DSM-IV criteria) and able to take antipsychotic medications (as determined by study doctors). Mean age 41, 74% male, 26% female.
- Intervention: 1 to 4 capsules daily of olanzapine (20.1 mg), quetiapine (514.3 mg), risperidone (3.9 mg), perphenazine (20.8 mg), or ziprasidone (112.8 mg), with dosage at the discretion of the study doctor. Mean modal doses in parentheses.
- Main Outcome: Discontinuation of treatment for any cause
- Results: Olanzapine group had statistically significant lower rate of discontinuation for any cause (84%) compared to other antipsychotics (70-76%). Quetiapine was associated with a significantly higher rate of metabolic side effects.
### Table 16. Pathophysiology of Schizophrenia vs. Mechanism of Action of Antipsychotics

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Pathophysiology in Schizophrenia</th>
<th>Typical Antipsychotic</th>
<th>Atypical Antipsychotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Limbic System</strong></td>
<td>Excess DA +ve symptoms (hallucinations, delusions)</td>
<td>D2 blockade</td>
<td>Weak 5-HT block, D2/1 blockade maintained</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treats +ve symptoms</td>
<td>Treats +ve symptoms</td>
</tr>
<tr>
<td><strong>Frontal Cortex</strong></td>
<td>Decreased DA –ve symptoms (flat affect, anhedonia, avolition), cognitive impairment</td>
<td>D2 blockade</td>
<td>Robust 5-HT block increases DA transmission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May worsen –ve symptoms and cognitive impairment</td>
<td>Theoretical improvement in negative/cognitive symptoms only observed with clozapine</td>
</tr>
<tr>
<td><strong>Basal Ganglia</strong></td>
<td>Unchanged</td>
<td>D2 blockade</td>
<td>Robust 5-HT block increases DA transmission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative ACh excess causes EPS symptoms</td>
<td>Decreased EPS incidence</td>
</tr>
<tr>
<td><strong>Tuberoinfundibular Tract</strong></td>
<td>Unchanged</td>
<td>D2 blockade</td>
<td>5-HT block increases DA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperprolactinemia</td>
<td>Less hyperprolactinemia</td>
</tr>
</tbody>
</table>

DA = dopamine; 5-HT = serotonin; ACh = acetylcholine; EPS = extrapyramidal symptoms

Note: specific “typical” and “atypical” antipsychotics vary in terms of binding to adrenergic, 5-HT, cholinergic and histaminergic sites leading to different side effect profiles.

### Table 17. Common Antipsychotic Agents

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>starting Dose</th>
<th>Maintenance</th>
<th>maximum</th>
<th>relative Potency (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typicals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol (Haldol®)</td>
<td>2.5-10 mg IM q8h</td>
<td>Based on clinical effect</td>
<td>20 mg/d PO</td>
<td>2</td>
</tr>
<tr>
<td>Fluphenazine enanthate (Moditen®, Modecate® for IM formulation)</td>
<td>2.5-10 mg/d PO</td>
<td>1.5 mg PO qhs</td>
<td>20 mg/d PO</td>
<td>2</td>
</tr>
<tr>
<td>Zuclopenthixol HCl (Clopixol®)</td>
<td>20-30 mg/d PO</td>
<td>20-40 mg/d PO</td>
<td>100 mg/d PO</td>
<td>4</td>
</tr>
<tr>
<td>Zuclopenthixol acetate (Acuphase®)</td>
<td>50-150 mg IM q48-72h</td>
<td>25 mg IM/SC q3-72h</td>
<td>400 mg IM (q2wk)</td>
<td></td>
</tr>
<tr>
<td>Zuclopenthixol decanoate (Cloxipol Depot®)</td>
<td>100 mg IM q1-4wk</td>
<td>150-300 mg IM q2wk</td>
<td>600 mg IM/qwk</td>
<td></td>
</tr>
<tr>
<td>Perphenazine (Trilafon®)</td>
<td>8-16 mg PO b/tid</td>
<td>4-8 mg PO t/qid</td>
<td>64 mg/d PO</td>
<td>10</td>
</tr>
<tr>
<td>Loxapine HCl (Loxitane®)</td>
<td>10 mg PO tid</td>
<td>12.5-50 mg IM q4-6h</td>
<td>250 mg/d PO</td>
<td>10</td>
</tr>
<tr>
<td>Chlorpromazine (Largactil®)</td>
<td>10-15 mg PO b/tqid</td>
<td>400 mg/d PO</td>
<td>1000 mg/d PO</td>
<td>100</td>
</tr>
<tr>
<td><strong>Atypicals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone (Risperdal®, Risperdal Consta® for IM long acting preparation, Risperdal M-Tab for melting form – placed on tongue)</td>
<td>1-2 mg OD/bid</td>
<td>4-8 mg/d PO</td>
<td>90 mg/d PO</td>
<td>2</td>
</tr>
<tr>
<td>Paliperidone (Invega®)</td>
<td>3 mg/d PO</td>
<td>3-12 mg /d PO</td>
<td>12 mg/d PO</td>
<td>4</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa®, Zyprexa Zydis® for melting form – placed on tongue, Zyprexa Intramuscular®)</td>
<td>5 mg/d PO</td>
<td>10-20 mg/d PO</td>
<td>30 mg/d PO</td>
<td>5</td>
</tr>
<tr>
<td>Asenapine (Saphris®)</td>
<td>5 mg SL bid</td>
<td>5-10 mg SL bid</td>
<td>10 mg bid</td>
<td>5</td>
</tr>
<tr>
<td>Ziprasidone (Zeldox®)</td>
<td>20 mg bid PO</td>
<td>40-80 mg bid PO</td>
<td>160 mg/d PO</td>
<td>6</td>
</tr>
<tr>
<td>Aripiprazole (Abilify®)</td>
<td>10-15 mg/d PO</td>
<td>10-15 mg/d PO</td>
<td>30 mg/d PO</td>
<td>5</td>
</tr>
<tr>
<td>Quetiapine (Seroquel®, Seroquel XR for extended release®)</td>
<td>25 mg PO bid</td>
<td>400-800 mg/d PO</td>
<td>800 mg/d PO</td>
<td>75</td>
</tr>
<tr>
<td>Clozapine (Clozaril®)</td>
<td>25 mg PO bid</td>
<td>300-800 mg/d PO</td>
<td>600 mg/d PO</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 18. Commonly Used Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Commonly Used Atypical Antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blocks 5-HT2, D2 and adrenergic receptors</td>
<td><strong>Risperidone</strong> (Risperdal®)</td>
</tr>
<tr>
<td>Blocks 5-HT1A, D1-D4, muscarinic, adrenergic,</td>
<td><strong>Olanzapine</strong> (Zyprexa®, Zydis®)</td>
</tr>
<tr>
<td>histaminergic receptors</td>
<td><strong>Quetiapine</strong> (Seroquel®)</td>
</tr>
<tr>
<td>Blocks 5-HT2, D1-2, adrenergic and histaminerg</td>
<td><strong>Clozapine</strong> (Clozaril®)</td>
</tr>
<tr>
<td>ic receptors</td>
<td><strong>Aripiprazole</strong> (Abilify®)</td>
</tr>
</tbody>
</table>

**Advantages**
- Low incidence of EPS at lower doses (<8 mg)
- Better overall efficacy compared to haloperidol
- Well tolerated
- Low incidence of EPS and TD

**Disadvantages**
- SE: insomnia, agitation, EPS, H/A, anxiety, prolactin, postural hypotension, constipation, dizziness, weight gain
- SE: mild sedation, insomnia, dizziness, minimal anticholinergic, early AST and ALT elevation, restlessness
- Weight gain associated with increased risk of diabetes mellitus and hyperlipidemia

**Comments**
- Quick dissolve (M-tabs), and long-acting (Consta®) formulations available
- Quick dissolve formulation (Zydis®) used commonly in ER setting for better compliance
- IM form available

**Note:** Risk of weight gain: Clozapine > Olanzapine > Quetiapine > Risperidone

Table 19. Side Effects of Antipsychotics

<table>
<thead>
<tr>
<th>System</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic</td>
<td>Dry mouth, urinary retention, constipation, blurred vision, toxic-confusional states</td>
</tr>
<tr>
<td>α-adrenergic blockage</td>
<td>Orthostatic hypotension, impotence, failure to ejaculate</td>
</tr>
<tr>
<td>Dopaminergic blockage</td>
<td>Extrapyramidal syndromes (dystonia, akathisia, pseudoparkinsonism, dyskinesia), galactorrhea, amenorrhea, impotence, weight gain</td>
</tr>
<tr>
<td>Anti-histamine</td>
<td>Sedation</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Agranulocytosis (clozapine)</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>Liver dysfunction, blood dyscrasias, skin rashes, neuroleptic malignant syndrome, altered temperature regulation (hyperthermia or hypothermia)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Metabolic syndrome (see sidebar on PS42)</td>
</tr>
</tbody>
</table>

Neuroleptic Malignant Syndrome (NMS)
- psychiatric emergency
- due to massive dopamine blockade; increased incidence with high potency and depot neuroleptics
- risk factors
  - medication factors
    - sudden increase in dosage, or starting a new drug
  - patient factors
    - medical illness
    - dehydration
    - exhaustion
    - poor nutrition
    - external heat load
    - sex: male
    - age: young adults

Anticholinergic Effects
- Red as a beet
- Hot as a hare
- Dry as a bone
- Blind as a bat
- Mad as a hatter

Metabolic and Cardiovascular Adverse Effects Associated with Antipsychotic Drugs
- Nat Rev Endocrinol 2012;8:114-126
- Study: Review
- Conclusions: All antipsychotics can cause cardiovascular and metabolic side effects, such as obesity, dyslipidemia, hyperglycemia and metabolic syndrome. Olanzapine and clozapine are most likely to cause these side effects. The mechanism that underlies the metabolic and cardiovascular effects is not fully understood, however, the histamine, dopamine, serotonin and muscarinic receptors are implicated.
• clinical presentation
  - mental status changes (usually occur first), fever, autonomic reactivity, rigidity
  - develops over 24-72 h
  - labs: increased creatine phosphokinase, leukocytosis, myoglobinuria
• treatment: discontinue drug, hydration, cooling blankets, dantrolene (hydrantoin derivative, used as a muscle relaxant), bromocriptine (DA agonist)
• mortality: 5%

Extrapyramidal Symptoms (EPS)

• incidence related to increased dose and potency
• acute (early-onset; reversible) vs. tardive (late-onset; often irreversible)

<table>
<thead>
<tr>
<th>Table 20 Extrapyramidal Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dystonia</strong></td>
</tr>
<tr>
<td><strong>Acute or Tardive</strong></td>
</tr>
<tr>
<td><strong>Risk Group</strong></td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
</tr>
<tr>
<td><strong>Onset</strong></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
</tr>
</tbody>
</table>

Antiparkinsonian Agents (Anticholinergic Agents)

• types
  - benztropine (Cogentin®) 2 mg PO, IM or IV OD (~1-6 mg)
  - amantadine (Symmetrel®) 100 mg PO bid (100-400 mg)
  - diphenhydramine (Benadryl®) 25-50 mg PO/IM qid
• do not always prescribe with neuroleptics
  - give only if at high risk for acute EPS or if acute EPS develops
• do not give these for tardive syndromes because they worsen the condition

Antidepressants

• onset of effect
  - relief of neurovegetative symptoms: 1-3 wk
  - relief of emotional/cognitive symptoms: 2-6 wk
• may use mild stimulant (e.g. methylphenidate) for severe neurovegetative symptoms briefly and taper down as antidepredant effect increases
• taper TCAs slowly (over weeks-months) because they can cause withdrawal reactions
• tapering of any kind of antidepressant may be required based on the half-life of the medication and the patient’s individual sensitivity
• it is important to be particularly vigilant over the first 2 wk of therapy as neurovegetative symptoms may start to resolve while emotional and cognitive symptoms may not (patients may be particularly at risk for suicidal behaviour during this time)
• treatment of bipolar depression:
  - monotherapy with antidepressants is not advisable as a switch from depression to mania can occur
  - patients with bipolar disorder should only be treated with an antidepressant if it is combined with a mood stabilizer and antipsychotic
  - for patients taking mood stabilizers or antipsychotics, consider adding or switching to lithium or lamotrigine, or adding an SSRI or buproprion

Features of Neuroleptic Malignant Syndrome

FARM
- Fever
- Autonomic changes (e.g. increased HR/ BP, sweating)
- Rigidity of muscles
- Mental status changes (e.g. confusion)

FARM symptoms are also seen in Serotonin Syndrome (SS).

SS can be distinguished from NMS by the following:

<table>
<thead>
<tr>
<th>SS</th>
<th>NMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twitchy, shivering, restless</td>
<td>Severe global rigidity</td>
</tr>
<tr>
<td>Flushed, sweaty</td>
<td>Pallor</td>
</tr>
<tr>
<td>Vomiting, diarrhea, abdominal pain</td>
<td>No GI symptoms</td>
</tr>
</tbody>
</table>

Tardive Dyskinesia may include grimacing, tongue protrusion, lip smacking, and rapid eye movement.

Selective Serotonin Reuptake Inhibitors (SSRIs) versus Other Antidepressants for Depression

Cochrane DB Syst Rev 2004; Issue 3
This systematic review of 98 RCTs compared the efficacy of SSRIs with other kinds of antidepressants in the treatment of patients with depressive disorders.

Conclusions: There is no significant difference in the effectiveness of SSRIs versus TCAs. Consider relative patient acceptability, toxicity and cost when choosing.
Table 21. Common Antidepressants

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Daily Starting Dose (mg)</th>
<th>Therapeutic Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>fluoxetine (Prozac®)</td>
<td>20</td>
<td>20-80</td>
</tr>
<tr>
<td></td>
<td>fluvoxamine (Luvox®)</td>
<td>50-100</td>
<td>150-300</td>
</tr>
<tr>
<td></td>
<td>paroxetine (Paxil®)</td>
<td>10</td>
<td>20-60</td>
</tr>
<tr>
<td></td>
<td>sertraline (Zoloft®)</td>
<td>50</td>
<td>50-200</td>
</tr>
<tr>
<td></td>
<td>citalopram (Celexa®)</td>
<td>20</td>
<td>20-40</td>
</tr>
<tr>
<td></td>
<td>escitalopram (Cipralex®)</td>
<td>10</td>
<td>10-20</td>
</tr>
<tr>
<td>SNRI</td>
<td>venlafaxine (Effexor®)</td>
<td>37.5-75</td>
<td>75-225</td>
</tr>
<tr>
<td></td>
<td>duloxetine (Cymbalta®)</td>
<td>40</td>
<td>40-60</td>
</tr>
<tr>
<td>NDRI</td>
<td>bupropion (Wellbutrin®)</td>
<td>100</td>
<td>300-450</td>
</tr>
<tr>
<td>TCA (3° Amines)</td>
<td>amitriptyline (Elavil®)</td>
<td>75-100</td>
<td>150-300</td>
</tr>
<tr>
<td></td>
<td>imipramine (Tofranil®)</td>
<td>75-100</td>
<td>150-300</td>
</tr>
<tr>
<td>TCA (2° Amines)</td>
<td>nortriptyline (Aventyl®)</td>
<td>75-100</td>
<td>75-150</td>
</tr>
<tr>
<td></td>
<td>desipramine (Norpramin®)</td>
<td>100-200</td>
<td>150-300</td>
</tr>
<tr>
<td>MAOI</td>
<td>phenelzine (Nardil®)</td>
<td>45</td>
<td>60-90</td>
</tr>
<tr>
<td></td>
<td>tranylcypromine (Parnate®)</td>
<td>30</td>
<td>10-60</td>
</tr>
<tr>
<td>RIMA</td>
<td>moclobemide (Manerix®)</td>
<td>300</td>
<td>300-600</td>
</tr>
<tr>
<td>NASSA</td>
<td>mirtazapine (Remeron®)</td>
<td>15</td>
<td>15-45</td>
</tr>
</tbody>
</table>

(SSRI=selective serotonin reuptake inhibitors; SNRI=serotonin and norepinephrine reuptake inhibitors; NDRI=norepinephrine and dopamine reuptake inhibitors; TCA=tricyclic antidepressants; MAOI= monoamine oxidase inhibitors; RIMA=reversible inhibition of MAO-A; NASSA=noradrenergic and specific serotonin antagonists)

Tips On Choosing Antidepressants
- All SSRI s have similar effectiveness, but consider side effect profiles and half-lives
- Bupropion causes less sexual dysfunction, weight gain, and sedation but is contraindicated for patients with history of seizure, stroke, brain tumour, brain surgery or closed head injury. Also used to treat eating disorders. Not recommended for anxiety because of stimulating effects
- Mirtazapine useful if insomnia or agitation are prominent, or to treat depression with cachexia
- Tramadol mainly used as adjunct for SSRI-induced sleep disturbances
- Sertraline, citalopram, and escitalopram have the least interactions with other drugs and are sleep-wake neutral
- Fluoxetine and paroxetine are the most activating drugs and should be taken in the morning
- Fluvoxamine is always sedating and should be taken in the evening

How Long to Treat?
6-12 mo: if first or second episode.
2 yr: third episode, elderly, psychotic features, refractory depression, > 2 episodes in 5 yr.

Psychopharmacology of SSRIs

<table>
<thead>
<tr>
<th>Post-Synaptic Receptor</th>
<th>Effect/Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>5HT1A centrally</td>
<td>Relief of depression, Anxiolytic effect</td>
</tr>
<tr>
<td>5HT2A in spinal cord</td>
<td>Sexual dysfunction: delayed ejaculation, anorgasmia, decreased libido</td>
</tr>
<tr>
<td>5HT2C/5HT2A in brain</td>
<td>Activation: anxiety, insomnia</td>
</tr>
<tr>
<td>5HT3A in gut</td>
<td>GI upset: nausea, vomiting, bloating</td>
</tr>
</tbody>
</table>
- optimization: ensuring adequate drug doses for the individual
- augmentation: the addition of a medication that is not considered an antidepressant to an antidepressant regimen (e.g. thyroid hormone, lithium, atypical antipsychotics)
- combination: the addition of another antidepressant to an existing treatment regimen (e.g. the addition of bupropion to an SSRI or SNRI)
- substitute: change in the primary antidepressant (within or outside a class)
- note: it is important to fully treat the symptoms of depression in order to decrease rates and severity of relapses
### Table 22. Commonly Used Antidepressants

<table>
<thead>
<tr>
<th>TCA</th>
<th>SSRI</th>
<th>MAOI</th>
<th>SNRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Considerations</strong></td>
<td>OCD (clomipramine), melancholic depression</td>
<td>Anxiety states, OCD, eating disorders, seasonal depression, typical and atypical depression</td>
<td>For moderate/severe depression that does not respond to SSRI, atypical depression</td>
</tr>
<tr>
<td><strong>Mode of Action</strong></td>
<td>Block norepinephrine and serotonin reuptake</td>
<td>Block serotonin reuptake only</td>
<td>Irreversible inhibition of monoamine oxidase A and B</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>Anticholinergic effects: (see Table 19)</td>
<td>Fewer than TCA, therefore increased compliance</td>
<td>Hypertensive crises with tyramine rich foods (e.g. wine, cheese), headache, flushes, palpitations, N/V, photophobia</td>
</tr>
<tr>
<td></td>
<td>Noradrenergic effects: tremors, tachycardia, sweating, insomnia, erectile and ejaculation problems</td>
<td>CNS: restlessness, tremor, insomnia, headache, drowsiness</td>
<td>Dizziness, reflex tachycardia, postural hypotension, sedation, insomnia</td>
</tr>
<tr>
<td></td>
<td>α₁ adrenergic effects: orthostatic hypotension</td>
<td>GI: N/V, diarrhea, abdominal cramps, weight loss</td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td>Antihistamine effects: sedation, weight gain</td>
<td>Sexual dysfunction: impotence, anorgasmia</td>
<td>Social dysfunction</td>
</tr>
<tr>
<td></td>
<td>CNS: sedation, stimulation, ↓ seizure threshold</td>
<td>CNS: increased HR, conduction delay, serotonin syndrome, EPS, SIADH</td>
<td>Energizing</td>
</tr>
<tr>
<td></td>
<td>CVS: ↑ HR, conduction delay</td>
<td></td>
<td>Minimal anticholinergic and antihistamine effects</td>
</tr>
<tr>
<td><strong>Risk in Overdose</strong></td>
<td>Toxic in OD 3 times therapeutic dose is lethal</td>
<td>Relatively safe in OD</td>
<td>Toxic in OD, but wider margin of safety than TCA</td>
</tr>
<tr>
<td></td>
<td>Presentation: anticholinergic effects, CNS stimulation, then depression and seizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ECG: prolonged QT (duration reflects severity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment: activated charcoal, cathartics, supportive treatment, IV diazepam for seizure, physostigmine salicylate for coma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not give ipecac, as can cause rapid neurologic deterioration and seizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>MAOI, SSRI, EtOH</td>
<td>SSRIs inhibit P450 enzymes, therefore will affect levels of drugs metabolized by P450 system</td>
<td>EtOH Hypertensive crises with noradrenergic medications (e.g. TCA, decongestants, amphetamines)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Serotonin syndrome with serotonergic drugs (e.g. SSRIs, tryptophan, dextromethorphan)</td>
</tr>
<tr>
<td>NDRI</td>
<td>RIMA</td>
<td>NASSA</td>
<td></td>
</tr>
<tr>
<td><strong>Considerations</strong></td>
<td>Depression, seasonal depression</td>
<td>Depression unresponsive to other therapies</td>
<td>Useful in patients with insomnia, agitation or depression with cachexia</td>
</tr>
<tr>
<td><strong>Mode of Action</strong></td>
<td>Block norepinephrine and dopamine reuptake</td>
<td>Reversible inhibitor of monoamine oxidase A</td>
<td>Enhance central noradrenergic and serotonergic activity by inhibiting presynaptic α₂ adrenergic receptors</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>CNS: dizziness, headache, tremor, insomnia</td>
<td>CNS: dizziness, headache, tremor, insomnia</td>
<td>CNS: somnolence, dizziness, seizure (rare)</td>
</tr>
<tr>
<td></td>
<td>CVS: dysrhythmia, hypertension</td>
<td>CNS: dizziness, headache, tremor, insomnia</td>
<td>Endocrine: ↑ cholesterol, ↑ triglycerides</td>
</tr>
<tr>
<td></td>
<td>GI: dry mouth, N/V, constipation, ↓ appetite</td>
<td>CVS: dysrhythmia, hypertension</td>
<td>GI: constipation, ↑ ALT</td>
</tr>
<tr>
<td></td>
<td>Other: agitation, anxiety, anaphylactoid reaction</td>
<td>GI: dry mouth, N/V, diarrhea, abdominal pain, dyspepsia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GI: delayed ejaculation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other: diaphoresis</td>
<td></td>
</tr>
<tr>
<td><strong>Risk in Overdose</strong></td>
<td>Tremors and seizures seen in acute overdose</td>
<td>Risk of fatal overdose when combined with citalopram or clomipramine</td>
<td>Mild symptoms with overdose</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>MAOI, SSRI, TCA Opioids</td>
<td>Drugs that reduce seizure threshold: antipsychotics, systemic steroids, quinolone antibiotics, antimalarial drugs</td>
<td>MAOI, SSRI, SNRI, RIMA</td>
</tr>
</tbody>
</table>
Serotonin Syndrome
- thought to be due to over-stimulation of the serotonergic system
- can result from medication combinations such as SSRI + MAOI, SSRI + tryptophan, MAOI + meperidine, MAOI + tryptophan
- rare but potentially life-threatening adverse reaction to SSRIs, especially when switching from an SSRI to an MAOI
- symptoms include nausea, diarrhea, palpitations, chills, restlessness, confusion, and lethargy but can progress to myoclonus, hyperthermia, rigor and hypertonicity
- treatment: discontinue medication and administer emergency medical care as needed
- important to distinguish from NMS (see sidebar, PS44)

Discontinuation Syndrome
- caused by the abrupt cessation of an antidepressant
- observed most frequently with paroxetine, fluvoxamine, and venlafaxine
- symptoms usually begin within 1-3 d and include: anxiety, insomnia, irritability, mood lability, N/V, dizziness, headache, dystonia, tremor, chills, fatigue, lethargy and myalgia
- treatment: symptoms may last between 1-3 wk, but can be relieved within 24 h by restarting antidepressant therapy at the same dose the patient was taking and initiating a slow taper over several weeks
- consider drug with longer half-life such as fluoxetine

**Mood Stabilizers**

First-Line
Lithium or Valproic Acid (± antipsychotic)
- before initiating, get baseline: CBC, ECG (if patient >45 yr old or cardiovascular risk), urinalysis, BUN, Cr, electrolytes, TSH
- before initiating lithium: screen for pregnancy, thyroid disease, seizure disorder, neurological, renal, cardiovascular diseases
- may need acute coverage with benzodiazepines or antipsychotics
- use carbamazepine in non-responders and rapid cycling bipolar disorder
- can combine lithium and carbamazepine or valproic acid safely in lithium non-responders
- olanzapine may be used as a mood stabilizer, in conjunction with other mood stabilizers
- lithium and lamotrigine have established antidepressant efficacy

Lithium Toxicity (see Table 23)
- clinical diagnosis as toxicity can occur at therapeutic levels
  - common causes
    - overdose
    - sodium or fluid loss
    - concurrent medical illness
  - clinical presentation
    - GI: severe nausea/vomiting and diarrhea
    - cerebellar: ataxia, slurred speech, lack of coordination
    - cerebral: drowsiness, myoclonus, choreiform or Parkinsonian movements, upper motor neuron signs, seizures, delirium, coma
  - management
    - discontinue lithium for several doses and begin again at a lower dose when lithium level has fallen to a non-toxic range
    - serum lithium levels, BUN, electrolytes
    - saline infusion
    - hemodialysis if lithium >2 mmol/L, coma, shock, severe dehydration, failure to respond to treatment after 24 h, or deterioration

Second-Line/Adjuvant Mood Stabilizers
Lithium, lamotrigine, divalproex, carbamazepine

**Symptoms of Antidepressant Discontinuation**
FINISH
Flu-like symptoms
Insomnia
Nausea
Imbalance
Sensory disturbances
Hyperarousal (anxiety/agitation)

**Sequenced Treatment Alternatives to Relieve Depression**
Study: Prospective randomized anti-depressant treatment trial.
Patients: 4000 patients with major depressive disorder.
Objective: To compare the efficacy and tolerability of various antidepressant therapies through four sequential treatment levels.
Intervention: Level 1-citalopram → if relapse → Level 2-citalopram + bupropion SR, sertraline, venlafaxine XR, or cognitive psychotherapy. Level 2A-switch to bupropion or venlafaxine XR. Level 3-either mirtazapine or nortriptyline + lithium, T3. Level 4-tranylcypromine or venlafaxine XR + mirtazapine.
Results: Remission rates were 28% for Level 1, 17% for Level 2, 12-25% for Level 3, and 7-14% for Level 4. When more treatment steps are required, there are lower remission rates, greater degrees of tolerance, and higher rates of relapse.

Long term lithium use can lead to a nephropathy and diabetes insipidus in some patients.

**Lithium Side Effects**
Lithivm
Leukocytosis
Insipidus (diabetes)
Tremor, teratogenicity
Hyperthyroidism
Increased weight
“V”omiting, nausea
Miscellaneous (e.g. ECG changes, acne)
### Table 23. Commonly Used Mood Stabilizers

<table>
<thead>
<tr>
<th>Lithium</th>
<th>Lamotrigine (Lamictal®)</th>
<th>Divalproex (Epival®)</th>
<th>Carbamazepine (Tegretol®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications</td>
<td>Maintenance therapy of bipolar disorder</td>
<td>Treatment of bipolar disorder</td>
<td>Maintenance therapy of bipolar disorder</td>
</tr>
<tr>
<td></td>
<td>Treatment of acute mania</td>
<td></td>
<td>Treatment of acute mania</td>
</tr>
<tr>
<td></td>
<td>Augmentation of antidepressants in MDE and OCD</td>
<td>Rapid cycling bipolar disorder</td>
<td>Rapid cycling bipolar disorder</td>
</tr>
<tr>
<td></td>
<td>Schizoaffective disorder</td>
<td>Mixed phase/Dysphoric mania</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic aggression and antisocial behaviour</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrent depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of Action</td>
<td>Unknown</td>
<td>May inhibit 5-HT3 receptors</td>
<td>Depresses synaptic transmission</td>
</tr>
<tr>
<td></td>
<td>Therapeutic response within 7-14 d</td>
<td>May potentiate DA activity</td>
<td>Raises seizure threshold</td>
</tr>
<tr>
<td>Dosage</td>
<td>Adult: 600-1500 mg/d</td>
<td>Depresses synaptic transmission</td>
<td>Raises seizure threshold</td>
</tr>
<tr>
<td></td>
<td>Geriatric: 150-600 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Usually daily dosing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Starting: 12.5-15 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Daily dose: 100-200 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose adjusted in patients taking other anticonvulsants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic Level</td>
<td>Adult: 0.5-1.2 mmol/L (1.0-1.25 mmol/L for acute mania)</td>
<td>Therapeutic plasma level not established</td>
<td>17-50 mmol/L</td>
</tr>
<tr>
<td></td>
<td>Geriatric: 0.3-0.8 mmol/L</td>
<td>Dosing based on therapeutic response</td>
<td>350-700 µmol/L</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Monitor serum levels until therapeutic (always wait 12 h after dose)</td>
<td>Monitor for suicidality, particularly when initiating treatment</td>
<td>Weekly blood counts for first month, due to risk of agranulocytosis</td>
</tr>
<tr>
<td></td>
<td>Then monitor biweekly or monthly until a steady state is reached, then q2mo</td>
<td>Watch for signs of liver dysfunction: nausea, edema, malaise</td>
<td>Watch for signs of blood dyscrasias: fever, rash, sore throat, easy bruising</td>
</tr>
<tr>
<td>Side Effects</td>
<td>GI: N/V, diarrhea, stomach pain</td>
<td>GI: N/V, diarrhea</td>
<td>GI: N/V, diarrhea, hepatic toxicity</td>
</tr>
<tr>
<td></td>
<td>GU: polyuria, polydipsia, GN, renal failure, nephrogenic DI</td>
<td>CNS: ataxia, dizziness, diplopia, headache, somnolence</td>
<td>CNS: ataxia, dizziness, slurred speech, drowsiness, confusion, nyctaglobin, diplopia</td>
</tr>
<tr>
<td></td>
<td>CNS: fine tremor, lethargy, fatigue, headache</td>
<td>Skin: rash (should d/c drug because of risk of Stevens-Johnson syndrome), increased lamotrigine levels = increased risk of rash</td>
<td>Hematologic: transient leukopenia (10%), agranulocytosis, aplastic anemia</td>
</tr>
<tr>
<td></td>
<td>Hematologic: reversible leukocytosis</td>
<td>Other: anxiety</td>
<td>Skin: rash (5% risk; should d/c drug because of risk of Stevens-Johnson syndrome)</td>
</tr>
<tr>
<td></td>
<td>Other: teratogenic (Ebstein’s anomaly), weight gain, edema, psoriasis, hypertension, hair thinning, muscle weakness, ECG changes</td>
<td></td>
<td>Other: neural tube defects when used in pregnancy</td>
</tr>
<tr>
<td>Interactions</td>
<td>NSAIDs decrease clearance</td>
<td>OCP</td>
<td>OCP</td>
</tr>
</tbody>
</table>

### Anxiolytics

- **anxiolytics** mask or alleviate symptoms; they do not cure them
- **indications**
  - short term treatment of transient forms of anxiety disorders, insomnia, alcohol withdrawal (especially delirium tremens), barbiturate withdrawal, organic brain syndrome (agitation in dementia), EPS and akathisia due to antipsychotics, seizure disorders, musculoskeletal disorders
- **relative contraindications**
  - major depression (except as an adjunct to other treatment), history of drug/alcohol abuse, pregnancy, breast feeding
- **mechanism of action**
  - benzodiazepines: potentiates binding of GABA to its receptors; results in decreased neuronal activity
  - buspirone: partial agonist of 5-HT1A receptors

### Benzodiazepines

- should be used for limited periods (weeks-months) to avoid dependence
- all benzodiazepines are sedating; be wary in use for the elderly
- have similar efficacy, so choice depends on half-life, metabolites and route of administration, OD or bid
- taper slowly over weeks-mo because they can cause withdrawal reactions
- low dose withdrawal: tachycardia, hypertension, panic, insomnia, anxiety, impaired memory and concentration, perceptive disturbances
- high dose withdrawal: hyperpyrexia, seizures, psychosis, death
- avoid alcohol because of potentiation of CNS depression; caution with drinking and use of machinery
• side effects
  • CNS: drowsiness, cognitive impairment, reduced motor coordination, memory impairment
  • physical dependence, tolerance develops
• withdrawal
  • symptoms: anxiety, insomnia, autonomic hyperactivity (less common)
  • onset: 1-2 d (short-acting), 2-4 d (long-acting)
  • duration: weeks/months
  • complications: above 50 mg diazepam/day: seizures, delirium, arrhythmias, psychosis
  • management: taper with long-acting benzodiazepine
  • similar to but less severe than alcohol withdrawal; can be fatal
• overdose
  • commonly used drug in overdose
  • overdose is rarely fatal
  • benzodiazepines are more dangerous and may cause death when combined with alcohol, other CNS depressants or TCAs

Benzodiazepine Antagonist – Flumazenil (Anexate®)
• use for suspected benzodiazepine overdose
• specific antagonist at the benzodiazepine receptor site

Buspirone (Buspar®)
• primary use: GAD
• may be preferred over benzodiazepines because:
  • non-sedating
  • no interaction with alcohol
  • does not alter seizure threshold
  • not prone to abuse
• onset of action: 2 wk
• side effects: dizziness, drowsiness, nausea, headache, nervousness, EPS

Table 24. Common Anxiolytics

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dose Range (mg/d)</th>
<th>t½ (h)</th>
<th>Appropriate Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>clonazepam (Rivotril®)</td>
<td>0.25-4</td>
<td>18-50</td>
<td>Akathisia, generalized anxiety, seizure prevention, panic disorder</td>
</tr>
<tr>
<td></td>
<td>diazepam (Valium®)</td>
<td>2-40</td>
<td>30-100</td>
<td>Generalized anxiety, seizure prevention, muscle relaxant, alcohol withdrawal</td>
</tr>
<tr>
<td></td>
<td>chlorazepoxide (Librium®)</td>
<td>5-300</td>
<td>30-100</td>
<td>Sleep, anxiety, alcohol withdrawal</td>
</tr>
<tr>
<td></td>
<td>flurazepam (Dalmane®)</td>
<td>15-30</td>
<td>50-160</td>
<td>Sleep</td>
</tr>
<tr>
<td></td>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>alprazolam (Xanax®)</td>
<td>0.25-4.0</td>
<td>6-20</td>
<td>Panic disorder, high dependency rate</td>
</tr>
<tr>
<td></td>
<td>lorazepam (Ativan®)</td>
<td>0.5-6.0</td>
<td>10-20</td>
<td>Sleep, generalized anxiety, akathisia, alcohol withdrawal, sublingual available for very rapid action</td>
</tr>
<tr>
<td></td>
<td>oxazepam (Serax®)</td>
<td>10-120</td>
<td>8-12</td>
<td>Sleep, generalized anxiety, alcohol withdrawal</td>
</tr>
<tr>
<td></td>
<td>temazepam (Restoril®)</td>
<td>7.5-30</td>
<td>8-20</td>
<td>Sleep</td>
</tr>
<tr>
<td></td>
<td>triazolam (Halcion®)</td>
<td>0.125-0.5</td>
<td>1.5-5</td>
<td>Shortest t½, rapid sleep, but rebound insomnia</td>
</tr>
<tr>
<td>Azapirones</td>
<td>buspirone (Buspar®)</td>
<td>20-60</td>
<td>2-11</td>
<td>Generalized anxiety</td>
</tr>
<tr>
<td></td>
<td>zopiclone (Imovane®)</td>
<td>5-7.5</td>
<td>3.8-6.5</td>
<td>Sleep</td>
</tr>
</tbody>
</table>

**Electroconvulsive Therapy**
• induction of a grand mal seizure using an electrical pulse through the brain while the patient is under general anesthesia with a muscle relaxant
• unilateral vs. bilateral electrode placement
• indications
  • depression refractory to adequate pharmacological trial
  • high suicide risk
  • medical risk in addition to depression (dehydration, electrolytes, pregnancy)
  • previous good response to ECT
  • familial response to ECT
  • elderly

**Benzodiazepines used for Alcohol Withdrawal**
• Diazepam 20 mg PO/IV q1h prn
• Lorazepam 2-5 mg PO/IV/SI for patients with liver disease, chronic lung disease, or elderly

**Geriatric Benzodiazepines**
LOT
lorazepam
Oxazepam
Temazepam
Safe in liver disease because not metabolized by liver

**ECT in Society**
Prior to the 1940’s, ECT was performed without the use of muscle relaxants, resulting in seizures with full-scale convulsions and rare but serious complications such as vertebral and long-bone fractures. This practice may have led to negative societal perceptions of ECT, further perpetuated by barbaric depictions in popular culture. Despite ongoing stigmatization, ECT as it is practiced today is an effective and safe option for patients struggling with mental illness.
- psychotic depression
- catatonic features
- marked vegetative features
- acute schizophrenia
- mania unresponsive to medications
- side effects: risk of anesthesia, memory loss (may be retrograde and/or anterograde, tends to resolve by 6 to 9 mo, permanent impairment controversial), headaches, myalgias
- evidence that unilateral ECT causes less memory loss than bilateral but may not be as effective
- contraindications: increased intracranial pressure

### Experimental Therapies

**Deep Brain Stimulation (DBS)**
- constant electrical stimulation of neuroanatomical targets that have been identified in the biological model of depression
- areas identified include the nucleus accumbens, internal capsule and subgenual cingulate cortex
- parameters such as active electrode location, pulse width, frequency and voltage may be manipulated

**Transcranial Magnetic Stimulation (TMS)**
- non-invasive magnetic stimulation of superficial neurons in the frontal cortex (main target: dorsolateral prefrontal cortex) hypothesized to normalize cortical activity in depressed patients
- meta-analyses show modest acute efficacy

**Vagal Nerve Stimulation**
- an invasive surgical procedure: a battery powered pulse generator is implanted in the chest wall and connected to an electrode that is attached around one (typically the left) vagus nerve
- meta-analyses show a greater response and remission rates for treatment resistant depression if combined with usual treatment (versus usual treatment alone)
- not indicated for use in acute illness

### Canadian Legal Issues

**Table 25. Common Forms Under the Mental Health Act (in Ontario)**

<table>
<thead>
<tr>
<th>Form</th>
<th>Who Signs</th>
<th>When</th>
<th>Expiration Date</th>
<th>Right of Patient to Review Board Hearing</th>
<th>Options Before Form Expires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form 1: Application by physician to hospitalize a patient for psychiatric assessment against his/her will to a schedule 1 facility (Form 42 given to patient)</td>
<td>Any MD</td>
<td>Within 7 d after examination of the patient</td>
<td>72 h after hospitalization Void if not implemented within 7 d</td>
<td>No</td>
<td>Form 3 or voluntary admission (Form 5) or Send home ± Follow up</td>
</tr>
<tr>
<td>Form 2: Order for hospitalization and medical examination against his/her will by Justice of the Peace</td>
<td>Justice of the Peace</td>
<td>No statutory time restriction</td>
<td>7 d from when completed Purpose of form is complete once patient brought to hospital</td>
<td>No</td>
<td>Form 1 or Send home ± Follow up</td>
</tr>
<tr>
<td>Form 3: Certificate of involuntary admission to a schedule 1 facility (Form 30 given to patient, notice to rights advisor)</td>
<td>Attending MD (different than MD who completed Form 1)</td>
<td>Before expiration of Form 1 Any time to change status of involuntary patient</td>
<td>14 d</td>
<td>Yes (within 48 h)</td>
<td>Form 4 or Form 5</td>
</tr>
</tbody>
</table>

**Form 1: Application for Psychiatric Assessment**
- Filled out when a patient is suspected of being an imminent harm to themselves (suicide) or others (homicide) or when they are incapable of self-care (e.g. not dressed for freezing weather) and are suffering from an apparent mental disorder
- Based on any combination of the physician’s own observations and facts communicated by others
- Box A or Box B completed
- Box A: Serious Harm Test
- The Past/Present Test assesses current behaviours/threats/attempts
- The Future Test assesses the likelihood of serious harm occurring as a result of the presenting mental disorder. In this section, one should document evidence of the mental disorder
- Box B: Patients with a known mental disorder, who are incapable of consenting to treatment (existing substitute decision-maker), have previously received treatment and improved, and are currently at risk of serious harm due to the same mental disorder
Table 25. Common Forms Under the Mental Health Act (in Ontario) (continued)

<table>
<thead>
<tr>
<th>Form</th>
<th>Who Signs</th>
<th>When</th>
<th>Expiration Date</th>
<th>Right of Patient to Review Board Hearing</th>
<th>Options Before Form Expires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form 4: Certificate of renewal of involuntary admission to a schedule 1 facility (Form 30 given to patient, notice to rights advisor)</td>
<td>Attending MD following patient on Form 3</td>
<td>Prior to expiration of Form 3</td>
<td>First: 1 mo Second: 2 mo Third: 3 mo (max)</td>
<td>Yes (within 48 h)</td>
<td>Form 4 or Form 5</td>
</tr>
<tr>
<td>Form 5: Change to informal/voluntary status</td>
<td>Attending MD following patient on Form 3/4</td>
<td>Whenever deemed appropriate</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Form 30: Notice to patient on certification on Form 3 or Form 4</td>
<td>Attending MD</td>
<td>At time of completion of Form 3 or 4</td>
<td>N/A</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>Form 33: Notice to patient that patient is incompetent to consent to treatment of mental disorder and/or management of property</td>
<td>Attending MD</td>
<td>Whenever deemed appropriate</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Schedule 1 Facilities: Able to provide intensive inpatient and outpatient care

Consent

- see [Ethical, Legal and Organizational Aspects of Medicine, ELOAM5](#)

Community Treatment Order (CTO)

- known as “Brian’s Law,” Ontario passed legislature regarding CTOs on December 1, 2000
- similar CTOs have been implemented in Saskatchewan (1995), Manitoba (1997) and British Columbia (1999)
- purpose: to provide a person who suffers from a serious mental disorder with a comprehensive plan of community-based treatment and supervision that is less restrictive than being detained in a psychiatric facility
- intended for those who:
  - as a result of their serious mental disorder, experience a pattern of admission to a psychiatric facility where their condition is usually stabilized
  - after being released, these patients often lack supervision and stop treatment
  - due to the destabilization of their condition, these patients usually require re-admission to hospital
- criteria for a physician to issue a CTO
  - patient with a prior history of hospitalization
  - a community treatment plan for the person has been made
  - examination by a physician within the previous 72 h before entering into the CTO plan
  - ability of the person subject to the CTO to comply with it
  - consultation with a rights adviser and consent of the person and the person’s substitute decision maker, if any
- CTOs are valid for 6 mo unless they are renewed or terminated at an earlier date
  - where the person fails to comply with the CTO
  - when the person or his/her substitute decision-maker withdraws consent to the community treatment plan
- CTO process is consent-based and all statutory protections governing informed consent apply
- the rights of a person subject to a CTO include:
  - the right to a review by the Consent and Capacity Board with appeal to the courts each time a CTO is issued or renewed
  - a mandatory review by the Consent and Capacity Board every second time a CTO is renewed
  - the right to request a re-examination by the issuing physician to determine if the CTO is still necessary for the person to live in the community
  - the right to review findings of incapacity to consent to treatment
  - provisions for rights advice
Textbooks


Koch T. A tour of the psychotropics, 4th ed. Toronto: Mental Health Service, St Michael’s Hospital.


Journals


Linehan MM, et al. Two year randomized controlled trial and follow-up of dialectical behaviour therapy vs. therapy by experts for suicidal behaviours and boderline personality disorder. Arch Gen Psychiat 2001;63:757-768.


Websites
Respirology

Amanda Goldberg, Sicong Huang and Joanna Willms, chapter editors
Grace Lam and Hamed Nazzari, associate editors
Gautam Goel, EBM editor
Dr. Meyer Balter, staff editor

Acronyms ............................................ 2

Approach to the Respiratory Patient ........ 2
Basic Anatomy Review
Differential Diagnoses of Common Presentations
Pulmonary Function Tests (PFTs)
Chest X-Rays
Arterial Blood Gases

Diseases of Airway Obstruction ............. 6
Pneumonia
Asthma
Chronic Obstructive Pulmonary Disease (COPD)
Bronchiectasis
Cystic Fibrosis (CF)

Interstitial Lung Disease (ILD) ............... 12
Unknown Etiologic Agents
  Idiopathic Pulmonary Fibrosis (IPF)
  Sarcoïdosis
Known Etiologic Agents
  Hypersensitivity Pneumonitis
  Pneumoconioses
  ILD Associated with Drugs or Treatments

Pulmonary Vascular Disease .................. 16
Pulmonary Hypertension
  Idiopathic Pulmonary Arterial Hypertension
Pulmonary Embolism (PE)
Pulmonary Vasculitis
Pulmonary Edema

Diseases of the Mediastinum and Pleura . . . 20
Mediastinal Masses
Mediastinitis
Pleural Effusions
Complicated Parapneumonic Effusion
Empyema
Atelectasis
Pneumothorax
Asbestos-Related Pleural Disease and
Mesothelioma

Respiratory Failure ............................. 24
Hypoxemic Respiratory Failure
Hypercapnic Respiratory Failure
Acute Respiratory Distress Syndrome (ARDS)
Mechanical Ventilation

Neoplasms ........................................ 27
Lung Cancer
Approach to the Solitary Pulmonary Nodule

Sleep-Related Breathing Disorders ........... 31
Hypoventilation Syndromes
Sleep Apnea

Introduction to Intensive Care ............... 32
ICU Basics
Organ Failure
Shock
Sepsis

Common Medications ........................... 34

Landmark Respirology Trials ................. 35

References ........................................ 36
**Acronyms**

A-a  alveolar-arterial
A-aDO₂ alveolar-arterial oxygen diffusion gradient
ABG arterial blood gas
ACEI angiotensin converting enzyme inhibitor
ACH assist-control ventilation
AECOPD acute exacerbation of COPD
AFB acid-fast bacillus
AGP acute glomerulonephritis
AIH autoimmune hepatitis
ANA antinuclear antibody
ANCA anti-neutrophil cytoplasmic antibody
APAP acetaminophen
APTT activated partial thromboplastin time
AQP aquaporin
ASD atrial septal defect
ASA acetylsalicylic acid (Aspirin)
ASE angiographic stenting of the external carotid artery
ASYT syphilis
A-aDO₂ alveolar-arterial oxygen diffusion gradient
A-aDO₂ alveolar-arterial oxygen diffusion gradient
A-aDO₂ alveolar-arterial oxygen diffusion gradient
ARDS acute respiratory distress syndrome
ART ECO 2 ART ECO 2 ART ECO 2 ART ECO 2 ART ECO 2
eca 2 eca 2 eca 2 eca 2 eca 2
eca 2 eca 2 eca 2 eca 2 eca 2
eca 2 eca 2 eca 2 eca 2 eca 2
eca 2 eca 2 eca 2 eca 2 eca 2
eca 2 eca 2 eca 2 eca 2 eca 2
eca 2 eca 2 eca 2 eca 2 eca 2

**Approach to the Respiratory Patient**

**Basic Anatomy Review**

- **Figure 1. Lung lobes and bronchi**
- **Figure 2. Respiration patterns in normal and disease states**

- **Respiration Pattern**
  - Normal
  - Obstructive (prolonged expiration)
    - Asthma, COPD
  - Bradynea (slow respiratory rate)
    - Drug-induced respiratory depression
    - Diabetic coma (nonketotic)
    - Increased ICP
  - Kussmaul’s Breathing (fast and deep)
    - Metabolic acidosis
    - Exercise
    - Anxiety
  - Biot’s/Ataxic
    - Irregular with long apneic periods
    - Drug-induced respiratory depression
    - Increased ICP
    - Brain damage, especially medullary
  - Cheyne-Stokes Breathing (changing rates and depths with apneic periods)
    - Drug-induced respiratory depression
    - Brain damage (especially cerebral)
    - CHF
    - Uremia
  - Apneastic (prolonged inspiratory pause)
    - Pontine lesion

- **Normal ventilation**
  - **Obstructive (prolonged expiration)**
    - Asthma, COPD
  - **Bradynea (slow respiratory rate)**
    - Drug-induced respiratory depression
    - Diabetic coma (nonketotic)
    - Increased ICP
  - **Kussmaul’s Breathing (fast and deep)**
    - Metabolic acidosis
    - Exercise
    - Anxiety
  - **Biot’s/Ataxic**
    - Irregular with long apneic periods
    - Drug-induced respiratory depression
    - Increased ICP
    - Brain damage, especially medullary
  - **Cheyne-Stokes Breathing** (changing rates and depths with apneic periods)
    - Drug-induced respiratory depression
    - Brain damage (especially cerebral)
    - CHF
    - Uremia
  - **Apneastic (prolonged inspiratory pause)**
    - Pontine lesion

© Hyun-Joo Lee 2005

---

© Bonnie Tang 2012
Differential Diagnoses of Common Presentations

Table 1. Differential Diagnosis of Dyspnea

<table>
<thead>
<tr>
<th>Acute dyspnea (minutes-hours)</th>
<th>Nonpleuritic Pulmonary</th>
<th>Pleuritic Pulmonary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac causes</td>
<td>Pulmonary</td>
<td>Pulmonary</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>Pneumonia</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>CHF exacerbation</td>
<td>PE</td>
<td>PE</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>Neoplastic</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Upper airway obstruction</td>
<td>MI</td>
<td>Hemothorax</td>
</tr>
<tr>
<td>(anaphylaxis, foreign body)</td>
<td>Myocarditis/pericarditis</td>
<td>Neoplasm</td>
</tr>
<tr>
<td>Chronic dyspnea (weeks-months)</td>
<td>Pulmonary</td>
<td>TB</td>
</tr>
<tr>
<td>Pulmonary causes</td>
<td>Esophageal</td>
<td>Empyema</td>
</tr>
<tr>
<td>Acute dyspnea (minutes-hours)</td>
<td>GERD</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Upper airway obstruction</td>
<td>Spasm</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>(anaphylaxis, foreign body)</td>
<td>Esophagitis</td>
<td>Dressler’s syndrome</td>
</tr>
<tr>
<td>Parenchymal lung disease</td>
<td>Ulceration</td>
<td>GI</td>
</tr>
<tr>
<td>(ARDS, pneumonia)</td>
<td>Achalasia</td>
<td>Subphrenic</td>
</tr>
<tr>
<td>Pulmonary vascular disease</td>
<td>Neoplasm</td>
<td>abscess</td>
</tr>
<tr>
<td>(PE, vasculitis)</td>
<td>Esophageal rupture</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Pleural disease (PE, vasculitis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory causes</td>
<td>Mediastinal</td>
<td></td>
</tr>
<tr>
<td>Chronic dyspnea (weeks-months)</td>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td>Cardiac causes</td>
<td>Thymoma</td>
<td></td>
</tr>
<tr>
<td>Upper airway obstruction</td>
<td>Subdiaphragmatic</td>
<td></td>
</tr>
<tr>
<td>(anaphylaxis, foreign body)</td>
<td>PUD</td>
<td></td>
</tr>
<tr>
<td>Parenchymal lung disease</td>
<td>Gastritis</td>
<td></td>
</tr>
<tr>
<td>(interstitial disease)</td>
<td>Biliary colic</td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular disease</td>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>(pulmonary HTN, vasculitis)</td>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Airway disease – asthma, COPD</td>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Hematologic causes</td>
<td>Musculoskeletal (MSK)</td>
<td></td>
</tr>
<tr>
<td>Severe anemia</td>
<td>Cardiac</td>
<td></td>
</tr>
<tr>
<td>Neurmuscular and chest wall disorders</td>
<td>Respiratory control (metabolic acidosis, ASA toxicity)</td>
<td></td>
</tr>
<tr>
<td>Deconditioning, obesity, pregnancy, neuromuscular disease</td>
<td>Respiratory control (metabolic acidosis, ASA toxicity)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Differential Diagnosis of Clubbing

<table>
<thead>
<tr>
<th>Pulmonary</th>
<th>Gastrointestinal</th>
<th>Mediastinal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>IBD (UC, CD)</td>
<td>Esophageal CA</td>
<td>Grave’s Disease</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>Chronic infections</td>
<td>Thymoma</td>
<td>Thalassemia</td>
</tr>
<tr>
<td>Chronic pus in the lung</td>
<td>Laxative abuse</td>
<td>Other</td>
<td>Other malignancies</td>
</tr>
<tr>
<td>(bronchiectasis, abscess, infections, etc.)</td>
<td>Polyposis</td>
<td>Other</td>
<td>Primary hypertrophic osteoarthropathy</td>
</tr>
<tr>
<td>Lung CA (primary or mets)</td>
<td>Malignant tumours</td>
<td>Mediastinal</td>
<td>Lung abscess</td>
</tr>
<tr>
<td>A-V fistula</td>
<td>Cirrhosis</td>
<td>Other</td>
<td>Other malignancies</td>
</tr>
<tr>
<td>Solitary fibrous tumour of pleura</td>
<td>Hepatocellular carcinoma</td>
<td>Other</td>
<td>Primary hypertrophic osteoarthropathy</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Cardiac</td>
<td>Other</td>
<td>Primary hypertrophic osteoarthropathy</td>
</tr>
<tr>
<td>Cystic congenital heart disease</td>
<td>Infective endocarditis</td>
<td>Other</td>
<td>Primary hypertrophic osteoarthropathy</td>
</tr>
</tbody>
</table>

Table 3. Differential Diagnosis of Hemoptysis

<table>
<thead>
<tr>
<th>Airway Disease</th>
<th>Inhaled smoke, dusts, fumes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute or chronic bronchitis</td>
<td>Postnasal drip (upper airway cough syndrome)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Bronchogenic CA</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Bronchial carcinoma tumour</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Parenchymal Disease</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>TB</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Lung abscess</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Vascular Disease</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>PE</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Elevated pulmonary venous pressure:</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>LVF</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Vascular malformation</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Vascularity</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Goodpasture’s syndrome</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Idiopathic pulmonary hemosiderosis</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Impaired coagulation</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Pulmonary endometriosis</td>
<td>Bronchitis</td>
</tr>
</tbody>
</table>

Table 4. Differential Diagnosis of Cough

<table>
<thead>
<tr>
<th>Airway Irritants</th>
<th>Inhaled smoke, dusts, fumes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-nasal drip</td>
<td>Postnasal drip (upper airway cough syndrome)</td>
</tr>
<tr>
<td>Asthma</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>GERD</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Post-nasal drip syndrome</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Foreign body</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Airway Disease</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>URTI including postnasal drip and sinusitis</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Acute or chronic bronchitis</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Normal</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Respiratory Distress</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Increased RR</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Nasal flaring</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Central/peripheral cyanosis</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Tracheal tug</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Inability to speak</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Accessory muscle use and tripoding</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Intercostal indrawing</td>
<td>Bronchitis</td>
</tr>
</tbody>
</table>

Table 5. Differential Diagnosis of Clubbing

<table>
<thead>
<tr>
<th>Pulmonary</th>
<th>Gastrointestinal</th>
<th>Mediastinal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>IBD (UC, CD)</td>
<td>Esophageal CA</td>
<td>Grave’s Disease</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>Chronic infections</td>
<td>Thymoma</td>
<td>Thalassemia</td>
</tr>
<tr>
<td>Chronic pus in the lung</td>
<td>Laxative abuse</td>
<td>Other</td>
<td>Other malignancies</td>
</tr>
<tr>
<td>(bronchiectasis, abscess, infections, etc.)</td>
<td>Polyposis</td>
<td>Other</td>
<td>Primary hypertrophic osteoarthropathy</td>
</tr>
<tr>
<td>Lung CA (primary or mets)</td>
<td>Malignant tumours</td>
<td>Mediastinal</td>
<td>Other malignancies</td>
</tr>
<tr>
<td>A-V fistula</td>
<td>Cirrhosis</td>
<td>Other</td>
<td>Primary hypertrophic osteoarthropathy</td>
</tr>
<tr>
<td>Solitary fibrous tumour of pleura</td>
<td>Hepatocellular carcinoma</td>
<td>Other</td>
<td>Primary hypertrophic osteoarthropathy</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Cardiac</td>
<td>Other</td>
<td>Primary hypertrophic osteoarthropathy</td>
</tr>
<tr>
<td>Cystic congenital heart disease</td>
<td>Infective endocarditis</td>
<td>Other</td>
<td>Primary hypertrophic osteoarthropathy</td>
</tr>
</tbody>
</table>

Adapted from Principles of Pulmonary Medicine, 5th edition, SE Weinberger, Copyright (2008), with permission from Elsevier.
Pulmonary Function Tests (PFTs)

- useful in differentiating the pattern of lung disease (obstructive vs. restrictive) (Table 6)
- assess lung volumes, flow rates, and diffusion capacity (see Figures 4a and 4b)
- note: normal values for FEV₁ are approximately ±20% of the predicted values (for age, sex and height); ethnicity may affect predicted values

Table 6. Comparison of Lung Flow and Volume Parameters in Obstructive vs. Restrictive Lung Disease

<table>
<thead>
<tr>
<th></th>
<th>Obstructive</th>
<th>Restrictive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DDx</strong></td>
<td>Asthma, COPD, CF, bronchiolitis, bronchiectasis*</td>
<td>ILD, pleural disease, neuromuscular disease, chest wall disease</td>
</tr>
<tr>
<td><strong>FEV₁/FVC</strong></td>
<td>↓ or N</td>
<td>↑ or N</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td>↑ or N</td>
<td>↓ or N</td>
</tr>
<tr>
<td><strong>RV</strong></td>
<td>↑ or N</td>
<td>↓ or N</td>
</tr>
<tr>
<td><strong>RV/TLC</strong></td>
<td>↑ or N</td>
<td>↓ or N</td>
</tr>
<tr>
<td><strong>DLCO</strong></td>
<td>↓ or N</td>
<td>↓ or N</td>
</tr>
</tbody>
</table>

*Bronchiectasis can be obstructive or mixed

Plethysmography: involves the use of a plethysmograph (or “body box”) and used to measure FRC. After a normal expiration the patient inhales against a closed mouthpiece. Resultant changes in the volume and pressure of the plethysmograph are used to calculate the volume of gas in the thorax. Useful for patients with air trapping since all air in the thoracic cavity is determined by the calculation.

He dilution: used to measure FRC by diluting a known amount of helium into a patient’s lungs following inspiration. Since the amount of helium remains constant, FRC is determined based on the final concentration of the helium in the closed system. Only includes airspaces that communicate with the bronchial tree.

Bronchoscopy: a flexible or rigid bronchoscope is used for visualization of a patient’s airways for diagnostic and therapeutic indications. It is used to obtain tissue washings for culture and cytology, endobronchial or transbronchial tissue biopsies, remove secretions/foreign bodies/blood, laser resections, airway stenting, etc. Mediastinal lymph nodes can also be sampled using a special bronchoscope equipped with an U/S probe (EBUS).

**Figure 4A. Subcompartments of lung volumes**

Adapted with permission from Elsevier. Weinberger SE. Principles of pulmonary medicine, 5th ed. ©2008

**Figure 4B. Expiratory flow volume curves**

Chest X-Rays

- see also Medical Imaging, MI4

Table 7. CXR Patterns and Differential Diagnosis

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Signs</th>
<th>Common DDx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation</td>
<td>Air bronchogram, Silhouette sign, Less visible blood vessels</td>
<td>Acute: water (pulmonary edema), ase (pneumonia), blood (hemorrhage) Chronic: neoplasm (lymphoma), inflammatory (eosinophilic pneumonia), chronic infection (TB, fungal)</td>
</tr>
<tr>
<td>Reticular</td>
<td>Increased pulmonary markings</td>
<td>ILD (IPF, collagen vascular disease, asbestos, drugs)</td>
</tr>
<tr>
<td>Nodular</td>
<td>Cavity vs. non-cavity</td>
<td>Cavity: neoplasm (primary vs. metastatic lung cancer), infectious (anaerobic or Gram negative, TB, fungal), inflammatory [RA, Granulomatosis with Polyangiitis (GPA)] Non-cavity: above + sarco, Kaposi’s sarcoma (in HIV), silicosis and other pneumoconiosis</td>
</tr>
</tbody>
</table>

Lung Volumes

- **ERV** – Expiratory Reserve Volume
- **FFR** – Forcible Expiratory Flow Rate
- **FEV₁** – Forcible Expiratory Volume (in one second)
- **FRC** – Functional Residual Capacity
- **IC** – Inspiratory Capacity
- **RV** – Residual Volume
- **TLC** – Total Lung Capacity
- **VC** – Vital Capacity
- **V₁** – Tidal Volume
Arterial Blood Gases

- provides information on acid-base and oxygenation status
- see also Nephrology, NP14

Approach to Acid-Base Status

1. Is the pH acidemic (pH < 7.35), alkalemic (pH > 7.45), or normal (pH 7.35-7.45)?
   - metabolic: change in HCO₃⁻ and pH in same direction
   - respiratory: change in HCO₃⁻ and pH in opposite direction

2. What is the primary disturbance?
   - metabolic compensation occurs over 2-3 d reflecting altered renal HCO₃⁻ production and excretion
   - respiratory compensation through ventilatory control of PₐCO₂ occurs immediately
   - inadequate compensation may indicate a second acid-base disorder

<table>
<thead>
<tr>
<th>Disturbance</th>
<th>PₐCO₂ (mmHg)</th>
<th>HCO₃⁻ (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Acidosis</td>
<td>↑ 10</td>
<td>↑ 1</td>
</tr>
<tr>
<td>Respiratory Alkalosis</td>
<td>↓ 10</td>
<td>↓ 2</td>
</tr>
<tr>
<td>Metabolic Acidosis</td>
<td>↓ 1</td>
<td>↓ 1</td>
</tr>
<tr>
<td>Metabolic Alkalosis</td>
<td>↑ 5-7</td>
<td>↑ 10</td>
</tr>
</tbody>
</table>

4. If there is metabolic acidosis, what is the anion gap and osmolar gap?
   - anion gap = [Na⁺]–([Cl⁻]+[HCO₃⁻]); normal ≤10-15 mmol/L
   - osmolar gap = measured osmolarity – calculated osmolarity = measured – (2[Na⁺] + glucose + urea); normal ≤10

5. If anion gap is increased, is the change in bicarbonate the same as the change in anion gap?
   - if not, consider a mixed metabolic picture

Table 8. Expected Compensation for Specific Acid-Base Disorders

- see Nephrology, NP14 for differential diagnosis of metabolic acidosis and alkalosis

Diffusion Capacity for Carbon Monoxide (DLCO)
DLCO decreases with:
- Decreased surface area (e.g. emphysema)
- Decreased hemoglobin
- Interstitial lung disease
- Pulmonary vascular disease
DLCO increases with:
- Asthma
- Pulmonary hemorrhage
- Polythemia
- Increased pulmonary blood volume

Note: Mixed acid-base disturbances can still have a “normal pH”

Ventilation Failure:
Think “Can’t Breathe” vs. “Won’t Breathe” (increased PₐCO₂)
Can’t Breathe
- Neuromuscular disorders
- Airway obstruction
- Parenchymal disease
Won’t Breathe
- Respiratory centre depression
- Hypothyroidism
- Sleep apnea (central)

Anion Gap Metabolic Acidosis
KARMEL
Ketoacidosis
ASA
Renal failure (uremia)
Methanol
Ethylene glycol
Lactic acidosis
MUDPILES CAT
Methanol
Uremia
Diabetic ketoacidosis/starvation ketoacidosis
Phenformin/Paraldehyde
Isoniazid, Iron, Ibuprofen
Lactate
Ethylene glycol
Salicylates
Cyanide, Carbon dioxide
Alcoholic ketoacidosis
Tokena, Theophylline

Acidosis ↔ Hyperkalemia
Alkalosis ↔ Hypokalemia

- see Nephrology, NP14 for differential diagnosis of metabolic acidosis and alkalosis
Approach to Hypoxemia

1. $P_aO_2$: What is the arterial oxygen tension? (Measured by ABG. Normal = 95-100 mmHg)
2. A-aDO$_2$: What is the oxygen gradient between alveoli and pulmonary capillaries? (Calculate. See sidebar. Normal <15 mmHg but increases with age)
3. What is the cause of the hypoxemia? (see Figure 7)

Figure 7. Approach to hypoxemia

Figure 8. Pathophysiology of shunt

Diseases of Airway Obstruction

Pneumonia

• see Infectious Diseases, ID8

Asthma

• see also Family Medicine, FM16 and Pediatrics, P94

Definition

• chronic inflammatory disorder of the airways resulting in episodes of reversible bronchospasm causing airflow obstruction
• associated with reversible airflow limitation and airway hyper-responsiveness to endogenous or exogenous stimuli

Epidemiology

• common, 7-10% of adults, 10-15% of children
• most children with asthma significantly improve in adolescence
• often family history of atopy (asthma, allergic rhinitis, eczema)
• occupational asthma (organic allergies, isocyanates, animals, etc.)
Pathophysiology
- airway obstruction → V/Q mismatch → hypoxemia → ↑ ventilation → ↓ P\textsubscript{a}CO\textsubscript{2} → ↑ pH and muscle fatigue → ↓ ventilation, ↑ P\textsubscript{a}CO\textsubscript{2}/↓ pH

Triggers
- URTIs, allergens (pet dander, house dust, moulds), irritants (cigarette smoke, air pollution), drugs (NSAIDs, β-blockers), preservatives (sulphites, MSG), other (emotion/anxiety, cold air, exercise, GERD)

Signs and Symptoms
- dyspnea, wheezing, chest tightness, cough (especially nocturnal), sputum
- symptoms can be paroxysmal or persistent
- signs of respiratory distress (see sidebar R3)
- pulsus paradoxus

Table 11. Criteria for Determining if Asthma is Well Controlled

<table>
<thead>
<tr>
<th>Daytime symptoms &lt;4 d/wk</th>
<th>Night-time symptoms &lt;1 night/wk</th>
<th>Physical activity normal</th>
<th>Exacerbations mild, infrequent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No asthma-related absence from work/school</td>
<td>↓ FEV\textsubscript{1}/FVC &lt; lower limit of normal (&lt;0.75 to 0.8 in adults, &lt;0.8-0.9 in children age 6+)</td>
<td>FEV\textsubscript{1} or PEF &gt;90% of personal best</td>
<td>PEF diurnal variation &lt;10-15%</td>
</tr>
</tbody>
</table>

Adapted from Can Respir J 2012; 19:127-164

Investigations
- O\textsubscript{2} saturation
- ABGs (consider in acute exacerbation, along with peak flows, in Emergency Department) decreased P\textsubscript{a}CO\textsubscript{2} during attack (V/Q mismatch)
  - decreased P\textsubscript{a}CO\textsubscript{2} in mild asthma (hyperventilation)
  - normal or increased P\textsubscript{a}CO\textsubscript{2} is an ominous sign: patient is no longer able to hyperventilate (worsened airway obstruction or respiratory muscle fatigue)
- PFTs (do when stable) (see Table 12)

Table 12. Pulmonary Function Criteria for Diagnosis of Asthma

<table>
<thead>
<tr>
<th>Preferred Measurement</th>
<th>Alternative Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry showing reversible airway obstruction</td>
<td>Peak Expiratory Flow Variability</td>
</tr>
<tr>
<td>(1) ↓ FEV\textsubscript{1}/FVC below lower limit of normal (&lt;0.75 to 0.8 in adults, &lt;0.8-0.9 in children age 6+)</td>
<td>(1) ↑ in PEF after a bronchodilator or course of controller therapy</td>
</tr>
<tr>
<td>AND</td>
<td>• Adults: PEF ↑ 60 L/min (min. 20%) OR</td>
</tr>
<tr>
<td>(2) ↑ FEV\textsubscript{1} ≥12% (min. 200 mL in adults) after bronchodilator or controller therapy</td>
<td>• Diurnal variation &gt;8% for twice daily readings (20% for multiple daily readings)</td>
</tr>
<tr>
<td></td>
<td>• Children age 6+: PEF ↑ 20%</td>
</tr>
<tr>
<td></td>
<td>Positive Challenge Test</td>
</tr>
<tr>
<td></td>
<td>(1) Methacholine challenge: PC\textsubscript{20} &lt;4 mg/mL (4-16 mg/mL is borderline; &gt;16 mg/mL is negative) OR</td>
</tr>
<tr>
<td></td>
<td>(2) Post-exercise: ↓ FEV\textsubscript{1} ≥10-15%</td>
</tr>
</tbody>
</table>

Adapted from Can Respir J 2012; 19:127-164

Treatment
- environment: avoid triggers
- patient education: features of the disease, goals of treatment, self-monitoring
- pharmacological
  - symptomatic relief in acute episodes: short-acting β\textsubscript{2}-agonist, anticholinergic bronchodilators, oral steroids, addition of a long acting β\textsubscript{2}-agonist
  - long-term prevention: inhaled/oral corticosteroids, anti-allergic agents, long-acting β\textsubscript{2}-agonists, methylxanthine, LTRA, anti-IgE antibodies (e.g. Xolair®)

Adapted from Can Respir J 2012; 19:127-164
Guidelines for Asthma Management

Regularly Reassess
- Control
- Spirometry or PEF
- Inhaler technique
- Adherence
- Triggers
- Comorbidities
- Sputum eosinophils

<table>
<thead>
<tr>
<th>Prednisone</th>
<th>≤12 yrs: Add LTRA</th>
<th>6-11 yrs: Add LABA or LTRA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥12 yrs: Add LABA*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6-11 yrs: Increase ICS</td>
<td></td>
</tr>
</tbody>
</table>

Inhaled Corticosteroid (ICS)*
*Second-line: Leukotriene Receptor Antagonist (LTRA)

<table>
<thead>
<tr>
<th>≥12 yrs</th>
<th>≤12 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤250 mcg/d</td>
<td>251-500 mcg/d</td>
</tr>
<tr>
<td>Low Dose</td>
<td>Medium Dose</td>
</tr>
<tr>
<td>SABA on Demand</td>
<td>SABA or ICS/LABA** on Demand</td>
</tr>
</tbody>
</table>

Environmental Control, Education, and Written Action Plan

Emergency Management of Asthma (see also Emergency Medicine, ER30)
1. inhaled β2-agonist first line (MDI route and spacer device recommended)
2. systemic steroids (PO or IV, if severe)
3. add anticholinergic therapy ± magnesium sulphate
4. rapid sequence intubation in life-threatening cases (plus 100% O₂, monitors, IV access)
5. SC/IV adrenaline, IV salbutamol if unresponsive
6. corticosteroid therapy at discharge

Chronic Obstructive Pulmonary Disease (COPD)

- see also Family Medicine, FM16

Definition
- progressive, and irreversible condition of the lung characterized by chronic obstruction to airflow with many patients having periodic exacerbations, gas trapping, lung hyperinflation and weight loss
- 2 subtypes (chronic bronchitis or emphysema): usually coexist to variable degrees
- gradual decrease in FEV₁ over time with episodes of acute exacerbations

Table 13. Clinical and Pathologic Features of COPD*

<table>
<thead>
<tr>
<th>Chronic Bronchitis</th>
<th>Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defined clinically: Productive cough on most days for at least 3 consecutive months in 2 successive years Obstruction is due to narrowing of the airway lumen by mucosal thickening and excess mucus</td>
<td></td>
</tr>
<tr>
<td>Defined pathologically: Dilation and destruction of air spaces distal to the terminal bronchiole without obvious fibrosis Decreased elastic recoil of lung parenchyma causes decreased expiratory driving pressure, airway collapse, and air trapping</td>
<td></td>
</tr>
<tr>
<td>2 types: 1) Centriacinar (respiratory bronchioles predominantly affected) Typical form seen in smokers, primarily affects upper lung zones 2) Panacinar (respiratory bronchioles, alveolar ducts, and alveolar sacs affected) Accounts for about 1% of emphysema cases α₁-antitrypsin deficiency, primarily affects lower lobes</td>
<td></td>
</tr>
</tbody>
</table>

*Note that both chronic bronchitis and emphysema can exist without obstruction. Only if obstruction is also present is it termed COPD

**Note that both chronic bronchitis and emphysema can exist without obstruction. Only if obstruction is also present is it termed COPD

Natural Progression of COPD

40s Chronic productive cough, wheezing occasionally
50s 1st acute chest illness
60s Dyspnea on exertion, increasing sputum, more frequent exacerbations
Late Hypoxemia with cyanosis, polycythemia, hypercapnia (morning headaches, cor pulmonale, weight loss

Remember, first line therapy for COPD is smoking cessation.
**Risk Factors**
- smoking is #1 risk factor
- others:
  - environmental: air pollution, occupational exposure, exposure to wood smoke or other bioaerosols, secondhand smoke
  - treatable factors: α-antitrypsin deficiency, bronchial hyperactivity
  - demographic factors: age, family history, male sex, history of childhood respiratory infections, low socioeconomic status

### Signs and Symptoms

#### Table 14. Clinical Presentation and Investigations for Chronic Bronchitis and Emphysema

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis (Blue Bloater*)</td>
<td>Cyanosis (2° to hypoxemia and hypercapnia)</td>
<td>PFT: ↓ FEV₁, ↓ FEV₁/FVC, ↓ TLO, ↓ or ↑ N DLCO</td>
</tr>
<tr>
<td>(Blue Bloater*)</td>
<td>Peripheral edema from RVF (cor pulmonale)</td>
<td>N TLC, ↓ or N DLCO</td>
</tr>
<tr>
<td></td>
<td>Crackles, wheezes</td>
<td>CXR: ↓ AP diameter, ↑ bronchovascular markings, ↑ enlarged heart with cor pulmonale</td>
</tr>
<tr>
<td></td>
<td>Prolonged expiration if obstructive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequently obese</td>
<td></td>
</tr>
<tr>
<td>Emphysema (Pink Puffer*)</td>
<td>Dyspnea (± exertion)</td>
<td>PFT: ↓ FEV₁, ↓ FEV₁/FVC, ↓ TLO (hyperinflation), ↓ RV (gas trapping)</td>
</tr>
<tr>
<td>(Pink Puffer*)</td>
<td>Pursed-lip breathing</td>
<td>↑ DLCO</td>
</tr>
<tr>
<td></td>
<td>Accessory muscle use</td>
<td>CXR: ↓ AP diameter, ↑ flat hemidiaphragm (on lateral CXR), ↑ heart shadow</td>
</tr>
<tr>
<td></td>
<td>Cachectic appearance due to anorexia and increased work of breathing</td>
<td>↑ ↑ retrosternal space</td>
</tr>
<tr>
<td></td>
<td>Hyperinflation/barrel chest, hyperresonant percussion</td>
<td>↑ ↑ ↑ bullae</td>
</tr>
<tr>
<td></td>
<td>Decreased breath sounds</td>
<td>↓ peripheral vascular markings</td>
</tr>
<tr>
<td></td>
<td>Decreased diaphragmatic excursion</td>
<td></td>
</tr>
</tbody>
</table>

*Note that the distinction between “blue bloaters” and “pink puffers” is more of historical than practical interest as most COPD patients have elements of both.

#### Table 15. Treatment of Stable COPD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation</td>
<td>Nicotine replacement, bupropion, varenicline</td>
</tr>
<tr>
<td>Home oxygen</td>
<td>Prevents cor pulmonale and decreases mortality if used &gt; 15% of time; indicated if (1) P₉₀₂ &lt; 55 mmHg or (2) ≥ 60 mmHg with cor pulmonale or polycythemia</td>
</tr>
</tbody>
</table>

**SYMPTOMATIC RELIEF** (no mortality benefit)

- Bronchodilators (mainstay of current drug therapy, used in combination):
  - Short-acting anticholinergics (e.g. ipratropium bromide) and short-acting β₂-agonists (e.g. salbutamol, terbutaline)
  - LABAs (e.g. salmeterol, formoterol, indacaterol) and long-acting anticholinergics (e.g. tiotropium bromide, glycopyrronium bromide)
  - More sustained effects for moderate to severe COPD
- Inhaled corticosteroids (ICS) + LABA combination (e.g. Advair®: fluticasone + salmeterol, Symbicort®: budenoside + formoterol):
  -ICS/LABA increases effectiveness vs. LABA alone
- Theophylline: weak bronchodilator; limited evidence to suggest combination with bronchodilator
- Side effects: nervous tremor, nausea/vomiting/diarrhea, tachycardia, arrhythmias, sleep changes
- PDE4 inhibitor: rufinum (Daxas®) – weak bronchodilator

- Corticosteroids:ICS monotherapy is contraindicated and ICS should only be used with a LABA in combination in patients with a history of exacerbations
- COPD airways are usually inflamed but often not responsive to steroids, therefore avoid chronic systemic glucocorticoids (although oral steroids are very important when treating exacerbations)

- Surgical:
  - Lung volume reduction surgery (section of emphysematous parts of lung, associated with further mortality if FEV₁ < 20%)
  - Lung transplant
  - Patient education, eliminate respiratory irritants/allergens (occupational/environmental), exercise rehabilitation to improve physical endurance

- Other:
  - Patient education, eliminate respiratory irritants/allergens (occupational/environmental), exercise rehabilitation to improve physical endurance

---

**α-1-Antitrypsin Deficiency**

Inherited disorder of defective production of α₁-antitrypsin, a protein produced by hepatocytes. Acts in the alveolar tissue by inhibiting the action of proteases from destroying alveolar tissue. When deficient, proteases can destroy lung alveoli resulting in emphysema.

**Pulmonary Embolism in Patients with Unexplained Exacerbation of COPD**

**Non-invasive Positive Pressure Ventilation for Treatment of Respiratory Failure due to Exacerbations of COPD**

**Primary Outcome:** Treatment failure, mortality, and tracheal intubation.

**Results:** The risks for all primary outcomes were reduced in the NPPV group. The results for mortality were significant (RR 0.52; 95% CI 0.32–0.85), and hospital length of stay was reduced in the NPPV group (0.61 vs. 0.87 days; RR 0.76; 95% CI 0.61–0.95). The results for treatment failure and tracheal intubation were also significant (RR 0.68; 95% CI 0.51–0.91, and RR 0.61; 95% CI 0.45–0.83, respectively).

**Conclusion:** Non-invasive positive pressure ventilation (NPPV) is effective in reducing mortality and tracheal intubation in patients with severe exacerbations of COPD.
Acute Exacerbations of COPD

- definition
  - sustained (>24-48 h) worsening of dyspnea, cough, or sputum production leading to an increased use of medications
- etiology: viral URI, bacteria, air pollution, CHF, PE, MI must be considered
- management
  - ABCs, consider assisted ventilation if decreasing LOC or poor ABGs
  - O₂: target 88-92% SaO₂ for CO₂ retainers
  - bronchodilators by MDI with spacer or nebulizer
  - SABA + anticholinergic, e.g. salbutamol and ipratropium bromide via nebulizers x 3 back-to-back
  - systemic corticosteroids: IV solumedrol or oral prednisone
  - antibiotics if purulent sputum
  - simple exacerbation (no risk factors): amoxicillin, 2nd or 3rd generation cephalosporin, macrolide, or TMP/SMX
  - complicated exacerbation (one of: FEV₁ ≤50% predicted, ≥4 exacerbations per year, ischemic heart disease, home O₂ use, chronic oral steroid use): fluoroquinolone or β-lactam + β-lactamase inhibitor (amoxicillin/clavulanate)
  - post exacerbation: rehabilitation with general conditioning to improve exercise tolerance
- ICU admission
  - for life threatening exacerbations
  - ventilatory support
  - non-invasive: NPPV, BiPAP
  - conventional mechanical ventilation

Prognosis in COPD

- prognostic factors
  - level of dyspnea is the single best predictor
  - development of complications, e.g. hypoxemia or cor pulmonale
  - 5-yr survival
    - FEV₁ <1.0 L = 50%
    - FEV₁ <0.75 L = 33%
  - BODE index for risk of death in COPD
    - greater score = higher probability the patient will die from COPD; score can also be used to predict hospitalization
    - 10 point index consisting of four factors:
      - Body mass index (BMI): <21 (+1 point)
      - Obstruction (FEV₁): 50-64% (+1), 36-49% (+2), <35% (+3)
      - Dyspnea (MRC scale): walks slower than people of same age on level surface, stops occasionally (+1), stops at 100 yards or a few minutes on the level (+2), too breathless to leave house or breathless when dressing/undressing (+3)
      - Exercise capacity (6 minute walk distance): 250-349 m (+1), 150-249 m (+2), <149 m (+3)
- Number of exacerbations: correlate with increased use of medications, increased hospitalization, FEV₁. Increased exacerbations contribute data for analysis.
- There appears to be a reduction in influenza-related infections, as well as exacerbations in patients with COPD receiving the vaccine.

Remember to step down therapy to lowest doses which control symptoms/signs of bronchoconstriction.

Complications of COPD

- Polycythemia 2° to hypoxemia
- Chronic hypoxemia
- Pulmonary HTN from vasoconstriction
- Cor pulmonale
- Pneumothorax due to rupture of emphysematous bullae
**Bronchiectasis**

**Definition**
- irreversible dilatation of airways due to inflammatory destruction of airway walls resulting from persistently infected mucus
- usually affects medium sized airways
- *P. aeruginosa* is the most common pathogen; *S. aureus, H. influenzae* and nontuberculous mycobacteria also common

**Table 16. Etiology and Pathophysiology of Bronchiectasis**

<table>
<thead>
<tr>
<th>Obstruction</th>
<th>Post-infection (results in dilatation of bronchial walls)</th>
<th>Impaired defenses (leads to interference of drainage, chronic infections and inflammation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour</td>
<td>Pneumonia</td>
<td>Hypogammaglobulinemia</td>
</tr>
<tr>
<td>Foreign body</td>
<td>TB</td>
<td>CF</td>
</tr>
<tr>
<td>Thick mucus</td>
<td>Measles</td>
<td>Defective leukocyte function</td>
</tr>
<tr>
<td></td>
<td>Pertussis</td>
<td>Ciliary dysfunction (Kartagener’s syndrome: bronchiectasis, sinusitis, situs inversus)</td>
</tr>
<tr>
<td></td>
<td>Allergic bronchopulmonary aspergillosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAC (Mycobacteria avium complex)</td>
<td></td>
</tr>
</tbody>
</table>

**Signs and Symptoms**
- chronic cough, purulent sputum (but 10-20% have dry cough), hemoptysis (can be massive), recurrent pneumonia, local crackles (inspiratory and expiratory), wheezes
- clubbing
- may be difficult to differentiate from chronic bronchitis

**Investigations**
- PFTs: often demonstrate obstructive pattern but may be normal
- CXR
  - nonspecific: increased markings, linear atelectasis, loss of volume in affected areas
  - specific: “tram tracking” – parallel narrow lines radiating from hilum, cystic spaces, honeycomb like structures
- high-resolution thoracic CT (diagnostic, gold standard):
  - 87-97% sensitivity, 93-100% specificity
  - “signet ring”: dilated bronchi with thickened walls where diameter bronchus > diameter of accompanying artery
- sputum cultures (routine + AFB)
- serum Ig levels
- sweat chloride if cystic fibrosis suspected (upper zone predominant)

**Treatment**
- vaccination: influenza and Pneumovax*
- antibiotics (oral, IV, inhaled): routinely used for mild exacerbations, driven by sputum sensitivity; macrolides may be used chronically for an anti-inflammatory effect
- inhaled corticosteroids: decrease inflammation and improve FEV₁
- oral corticosteroids for acute, major exacerbations
- chest physiotherapy, breathing exercises, physical exercise
- pulmonary resection: in selected cases with focal bronchiectasis

**Cystic Fibrosis (CF)**

- see also Pediatrics, P95

**Pathophysiology**
- chloride transport dysfunction: thick secretions from exocrine glands (lung, pancreas, skin, reproductive organs) and blockage of secretory ducts

**Clinical Features**
- results in severe lung disease, pancreatic insufficiency, diabetes and azoospermia
- other manifestations: meconium ileus in infancy, distal ileal obstruction in adults, sinusitis, liver disease
- chronic lung infections
  - *S. aureus*: early
  - *P. aeruginosa*: most common
  - *B. cepacia*: worse prognosis but less common
  - *Aspergillus fumigatus*

**Investigations**
- sweat chloride test
  - increased concentrations of NaCl and K⁺ ([Cl⁻] >60 mmol/L is diagnostic in children)
- heterozygotes have normal sweat tests (and no symptoms)
- PFTs
  - early: airflow limitation in small airways
  - late: severe airflow hyperinflation, gas trapping, decreased DLCO (very late)
• ABGs
  - hypoxemia, hypercapnia later in disease with eventual respiratory failure and cor pulmonale
• CXR
  - hyperinflation, increased pulmonary markings (especially upper lobes)

**Treatment**
- chest physiotherapy and postural drainage
- bronchodilators (salbutamol ± ipratropium bromide)
- inhaled mucolytic (reduces mucus viscosity), hypertonic saline DNase
- inhaled tobramycin
- antibiotics (e.g. ciprofloxacin)
- lung transplant
- pancreatic enzyme replacements

**Prognosis**
- depends on: infections (cepacia colonization), FEV1, acute pulmonary exacerbations, lung transplant vs. non-lung transplant

---

### Interstitial Lung Disease (ILD)

#### Pathophysiology
- inflammatory and/or fibrosing process in the alveolar walls → distortion and destruction of normal alveoli and microvasculature
- typically associated with:
  - lung restriction (decrease in TLC and VC)
  - decreased lung compliance (increased or normal FEV1/FVC)
  - impaired diffusion (decreased DLCO)
  - hypoxemia due to V/Q mismatch (usually without hypercapnia until end stage)
  - pulmonary HTN and cor pulmonale occur with advanced disease secondary to hypoxemia and blood vessel destruction

#### Etiology
- >100 known disorders can cause ILD
- majority due to unknown agents or cause

**Table 17. Interstitial Lung Diseases**

<table>
<thead>
<tr>
<th>UNKNOWN ETIOLOGY</th>
<th>KNOWN ETIOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic interstitial pneumonias</td>
<td>ILD Associated With Drugs or Treatments</td>
</tr>
<tr>
<td>UIP (usual interstitial pneumonia aka IPF)</td>
<td>Antibiotics (nitrofurantoin)</td>
</tr>
<tr>
<td>NSIP (non-specific interstitial pneumonia)</td>
<td>Anti-inflammatory agents (methotrexate)</td>
</tr>
<tr>
<td>UIP (lymphocytic interstitial pneumonia)</td>
<td>Cardiovascular drugs (amiodarone)</td>
</tr>
<tr>
<td>COP (cryptogenic organizing pneumonia aka BOOP)</td>
<td>Antineoplastic agents (chemotherapy agents)</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td>Langerhans-cell histiocytosis (eosinophilic granuloma)</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis</td>
<td>Pulmonary infiltrates with eosinophilia (PIE syndromes)</td>
</tr>
</tbody>
</table>

**In ILD think FASSTEN and BAD RASH**

**Upper Lung Disease (FASSTEN)**
- Farmer’s lung (hypersensitivity pneumonitis)
-ankylosing spondylitis
-Sarcoidosis
-Silicosis
-TB
-Eosinophilic granuloma (Langerhans cell histiocytosis)
-Neurofibromatosis

**Lower Lung Disease (BADRASH)**
- Bronchiolitis obliterans with organizing pneumonia (BOOP)
-Asbestosis
-Drugs (nitrofurantoin, hydralazine, INH, amiodarone, many chemo drugs)
-Rheumatologic disease
-Aspiration
-Scleroderma
-Hamman Rich (acute interstitial pneumonia) and IPF
Signs and Symptoms
- SOB, especially on exertion
- nonproductive cough
- crackles (dry, fine, end-inspiratory)
- clubbing (especially in IPF and asbestosis)
- features of cor pulmonale
- note that signs and symptoms vary with underlying disease process
  - e.g. sarcoidosis is seldom associated with crackles and clubbing

Investigations
- CXR/high resolution CT (see also Medical Imaging, MI7)
  - usually decreased lung volumes
  - reticular, nodular, or reticulonodular pattern (nodular < 3 mm)
  - hilar/mediastinal adenopathy (especially in sarcoidosis)
- PFTs
  - restrictive pattern: decreased lung volumes and compliance
  - normal or increased FEV1/FVC (>70-80%), i.e. flow rates are often normal or high when corrected for absolute lung volume
  - DLCO decreased due to V/Q mismatch less surface area for gas exchange ± pulmonary vascular disease
- ABGs
  - with progression of disease, hypoxemia and respiratory alkalosis may be present
- other
  - bronchoscopy, bronchoalveolar lavage, lung biopsy
  - ESR, ANA (lupus), RF (RA), serum-precipitating antibodies to inhaled organic antigens (hypersensitivity pneumonitis), c-ANCA (GPA), anti-GBM (Goodpasture’s)

Unknown Etiologic Agents

USUAL INTERSTITIAL PNEUMONIA (UIP) aka IDIOPATHIC PULMONARY FIBROSIS (IPF) aka CRYPTOGENIC FIBROSING ALVEOLITIS

Definition
- a progressive, irreversible condition characterized by fibrosis of lung parenchyma with no known cause
  - chest CT usually shows honeycomb lung, lung biopsy shows UIP (usual interstitial pneumonia) pattern
  - commonly presents over age 50, incidence rises with age; males > females
- DDx:
  - other idiopathic interstitial pneumonia, especially NSIP, but also COP and:
    - desquamative interstitial pneumonitis (DIP)
    - lymphocytic interstitial pneumonitis (LIP): usually 2nd to immune conditions such as HIV (mostly in children), Sjögren’s (now considered to be a hematological malignancy in most adult cases on a spectrum with lymphoma)

Signs and Symptoms
- commonly presents over age 50, incidence rises with age; males > females
- dyspnea on exertion, nonproductive cough, constitutional symptoms, late inspiratory fine crackles at lung bases, clubbing

Investigations
- labs (nonspecific, autoimmune serology usually negative)
- CXR: reticular or reticulonodular pattern with lower lung predominance; may appreciate honeycombing in advanced disease
- high resolution CT: lower zone peripheral reticular markings, traction bronchiectasis, honeycombing, ground glass not prominent in IPF
- biopsy: rarely for UIP as honeycombing makes radiologic diagnosis possible

Treatment
- O2
  - generally does not respond to immunosuppression
- N-acetylcysteine (anti-oxidant)
- lung transplantation for advanced disease
- mean survival of 3 to 5 yr after diagnosis

SARCOIDOSIS

Definition
- idiopathic non-infectious granulomatous multi-system disease with lung involvement in 90%
- characterized pathologically by non-caseating granulomas
- numerous HLA antigens have been shown to play a role and familial sarcoidosis is now recognized
Epidemiology
- typically affects young and middle-aged patients
- higher incidence among black Americans and people at northern latitudes e.g. Scandinavia, Canada

Signs and Symptoms
- asymptomatic, cough, dyspnea, fever, arthralgia, malaise, erythema nodosum, chest pain
- chest exam often normal
- common extrapulmonary manifestations
  - cardiac (arrhythmias, sudden death)
  - eye involvement (anterior or posterior uveitis)
  - skin involvement (skin papules, erythema nodosum, lupus pernio)
  - peripheral lymphadenopathy
  - arthralgia
  - hepatomegaly ± splenomegaly
- less common extra-pulmonary manifestations involve bone, CNS and kidney
- two acute sarcoid syndromes
  - Lofgren's syndrome: fever, erythema nodosum, bilateral hilar lymphadenopathy, arthralgias
  - Heerfordt-Waldenstrom syndrome: fever, parotid enlargement, anterior uveitis, facial nerve palsy

Investigations
- CBC (cytopenias from spleen or marrow involvement)
- serum electrolytes, creatinine, liver enzymes, calcium (hypercalcemia/hypercalciuria due to vitamin D activation by granulomas)
- hypergammaglobulinemia, occasionally RF positive
- elevated serum ACE (non-specific and non-sensitive)
- CXR: predominantly nodular opacities especially in upper lung zones ± hilar adenopathy
- PFTs: normal, obstructive pattern, restrictive pattern with normal flow rates and decreased DLCO
- ECG: to rule out conduction abnormalities
- slit-lamp eye exam: to rule out uveitis

Diagnosis
- biopsy
  - transbronchial lung biopsy, transbronchial lymph node aspiration, endobronchial ultrasound guided surgical (EBUS) biopsy or mediastinoscopic lymph node biopsy or granulomas
- in ~75% of cases, transbronchial biopsy shows granulomas in the parenchyma even if the CXR is normal

Staging
- radiographic, based on CXR
  - Stage 0: normal radiograph
  - Stage I: bilateral hilar lymphadenopathy ± right paratracheal lymphadenopathy
  - Stage II: bilateral hilar lymphadenopathy and diffuse interstitial disease
  - Stage III: interstitial disease only (reticulonodular pattern or nodular pattern)
  - Stage IV: pulmonary fibrosis (honeycombing)

Treatment
- 85% of stage I resolve spontaneously
- 50% of stage II resolve spontaneously
- steroids for symptoms, declining lung function, hypercalcemia, or involvement of eye, CNS, kidney, or heart (not for abnormal CXR alone)
- methotrexate or other immunosuppressives occasionally used

Prognosis
- approximately 10% mortality secondary to progressive fibrosis of lung parenchyma

Known Etiologic Agents

HYPERSENSITIVITY PNEUMONITIS
- also known as extrinsic allergic alveolitis
- non-IgE mediated inflammation of lung parenchyma (acute, subacute, and chronic forms)
- caused by sensitization to inhaled agents, usually organic dust
- pathology: airway-centered, poorly formed granulomas and lymphocytic inflammation
- exposure usually related to occupation or hobby
  - Farmer's Lung (Thermophilic actinomycetes)
  - Bird Breeder's/Bird Fancier's Lung (Chlamydia psittaci in bird droppings)
  - Humidifier Lung (Aureobasidium pullulans)
  - Sauna Taker's Lung (Aureobasidium spp.)

Corticosteroids for Pulmonary Sarcoidosis
Cochrane DB Syst Rev 2005;CD001114
Study: Meta-analysis of 13 RCTs involving 1066 participants examining the use of steroids (oral or inhaled) in sarcoidosis.
Results: Oral steroids demonstrated an improvement in CXR (RR 1.46, 1.01 to 2.09). For inhaled corticosteroids, two studies showed no improvement in lung function and one study showed an improvement in diffusing capacity. No data on side-effects.
Conclusions: Oral steroids improve CXR findings and global scores of CXR, symptoms and sputum over 3-24 mo, but do not improve lung function or modify disease course. Oral steroids may be of benefit for patients with Stage 2 and 3 disease.
Signs and Symptoms
- acute presentation: (4-6 h after exposure)
  - dyspnea, cough, fever, chills, malaise (lasting 18-24 h)
  - CXR: diffuse infiltrates
- subacute presentation: more insidious onset than acute presentation
- chronic presentation
  - insidious onset
  - dyspnea, cough, malaise, anorexia, weight loss
  - PFTs: progressively restrictive
  - CXR: predominantly upper lobe reticulonodular pattern
- type IV (cell mediated, delayed hypersensitivity) reaction (see Rheumatology, RH2)
- in both acute and chronic reactions, serum precipitins may be detectable (neither sensitive nor specific)

Treatment
- early diagnosis: avoidance of further exposure is critical as chronic changes are irreversible
- systemic corticosteroids can relieve symptoms and speed resolution

PNEUMOCONIOSES
- reaction to inhaled inorganic dusts 0.5-5 µm in size
- no effective treatment, therefore key is exposure prevention through the use of protective equipment
- smoking cessation, annual influenza and pneumococcal vaccination, rehabilitation, lung transplant for endstage disease

Table 18. Pneumoconioses

<table>
<thead>
<tr>
<th>Asbestosis</th>
<th>Silicosis</th>
<th>Coal Worker’s Pneumoconiosis (CWP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure risks: insulation, shipyard, construction, brake linings, pipe fitters, plumbers</td>
<td>At risk population: sandblasters, rock miners, stone cutters, quarry and highway workers</td>
<td>At risk population: coal workers, graphite workers</td>
</tr>
<tr>
<td>Slowly progressive diffuse interstitial fibrosis induced by inhaled asbestos fibres</td>
<td>Ecotology: generally requires &gt;20 yr exposure; may develop with much shorter but heavier exposure</td>
<td>Etiology: coal and silica, coal is less fibrogenic than silica</td>
</tr>
<tr>
<td>Ectostal usually &gt;10-20 yr: exposure may develop with shorter but heavier exposure</td>
<td>Investigations: CXR</td>
<td>Pathologic hallmark is coal macule</td>
</tr>
<tr>
<td>Signs and symptoms</td>
<td>Signs and symptoms: dyspnea, cough and wheezing</td>
<td>Simple CWP</td>
</tr>
<tr>
<td>Insidious onset</td>
<td>Early: nodular disease</td>
<td>No signs or symptoms, usually normal lung function</td>
</tr>
<tr>
<td>SOB</td>
<td>Late: nodules coalesce into masses (progressive massive fibrosis)</td>
<td>CXR: multiple nodular opacities, mostly upper lobe</td>
</tr>
<tr>
<td>Fine end-respiratory crackles (increased at bases)</td>
<td>Possible hilar lymph node enlargement (frequently calcified), especially “egg shell” calcification</td>
<td>Complicated CWP (also known as progressive massive fibrosis)</td>
</tr>
<tr>
<td>Clubbing (much more likely in asbestosis than silicosis or coal workers’ pneumoconioses)</td>
<td>Complications: mycobacterial infection (e.g. TB)</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Investigations: CXR</td>
<td></td>
<td>CXR: opacities larger and coalesce</td>
</tr>
<tr>
<td>Lower &gt; upper lobe</td>
<td>Course: few patients progress to complicated CWP</td>
<td>Course: few patients progress to complicated CWP</td>
</tr>
<tr>
<td>Reticulonodular pattern, may develop IPP-like honeycombing</td>
<td>Diaphragmatic plaques are highly suggestive of asbestosis, especially if bilateral.</td>
<td>Caplan’s syndrome: rheumatoid arthritis and CWP present as larger nodules</td>
</tr>
<tr>
<td>Asbestos exposure can also cause pleural and diaphragmatic plaques (± calcification), pleural effusion, round atelectasis</td>
<td>Dyspnea, cough and wheezing</td>
<td></td>
</tr>
<tr>
<td>Microscopic examination reveals ferromuscular bodies: yellow-brown red-shaped structures which represent asbestos fibres coated in macrophages</td>
<td>CXR: opacities larger and coalesce</td>
<td></td>
</tr>
<tr>
<td>Complications: asbestos exposure increases risk of bronchogenic CA and malignant mesothelioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of lung cancer dramatically increased for smokers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ILD ASSOCIATED WITH DRUGS OR TREATMENTS

Drug-Induced
- antineoplastic agents: bleomycin, mitomycin, busulfan, cyclophosphamide, methotrexate, chlorambucil, BCNU (carmustine)
- antibiotics: nitrofurantoin, penicillin, sulfonamide
- cardiovascular drugs: amiodarone, tocaindide
- anti-inflammatory agents: methotrexate, penicillamine
- gold salts
- illicit drugs (heroin, methadone)
- rituximab, anti-TNF α agents (infliximab, etanercept, adalimumab)

Radiation-Induced
- early pneumonitis: approximately 6 wk post-exposure
- late fibrosis: 6-12 mo post-exposure
- infiltrates conform to the shape of the radiation field
Pulmonary Vascular Disease

Pulmonary Hypertension

Definition
• mean pulmonary arterial pressure >25 mmHg at rest and >30 mmHg with exercise, or a systolic pulmonary artery pressure of >40 mmHg at rest
• in the past, pulmonary HTN was classified as primary or secondary pulmonary HTN, but this classification was modified to a more clinically useful, treatment based classification (Table 19)

Table 19. World Health Organization Classification of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Classification</th>
<th>Some Causes</th>
<th>Treatment Options</th>
<th>Consider in All Patient's with PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Pulmonary arterial HTN</td>
<td>Idiopathic</td>
<td>No effective treatment CCB’s or advanced therapy often needed</td>
<td>Oxygen therapy</td>
</tr>
<tr>
<td></td>
<td>Collagen vascular disease (scleroderma, SLE, RA)</td>
<td>The latter includes: prostanoids, endothelin receptor antagonists, PDE5 inhibitors</td>
<td>Exercise</td>
</tr>
<tr>
<td></td>
<td>Congenital systemic-to-pulmonary shunts (Eisenmenger syndrome)</td>
<td></td>
<td>Consider anticoagulation</td>
</tr>
<tr>
<td></td>
<td>Portopulmonary HTN</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drugs and toxins (e.g. anorexigens)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary veno-occlusive disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Schistosomiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary capillary hemangiomatosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sickle cell disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II. Pulmonary HTN due to the left heart disease</td>
<td>Left-sided atrial or ventricular heart disease (e.g. LV dysfunction)</td>
<td>Treat underlying heart disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left-sided valvular heart disease (e.g. aortic stenosis, mitral stenosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III. Pulmonary HTN due to lung disease and/or hypoxia</td>
<td>Parenchymal lung disease (COPD, interstitial fibrosis, cystic fibrosis)</td>
<td>Treat underlying cause of hypoxia and correct with supplemental oxygen (proven mortality benefit)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic alveolar hypoxia (chronic high altitude, alveolar hypoventilation disorders, sleep disordered breathing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV. Chronic thromboembolic pulmonary HTN (CTEPH)</td>
<td>Thromboembolic obstruction of proximal pulmonary arteries</td>
<td>Anticoagulation, thromboendarterectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obstruction of distal pulmonary arteries – PE (thrombus, foreign material, tumour, in situ thrombosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V. Pulmonary HTN with unclear multifactorial mechanisms</td>
<td>Hematologic disorders</td>
<td>Treat underlying cause</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systemic disorders (e.g. sarcoidosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metabolic disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extrinsic compression of central pulmonary veins (tumour, adenopathy, fibrosing mediastinitis)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Simonneau, et al. J Am Coll of Cardiol 2009

Mechanisms of Pulmonary Hypertension (simplified)
• hypoxic vasoconstriction
  ▪ chronic hypoxia causes pulmonary vasoconstriction by a variety of actions on the pulmonary artery endothelium and smooth muscle cells, such as: down regulation of endothelial nitric oxide synthase and alteration of voltage gated potassium channels leading to vasoconstriction
  ▪ causes: COPD, chronic alveolar hypoxia
• decreased area of pulmonary vascular bed
  ▪ leads to a rise in resting pulmonary arterial pressure
  ▪ causes: collagen vascular disease, HIV infection, drugs and toxins, thrombotic or embolic disease, inflammatory, pulmonary capillary hemangiomatosis, interstitial fibrosis, CF
• volume and pressure overload
  ▪ significant HTN only occurs with excessive volume overload, since pulmonary artery pressure will not rise in otherwise normal lung until pulmonary blood flow exceeds 2.5x the basal rate
  ▪ causes: congenital systemic to pulmonary shunts (e.g. VSD, ASD, PDA), portopulmonary HTN, left-sided heart conditions, pulmonary veno-occlusive disease, extrinsic compression of central pulmonary veins
IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION (aka PRIMARY PULMONARY HYPERTENSION)

Definition
- pulmonary HTN in the absence of a demonstrable cause
- exclude:
  - left-sided cardiac valvular disease
  - myocardial disease
  - congenital heart disease
  - any clinically significant parenchymal lung disease
  - systemic connective-tissue disease
  - chronic thromboembolic disease

Epidemiology
- usually presents in young women (20-40 yr); mean age of diagnosis is 36 yr
- most cases are sporadic; familial predisposition in 10% of cases, some linked to mutations in BMPR2
- may be associated with the use of anorexic drugs (e.g. Aminorex®, Fenfluramine*), also amphetamines and cocaine

Signs and Symptoms
- exertional dyspnea, fatigue, syncope, exertional chest pain, Raynaud's phenomenon
- see Table 20

Table 20. Signs and Symptoms of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Symptoms of underlying disease</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV failure: right sided S$_2$, increased JVP, positive HJR, peripheral edema, TR</td>
<td></td>
</tr>
</tbody>
</table>

Investigations
- CXR: enlarged central pulmonary arteries, cardiac changes due to RV enlargement (filling of retrosternal air space)
- ECG
  - RVH/right-sided strain (see Cardiology and Cardiovascular Surgery, C7)
- 2-D echo doppler assessment of right ventricular systolic pressure
- cardiac catheterization: direct measurement of pulmonary artery pressures (necessary to confirm diagnosis)
- PFTs to assess for underlying lung disease: DL$_CO$ usually reduced
- CT angiogram to assess lung parenchyma and possible PE
- V/Q scan ± pulmonary angiogram to rule out thromboembolic disease
- serology: ANA positive in 30% of patients with primary pulmonary HTN. Other serologic markers can be used in the appropriate clinical setting

Treatment
- see Table 19

Prognosis
- 2-3 yr mean survival from time of diagnosis
- survival decreases to approximately 1 yr if severe pulmonary HTN or right-heart failure

Pulmonary Embolism (PE)

Definition
- lodging of a blood clot in the pulmonary arterial tree with subsequent increase in pulmonary vascular resistance, impaired V/Q matching, and possibly reduced pulmonary blood flow

Etiology and Pathophysiology
- one of the most common causes of preventable death in the hospital
- proximal leg thrombi (popliteal, femoral or iliac veins) are the source of most clinically recognized pulmonary emboli
- thrombi often start in calf, but must propagate into proximal veins to create a sufficiently large thrombus for a clinically significant PE
- fewer than 30% of patients have clinical evidence of DVT (e.g. leg swelling, pain or tenderness)
- always suspect PE if patient develops fever, sudden dyspnea, chest pain, or collapse 1-2 wk after surgery
**Risk Factors**
- **Stasis**
  - Immobilization: paralysis, stroke, bed rest, prolonged sitting during travel, immobilization of an extremity after fracture
  - Obesity, CHF
  - Chronic venous insufficiency
- **Endothelial cell damage**
  - Post-operative injury, trauma
- **Hypercoagulable states**
  - Underlying malignancy (particularly adenocarcinoma)
  - Cancer treatment (chemotherapy, hormonal)
  - Exogenous estrogen administration (OCP, HRT)
  - Pregnancy, post-partum
  - Prior history of DVT/PE, family history
  - Nephrotic syndrome
- **Coagulopathies**: Factor V Leiden, Prothrombin 20210A variant, inherited deficiencies of antithrombin/protein C/protein S, antiphospholipid antibody, hyperhomocysteinemia, increased Factor VIII levels, and myeloproliferative disease

- Increasing age

**Investigations** (if highly suspicious, go straight to spiral CT angiogram)
- **See Emergency Medicine, Figure 12, ER34**
- **Pulmonary Angiogram (Gold Standard)**
  - Filling defect indicative of embolus; negative angiogram excludes clinically relevant PE
  - More invasive, and harder to perform than CT, therefore done infrequently
- **D-dimer**
  - Products of thrombotic/fibrinolytic process
  - Highly sensitive D-dimer result can exclude DVT/PE if pretest probability is already low
  - Low value if pretest probability is high
- **CT angiogram**
  - Both sensitive and specific for PE
  - Diagnosis and management uncertain for small filling defects
  - Spiral CT may identify an alternative diagnosis if PE is not present
  - CT scanning of the proximal leg and pelvic veins can be done at the same time and may be helpful
- **Venous duplex U/S or Doppler**
  - With leg symptoms
  - Positive test rules in proximal DVT
  - Negative test rules out proximal DVT
  - Without leg symptoms
  - Positive test rules in proximal DVT
  - Negative test does not rule out a DVT; patient may have non-occlusive or calf DVT
- **ECG**
  - Findings not sensitive or specific
  - Sinus tachycardia most common; may see non-specific ST segment and T wave changes
  - RV strain, RAD, RBBB, S1-Q3-T3 with massive embolization
- **CXR**
  - Frequently normal; no specific features
  - Atelectasis (subsegmental), elevation of a hemidiaphragm
  - Pleural effusion: usually small
  - Hampton's hump: cone-shaped area of peripheral opacification representing infarction
  - Westermark's sign: dilated proximal pulmonary artery with distal oligemia/decreased vascular markings (difficult to assess without prior films)
  - Dilatation of proximal PA: rare
- **V/Q scan**
  - Very sensitive but low specificity
  - With order scan if
    - CXR normal, no COPD
    - Contraindication to CT (contrast allergy, renal dysfunction, pregnancy)
  - Avoid V/Q scan if
    - CXR abnormal or COPD
    - Inpatient
    - Suspect massive PE
  - Results: normal: excludes the diagnosis of PE
  - High probability: most likely means PE present, unless pre-test probability is low
  - 60% of V/Q scans are nondiagnostic
- **Echocardiogram**
  - Useful to assess massive or chronic PE
  - Not routinely done
- **ABG**
  - No diagnostic use in PE (insensitive and nonspecific)
  - May show respiratory alkalosis (due to hyperventilation)

---

**Clinical Prediction Rule for Pulmonary Embolism**
*J Thromb Hemost* 2000;8:416-420

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of DVT</td>
<td>3.0</td>
</tr>
<tr>
<td>No more likely alternative diagnosis</td>
<td>3.0</td>
</tr>
<tr>
<td>Immobilization or surgery in the previous 4 wk</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous PE/DVT</td>
<td>1.5</td>
</tr>
<tr>
<td>HR &gt; 100 beats/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Clinical probability**
- Low (0-2): 3%
- Intermediate (3-6): 29%
- High (>6): 78%
- Modified Wells: >4 PE likely; <4 PE unlikely

---

**PE Rule-out Criteria (PERC)**
*Prospective Multicenter Evaluation of the Pulmonary Embolism Rule-out Criteria (PERC)*
*J Thromb Hemost* 2006;8:772

- Age less than 50 yr
- Heart rate less than 100 bpm
- Oxygenation saturation >95 percent
- No hemoptysis
- No estrogen use
- No prior DVT or PE
- No unilateral leg swelling
- No surgery or trauma requiring hospitalization within the past 4 wk

Acute PE can probably be excluded without further diagnostic testing if the patient meets all PERC criteria AND there is a low clinical suspicion for PE, according to either the Wells criteria or a low gestalt probability determined by the clinician prior to diagnostic testing for PE.

---

**Evaluation of a Suspected Pulmonary Embolism**

Low clinical probability of embolism:

<table>
<thead>
<tr>
<th>D-dimer (+ve)</th>
<th>CT scan (+ve)</th>
<th>ruled in</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-ve) ruled out</td>
<td>(-ve) ruled out</td>
<td></td>
</tr>
</tbody>
</table>

Intermediate or high probability:

<table>
<thead>
<tr>
<th>CT scan (+ve)</th>
<th>ruled out</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+ve) ruled in</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- Use D-dimers only if low clinical probability, otherwise, go straight to spiral CT
- If using V/Q scans (CT contrast allergy or renal failure):
  - Negative V/Q scan rules out the diagnosis
  - High probability V/Q scan only rules in the diagnosis if have high clinical suspicion
  - Inconclusive V/Q scan requires leg U/S to look for DVT or spiral CT

**Classic ECG finding of PE is S1-Q3-T3 (inverted T3), but most commonly see only sinus tachycardia.**

**D-dimer is elevated in patients with recent surgery, cancer, inflammation, infection, and severe renal dysfunction.**

It has good sensitivity and negative predictive value, but poor specificity and positive predictive value.
### Treatment
- admit for observation (patients with DVT only are often sent home on LMWH)
- oxygen: supplemental O<sub>2</sub> if hypoxemic or short of breath
- pain relief: analgesics if chest pain – narcotics or acetaminophen
- acute anticoagulation: therapeutic-dose SC LMWH or IV heparin – start ASAP
  - anticoagulation stops clot propagation, prevents new clots and allows endogenous fibrinolytic system to dissolve existing thromboemboli over months
  - get baseline CBC, INR, aPTT ± liver function
  - for SC LMWH: dalteparin 200 U/kg once daily or enoxaparin 1 mg/kg bid – no lab monitoring – avoid or reduce dose in renal dysfunction
  - for IV heparin: bolus of 75 U/kg (usually 5,000 U) followed by infusion starting at 20 U/kg/h – aim for aPTT 2-3x control
- long term anticoagulation
  - warfarin: start the same day as LMWH/heparin – overlap warfarin with LMWH/heparin for at least 5 d and until INR in target range of 2-3 for at least 2 d
  - LMWH instead of warfarin for pregnancy, active cancer, or high bleeding risk patients
  - dabigatran has been shown to have lower bleeding risk than warfarin
  - IV thrombolytic therapy
  - if patient has massive PE (hypotension or clinical right heart failure) and no contraindications
  - hastens resolution of PE but may not improve survival or long-term outcome and doubles risk of major bleeding
  - interventional thrombolytic therapy
  - massive PE is preferentially treated with catheter-directed thrombolysis by an interventional radiologist
  - works better than IV thrombolytic therapy and fewer contraindications
  - IVC filter: only if recent proximal DVT + absolute contraindication to anticoagulation
  - duration of long-term anticoagulation: individualized, however generally:
    - if reversible cause for PE (surgery, injury, pregnancy, etc.): 3-6 mo
    - if PE unprovoked: 6 mo to indefinite
    - if ongoing major risk factor (active cancer, antiphospholipid antibody, etc.): indefinite

### Thromboprophylaxis
- mandatory for most hospital patients: reduces DVT, PE, all-cause mortality, cost-effective
- start ASAP
- continue at least until discharge or recommend extending for 35 d postoperatively, if major orthopedic surgery

### Table 21. VTE Risk Categories and Prophylaxis (see Hematology, H32)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Prophylaxis Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low thrombosis risk:</strong></td>
<td></td>
</tr>
<tr>
<td>Medical patients: fully mobile Surgery: &lt;30 min, fully mobile</td>
<td>No specific prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Frequent ambulation</td>
</tr>
<tr>
<td><strong>Moderate thrombosis risk:</strong></td>
<td></td>
</tr>
<tr>
<td>Most general, gynecologic, urologic surgery Sick medical patients</td>
<td>LMWH Low dose unfractionated heparin Fondaparinux</td>
</tr>
<tr>
<td><strong>High thrombosis risk:</strong></td>
<td></td>
</tr>
<tr>
<td>Arthroplasty, hip fracture surgery Major trauma, spinal cord injury</td>
<td>LMWH Fondaparinux Warfarin (INR 2-3) Dabigatran Apixaban Rivaroxaban Low dose unfractionated heparin</td>
</tr>
<tr>
<td><strong>High bleeding risk:</strong></td>
<td></td>
</tr>
<tr>
<td>Neurosurgery, intracranial bleed Active bleeding</td>
<td>TED stockings, pneumatic compression devices LMWH or low dose heparin when bleeding risk decreases</td>
</tr>
</tbody>
</table>

### Workup for Idiopathic VTE
#### Thrombophilia Workup: recurrent or idiopathic DVT/PE: age > 50, FHx, unusual location, massive.

#### Malignancy Workup: 12% of patients with idiopathic VTE will have a malignancy.

### Extended Use of Dabigatran, Warfarin or Placebo in Venous Thromboembolism
NEJM 2013;369:709-718
- Study: Two double blind, RCTs; one comparing against placebo, the other against active treatment
- Population: 4,119 patients (2,856 in active-control study, 1,343 in placebo-control study) with VTE who had completed at least 3 mo of therapy
  - Intervention: In the active-control study, patients randomized to either 150 mg dabigatran or warfarin (INR 2.0-3.0). Patients in the placebo-control study received either 150 mg dabigatran or placebo.
- Outcome: Recurrence of VTE, risk of major or clinically relevant bleed.
  - Results: In the active-control study, there was a hazard ratio (HR) of 1.44 (95%, 0.78-2.64 for non-inferiority) of recurrent VTE with dabigatran vs. warfarin. HR of major or clinically relevant bleed was 0.95 (95%, 0.41-2.11). In the placebo-control study, the HR of VTE with dabigatran vs. placebo was 0.03 (95%, 0.00-0.25). HR of major or clinically relevant bleed was 2.92 (95%, 1.52-5.60).
  - Conclusions: Dabigatran appears to be non-inferior to warfarin in the prevention of VTE recurrence. Dabigatran is associated with a lower risk of major or clinically relevant bleed than warfarin, but greater than placebo.

### Excluding Pulmonary Embolism at Bedside without Diagnostic Imaging
- Study: Multicentre, prospective cohort study.
  - Patients: 930 patients with suspected PE at emergency departments at 4 tertiary care hospitals in Canada.
  - Intervention: A Wells score was used to determine patient’s pretest probability (PTP) of PE along with a D-dimer test was performed. Patients with low PTP and a negative D-dimer test had no further testing and the diagnosis of PE was excluded. All other patients had V/Q scanning, and if non-diagnostic, had bilateral deep venous ultrasonography. Further serial ultrasonography and angiography were done depending on the patients’ PTP and lung scanning results.
  - Main outcomes: Diagnosis of PE and the development of thromboembolic events at 3 mo follow-up.
  - Results: One of 798 patients in whom PE was initially ruled out developed a thromboembolic event during follow-up (0.1% [0.07%-0.2%]). One of the 437 patients with negative D-dimers and low clinical PTP developed PE during follow up (MPV 99.3, CI 99.1-100%).
  - Conclusion: Managing patients with suspected pulmonary embolism on the basis of PTP and D-dimer result is safe and decreases the need for diagnostic imaging.
## Pulmonary Vasculitis

### Table 22. Pulmonary Vasculitis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pulmonary Features</th>
<th>Extra-pulmonary Features</th>
<th>Investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulomatosis with Polyangiitis (Wegener’s Granulomatosis) (see Nephrology, NP24)</td>
<td>Systemic vasculitis of medium and small arteries</td>
<td>Necrotizing granulomatous lesions of the upper and lower respiratory tract</td>
<td>CXR: nodules, cavities, and alveolar opacities c-ANCA Tissue confirmation</td>
<td>Corticosteroids and cyclophosphamide or rituximab</td>
</tr>
<tr>
<td>Churg-Strauss Syndrome (Allergic Granulomatosis and Angiitis)</td>
<td>Multisystem disorder characterized by allergic rhinitis, asthma, and prominent peripheral eosinophilia</td>
<td>Asthma Infiltrates</td>
<td>Peripheral eosinophilia is the most common finding p-ANCA may be positive Biopsy involved tissue</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Goodpasture’s Disease (see Nephrology, NP24)</td>
<td>A disorder characterized by diffuse alveolar hemorrhage and glomerulonephritis caused by anti-GBM antibodies, which cross-react with basement membranes of the kidney and lung</td>
<td>Hemoptyis May follow an influenza infection</td>
<td>Anemia</td>
<td>Acutely: corticosteroids, plasmapheresis Immunosuppressive therapy Severe cases: bilateral nephrectomy</td>
</tr>
<tr>
<td>Goodpasture’s Disease (see Nephrology, NP24)</td>
<td>A disorder characterized by diffuse alveolar hemorrhage and glomerulonephritis caused by anti-GBM antibodies, which cross-react with basement membranes of the kidney and lung</td>
<td>Hemoptyis May follow an influenza infection</td>
<td>Anemia</td>
<td>Acutely: corticosteroids, plasmapheresis Immunosuppressive therapy Severe cases: bilateral nephrectomy</td>
</tr>
</tbody>
</table>

### Pulmonary Edema

- see [Cardiology and Cardiovascular Surgery, C32](#)

### Diseases of the Mediastinum and Pleura

#### Mediastinal Masses

**Definition**
- mediastinum: bound by the thoracic inlet, diaphragm, sternum, vertebral bodies and the pleura
- can be broken down into 3 compartments: anterior, middle and posterior (see sidebar)

**Etiology and Pathophysiology**
- diagnosis is made by location and patient’s age
- anterior compartment: more likely to be malignant
  - “Five Ts” (see sidebar), lymphoma, lipoma, pericardial cyst
- middle compartment
  - pericardial cyst, bronchogenic cyst/tumour, lymphoma, lymph node enlargement, aortic aneurysm
- posterior compartment
  - neurogenic tumours, meningocele, enteric cysts, lymphoma, diaphragmatic hernias, esophageal tumour, aortic aneurysm

**Signs and Symptoms**
- 50% asymptomatic (mainly benign); when symptomatic, 50% are malignant
- chest pain, cough, dyspnea, recurrent respiratory infections
- hoarseness, dysphagia, Horner’s syndrome, facial/upper extremity edema (SVC compression)
- paraneoplastic syndromes [e.g. myasthenia gravis (thymomas)]

**Investigations**
- CXR (compare to previous)
- CT with contrast (anatomic location, density, relation to mediastinal vascular structures)
- MRI: specifically indicated in the evaluation of neurogenic tumours
- U/S (best for assessment of structures in close proximity to the heart and pericardium)
- radionuclide scanning: 123I (for thyroid), gallium (for lymphoma)
- biochemical studies: thyroid function, serum calcium, phosphate, PTH, AFP, β-hCG
- biopsy (mediastinoscopy, percutaneous needle aspiration)
Management

- excision if symptomatic enlarging benign masses or concerns of malignancy
- resect bronchogenic cysts and localized neurogenic tumours via minimally invasive video assisted procedures
- exploration via sternotomy or thoracotomy
- diagnostic biopsy rather than major operation if mass is likely to be a lymphoma, germ cell tumour, or unresectable invasive malignancy
- ± post-op radiotherapy/chemotherapy if malignant

Mediastinitis

- commonest causes: postoperative complications of cardiovascular or thoracic surgical procedures

Acute

- etiology
  - complication of endoscopy (e.g. esophageal perforation providing entry point for infection)
  - esophageal or cardiac surgery
  - tumour necrosis
- signs and symptoms
  - fever, substernal pain
  - pneumomediastinum, mediastinal compression
  - Hamman’s sign (auscultatory “crunch” during cardiac systole)
- treatment
  - antibiotics, drainage, ± surgical closure of perforation

Chronic

- usually granulomatous process or fibrosis related to previous infection (e.g. histoplasmosis, TB, sarcoidosis, syphilis)

Pleural Effusions

Definition

- excess amount of fluid in the pleural space (normally up to 25 mL)

Etiology

- disruption of normal equilibrium between pleural fluid formation/entry and pleural fluid absorption/exit
- pleural effusions are classified as transudative or exudative
  - distinguish clinically using Light’s Criteria (Table 23), which has a sensitivity of 98% and specificity of 83% for identifying exudative pleural effusions

<table>
<thead>
<tr>
<th>Light’s Criteria</th>
<th>Modified Light’s Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein – pleural/serum</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>LDH – pleural/serum</td>
<td>&gt;0.6</td>
</tr>
<tr>
<td>Pleural LDH</td>
<td>&gt;2/3 upper limit of N serum LDH</td>
</tr>
</tbody>
</table>

Transudative Pleural Effusions

- pathophysiology: alteration of systemic factors that affect the formation and absorption of pleural fluid (e.g. increased capillary hydrostatic pressure, decreased plasma oncotic pressure)
- etiology
  - CHF: usually right-sided or bilateral cirrhosis
  - nephrotic syndrome, protein losing enteropathy, cirrhosis
  - pulmonary embolism (may cause transudative but more often causes exudative effusion)
  - peritoneal dialysis, hypothyroidism, CF, urinothorax

Exudative Pleural Effusions

- pathophysiology: increased permeability of pleural capillaries or lymphatic dysfunction
- etiology (see Table 24)
Table 24. Exudative Pleural Effusion Etiologies

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Parapneumonic effusion (associated with bacterial pneumonia, lung abscess)</td>
</tr>
<tr>
<td></td>
<td>Empyema (bacterial, fungal, TB)</td>
</tr>
<tr>
<td></td>
<td>TB pleuritis</td>
</tr>
<tr>
<td></td>
<td>Viral infection</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Lung carcinoma (35%)</td>
</tr>
<tr>
<td></td>
<td>Lymphoma (10%)</td>
</tr>
<tr>
<td></td>
<td>Metastases: breast (25%), ovary, kidney</td>
</tr>
<tr>
<td></td>
<td>Mesothelioma</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Collagen vascular diseases: RA, SLE</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>Post-CABG</td>
</tr>
<tr>
<td></td>
<td>Drug reaction</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>Subphrenic abscess</td>
</tr>
<tr>
<td></td>
<td>Pancreatic disease (elevated pleural fluid amylase)</td>
</tr>
<tr>
<td></td>
<td>Meigs’ syndrome (ascites and hydrothorax associated with an ovarian fibroma or other pelvic tumour)</td>
</tr>
<tr>
<td>Intra-thoracic</td>
<td>Chylothorax: thoracic duct disrupted and chyle accumulates in the pleural space, due to trauma, tumour</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage: rupture of a blood vessel, commonly by trauma or tumours</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax (spontaneous, traumatic, tension)</td>
</tr>
</tbody>
</table>

Signs and Symptoms
- often asymptomatic
- dyspnea: varies with size of effusion and underlying lung function
- pleuritic chest pain
- inspection: trachea deviates away from effusion, ipsilateral decreased expansion
- percussion: decreased tactile fremitus, dullness
- auscultation: decreased breath sounds, bronchial breathing and egophony at upper level, pleural friction rub

Investigations
- CXR
  - must have >200 mL of pleural fluid for visualization on PA film
  - lateral: >50 mL leads to blunting of posterior costophrenic angle
  - PA: blunting of lateral costophrenic angle
  - dense opacification of lung fields with concave meniscus
  - decubitus: fluid will shift unless it is loculated
  - supine: fluid will appear as general haziness
- thoracentesis: indicated if pleural effusion is a new finding; be sure to send off blood work (LDH, glucose, protein) at the same time for comparison
  - risk of re-expansion pulmonary edema if >1.5 L of fluid is removed
  - inspect for colour, character, and odour of fluid
  - analyze fluid (see Tables 23 and 25)
- pleural biopsy: indicated if suspect TB, mesothelioma, or other malignancy (and if cytology negative)
- ± U&S: detects small effusions and can guide thoracentesis
- treatment depends on cause, ± drainage if symptomatic
- CT can be helpful in differentiating parenchymal from pleural abnormalities

Table 25. Analysis of Pleural Effusion

<table>
<thead>
<tr>
<th>Measure</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein, LDH</td>
<td>Transudate vs. exudate (see Table 23)</td>
</tr>
<tr>
<td>Gram stain, Ziehl-Nielsen stain (TB), culture</td>
<td>Looking for specific organisms</td>
</tr>
<tr>
<td>Cell count differential</td>
<td>Neutrophils vs. lymphocytes (lymphocytic effusion in TB, cancer, lymphoma, serositis)</td>
</tr>
<tr>
<td>Cytology</td>
<td>Malignancy, infection</td>
</tr>
<tr>
<td>Glucose (low)</td>
<td>RA, TB, empyema, malignancy, chylophageal rupture</td>
</tr>
<tr>
<td>Rheumatoid factor, ANA, complement</td>
<td>Collagen vascular disease</td>
</tr>
<tr>
<td>Amylase</td>
<td>Pancreatitis, chylophageal perforation, malignancy</td>
</tr>
<tr>
<td>pH</td>
<td>Empyema &lt;7.2, TB and mesothelioma &lt;7.3</td>
</tr>
<tr>
<td>Blood</td>
<td>Mostly traumatic, malignancy, PE with infection, TB</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Chylophageal from thoracic duct leakage, mostly due to trauma, lung CA, or lymphoma</td>
</tr>
</tbody>
</table>
Treatment
• thoracentesis
• treat underlying cause
• consider indwelling pleural catheter or pleurodesis in refractory effusions

Complicated Parapneumonic Effusion
• persistent bacteria in the pleural space, but fluid is non-purulent
• neutrophils, pleural fluid acidosis (pH <7.00), and high LDH
• often no bacteria grown, since rapidly cleared from pleural space
• fibrin layer leading to loculation of pleural fluid
• treatment: antibiotics and drainage, treat as an empyema

Empyema
Definition
• pus in pleural space or an effusion with organisms seen on a Gram stain or culture (i.e. pleural fluid is grossly purulent)
• positive culture is not required for diagnosis

Etiology
• contiguous spread from lung infection (most commonly anaerobes), or infection through chest wall (e.g. trauma, surgery)

Signs and Symptoms
• fever, pleuritic chest pain

Investigations
• CT chest
• thoracentesis
• PMNs (lymphocytes in TB) ± visible organisms on Gram stain

Treatment
• antibiotic therapy for at least 4-6 wk (rarely effective alone)
• complete pleural drainage with chest tube
• if loculated, more difficult to drain – may require surgical drainage video-assisted thorascopic surgery (VATS)

Atelectasis
• see General Surgery, GS10

Pneumothorax
Definition
• presence of air in the pleural space

Pathophysiology
• increased intrapleural pressure reduces lung inflation

Etiology
• traumatic: penetrating or non-penetrating chest injuries
• iatrogenic (central venous catheter, thoracentesis, mechanical ventilation with barotrauma)
• spontaneous (no history of trauma)
  • primary (no underlying lung disease)
    • spontaneous rupture of apical subpleural bleb of lung into pleural space
    • predominantly tall, healthy, young males
  • secondary (underlying lung disease)
    • rupture of subpleural bleb which migrates along bronchialveolar sheath to the mediastinum then to the intrapleural space
    • necrosis of lung tissue adjacent to pleural surface (e.g. pneumonia, abscess, PCP, lung CA, emphysema)

Signs and Symptoms
• can be asymptomatic
• acute-onset pleuritic chest pain, dyspnea
• tachypnea, tachycardia

Pleural Effusions
Simple Effusion
pH >7.2, LDH <1/2 serum, glucose >2.2

Complicated Effusion
pH <7.2, LDH >1/2 serum, glucose <2.2, positive Gram stain
Needs drainage

When possible, organism-directed therapy, guided by culture sensitivities or local patterns of drug resistance, should be utilized.

Need to Rule Out Life-Threatening Tension Pneumothorax
If pneumothorax with:
• Severe respiratory distress
• Tracheal deviation to contralateral side
• Distended neck veins († JVP)
• Hypotension
Do not perform CXR.
See Emergency Medicine, ER11
• tracheal deviation (contralateral deviation in tension pneumothorax)
• ipsilateral diminished chest expansion
• decreased tactile/vocal fremitus
• hyperresonance
• ipsilateral diminished breath sounds

Investigations
• CXR
  ▪ small: separation of visceral and parietal pleura seen as fine crescentic line parallel to chest wall at apex
  ▪ large: increased density and decreased volume of lung on side of pneumothorax
  ▪ see Medical Imaging, M18

Treatment
• small pneumothoraces (<20% with no signs of respiratory/circulatory collapse) resolve spontaneously; breathing 100% oxygen accelerates resorption of air
• small intercostal tube with Heimlich valve for most spontaneous pneumothoraces
• large pneumothoraces or those complicating underlying lung disease require placement of a chest tube connected to underwater seal ± suction
• for repeated episodes: pleurodesis with sclerosing agent or apical bullectomy and abrasion
• treat underlying cause (e.g. antibiotic for PCP)

Asbestos-Related Pleural Disease and Mesothelioma

Etiology and Pathophysiology
• benign manifestations of asbestos exposure
  ▪ "benign asbestos pleural effusion"
    ▪ exudative effusion, typically ≈10 yr after exposure, resolves
  ▪ pleural plaques, usually calcified
    ▪ marker of exposure; usually an asymptomatic radiologic finding
• mesothelioma
  ▪ primary malignancy of the pleura
  ▪ decades after asbestos exposure (even with limited exposure)
  ▪ smoking not a risk factor, but asbestos and smoking synergistically increase risk of lung cancer

Signs and Symptoms
• persistent chest pain, dyspnea, cough, bloody pleural effusion, weight loss

Investigations
• biopsy (pleuroscopic or open)
• needle biopsy may seed needle tract with tumour

Treatment
• resection (extrapleural pneumonectomy) requires careful patient selection; rarely successful (average survival <1 yr)

Respiratory Failure

Definition
• failure of respiratory system to maintain normal blood gases
• hypoxemic ($P_{aO2} <60$ mmHg)
• hypercapnic ($P_{aCO2} >50$ mmHg)
• acute vs. chronic (compensatory mechanisms activated)

Signs and Symptoms
• signs of underlying disease
• hypoxemia: restlessness, confusion, cyanosis, coma, cor pulmonale
• hypercapnia: headache, dyspnea, drowsiness, asterixis, warm periphery, plethora, increased ICP (secondary to vasodilatation)

Investigations
• serial ABGs
• CXR and/or CT, bronchoscopy to characterize underlying cause if unclear
**Hypoxemic Respiratory Failure**

**Definition**
- $P_aO_2$ decreased, $P_aCO_2$ normal or decreased

**Treatment**
- reverse the underlying pathology
- oxygen therapy: maintain oxygenation (if shunt present, supplemental $O_2$ is less effective; see Anesthesia, A10, for oxygen delivery systems)
- ventilation, BiPAP and PEEP/CPAP (see Mechanical Ventilation, R26): positive pressure can recruit alveoli and redistribute lung fluid
- improve cardiac output: ± hemodynamic support (fluids, vasopressors, inotropes), reduction of $O_2$ requirements

### Table 26. Approach to Hypoxemia

<table>
<thead>
<tr>
<th>Type of Hypoxemia</th>
<th>Settings</th>
<th>$P_aCO_2$</th>
<th>A-aDO₂</th>
<th>Oxygen Therapy</th>
<th>Ventilation, BiPAP and PEEP</th>
<th>Improved Cardiac Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Low FiO₂</td>
<td>Postop, high altitude</td>
<td>N or ↓</td>
<td>N</td>
<td>Improves</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>2. Hypoventilation</td>
<td>Drug overdose</td>
<td>↑</td>
<td>N</td>
<td>Improves</td>
<td>Improves with ventilation</td>
<td>No change</td>
</tr>
<tr>
<td>3a. Shunt</td>
<td>ARDS, pneumonia</td>
<td>N or ↓</td>
<td>↑</td>
<td>No change</td>
<td>Improves (except if one-sided)</td>
<td>Improves</td>
</tr>
<tr>
<td>3b. Shunt (Right to Left)</td>
<td>Pulmonary HTN</td>
<td>N or ↓</td>
<td>↑</td>
<td>No change</td>
<td>Worsens</td>
<td>Worsens</td>
</tr>
<tr>
<td>4. Low mixed venous $O_2$ content</td>
<td>Shock</td>
<td>↓</td>
<td>↑</td>
<td>Improves or no change</td>
<td>Worsens</td>
<td>Improves</td>
</tr>
<tr>
<td>5. V/Q mismatch</td>
<td>COPD</td>
<td>N or ↑</td>
<td>↑</td>
<td>Improves (small amounts)</td>
<td>Often improves</td>
<td>Improves</td>
</tr>
<tr>
<td>6. Diffusion impairment</td>
<td>ILD, emphysema</td>
<td>N</td>
<td>↑</td>
<td>Improves</td>
<td>Improves with positive pressure</td>
<td>No change or worsens</td>
</tr>
</tbody>
</table>

Reprinted with permission from Dr. Ian Fraser

**Hypercapnic Respiratory Failure**

- $P_aCO_2$ increased, $P_aO_2$ decreased

**Pathophysiology**
- increased $CO_2$ production: fever, sepsis, seizure, acidosis, carbohydrate load
- alveolar hypoventilation: COPD, asthma, CF, chest wall disorder, dead space ventilation (rapid shallow breathing)
  - i.e. inefficient gas exchange results in inadequate $CO_2$ removal in spite of normal or increased minute volume
- hyperventilation
  - central: brainstem stroke, hypothyroidism, severe metabolic alkalosis, drugs (opiates, benzodiazepines)
  - neuromuscular: myasthenia gravis, Guillain-Barré, phrenic nerve injury, muscular dystrophy, polymyositis, kyphoscoliosis
  - muscle fatigue

**Treatment**
- reverse the underlying pathology
- if $P_aCO_2 > 50$ mmHg and pH is acidemic consider noninvasive or mechanical ventilation
- correct exacerbating factors
  - NTT/ETT suction: clearance of secretions
  - bronchodilators: reduction of airway resistance
  - antibiotics: treatment of infections
- maintain oxygenation (see above)
- diet: increased carbohydrate can increase $P_aCO_2$ in those with mechanical or limited alveolar ventilation; high lipids decrease $P_aCO_2$
Acute Respiratory Distress Syndrome (ARDS)

- clinical syndrome characterized by severe respiratory distress, hypoxemia, and noncardiogenic pulmonary edema
- The Berlin Criteria (JAMA 2012; 307:2526-2533) for ARDS:
  - acute onset
    - within 7 d of a defined event, such as sepsis, pneumonia, or patient noticing worsening of respiratory symptoms
    - usually occurs within 72 h of presumed trigger
  - bilateral opacities consistent with pulmonary edema on either CT or CXR
  - not fully explained by cardiac failure/fluid overload, but patient may have concurrent heart failure
  - an objective assessment (e.g. echocardiogram) should be performed if no clear risk factors

Etiology

- direct lung injury:
  - airway: aspiration (gastric contents, drowning), pneumonia, inhalation injury (oxygen toxicity, nitrogen dioxide, smoke)
  - circulation: embolism (fat, amniotic fluid), reperfusion injury
- indirect lung injury
  - circulation: sepsis, shock, trauma, blood transfusion, pancreatitis
  - neurogenic: head trauma, intracranial hemorrhage, drug overdose (narcotics, sedatives, TCAs)

Pathophysiology

- disruption of alveolar capillary membranes → leaky capillaries → interstitial and alveolar pulmonary edema → reduced compliance, V/Q mismatch, shunt, hypoxemia, pulmonary HTN

Clinical Course

A. Exudative Phase
- first 7 d of illness after exposure to ARDS precipitant
- alveolar capillary endothelial cells and type I pneumocytes are injured, resulting in loss of normally tight alveolar barrier
- patients develop dyspnea, tachypnea, increased work of breathing
  - these result in respiratory fatigue and eventually respiratory failure (see Hypoxic Respiratory Failure, R25)

B. Fibroproliferative Phase
- after day 7
- may still experience dyspnea, tachypnea, fatigue, and hypoxemia
- most patients clinically improve and are able to wean off mechanical ventilation
- some patients develop fibrotic lung changes that may require long-term support on supplemental oxygen or even mechanical ventilation
- if fibrosis present, associated with increased mortality

Treatment

- based on ARDS network (see Landmark Respiratory Trials, R35)
- treat underlying disorder (e.g. antibiotics if infection present)
- mechanical ventilation using low tidal volumes (<6 mL/kg) to prevent barotrauma
  - use optimal amount of PEEP (positive end-expiratory pressure) to keep airways open and allow the use of lower $P_{O_2}$
  - may consider using prone ventilation, and/or inhaled nitric oxide, high frequency oscillator or ECMO (extracorporeal membrane oxygenation) if conventional treatment is failing
- fluids and inotropic therapy (e.g. dopamine, vasopressin) if cardiac output inadequate
- pulmonary-arterial catheter now seldom used for monitoring hemodynamics
- mortality: 30-40%, usually due to non-pulmonary complications
- sequelae of ARDS include residual pulmonary impairment, severe debilitation, polynuropathy and psychologic difficulties, which gradually improve over time
- most survivors eventually regain near-normal lung function, often with mildly reduced diffusion capacity

Mechanical Ventilation

- see Anesthesia, A10

Definition

- artificial means of supporting ventilation and oxygenation
- mechanically ventilated patients may require some sedation and/or analgesia

Risk Factors for Aspiration Pneumonia

<table>
<thead>
<tr>
<th>Categories</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased level of consciousness</td>
<td>Alcoholism</td>
</tr>
<tr>
<td>Upper GI tract disorders</td>
<td>Dysphagia, esophageal disorders</td>
</tr>
<tr>
<td>Mechanical instrumentation</td>
<td>Intubation, nasogastric tube, feeding tubes</td>
</tr>
<tr>
<td>Neurologic conditions</td>
<td>Dementia, Parkinson disease</td>
</tr>
<tr>
<td>Others</td>
<td>Protracted vomiting</td>
</tr>
</tbody>
</table>

ALI versus ARDS: Definition is the same, except ALI is a $P_{O_2}/FiO_2 \leq 300$, while ARDS is a $P_{O_2}/FiO_2 \leq 200$
Indications
- general indications
  - hypoxic respiratory failure
  - hypercapnic respiratory failure
- specific indicators for mechanical ventilation
  - acute ventilation failure/acute respiratory acidosis
  - refractory hypoxemia
  - reduced level of consciousness
  - facilitation of surgical procedures

Ventilator Strategies
- mode and settings are determined based on patient factors (e.g., ideal body weight, compliance, resistance) and underlying reason for mechanical ventilation
- hypoxic respiratory failure: ventilator provides supplemental oxygen, recruits atelectatic lung segments, helps improve V/Q mismatch, and decreases intrapulmonary shunt
- hypercapnic respiratory failure: ventilator augments alveolar ventilation; may decrease the work of breathing, allowing respiratory muscles to rest

Modes of Ventilation
- assist-control ventilation (ACV)
  - every breath is delivered with a pre-set tidal volume and rate or minute ventilation
  - extra controlled breaths may be triggered by patient effort; if no effort is detected within a specified amount of time the ventilator will initiate the breath
- pressure control ventilation (PCV)
  - a minimum frequency is set and patient may trigger additional breaths above the ventilator
  - all breaths delivered at a preset constant inspiratory pressure
- synchronous intermittent mandatory ventilation (SIMV)
  - ventilator provides controlled breaths (either at a set volume or pressure)
  - patient can breathe spontaneously (these breaths may be pressure supported) between controlled breaths
- pressure support ventilation (PSV)
  - patient initiates all breaths and the ventilator supports each breath with a pre-set inspiratory pressure
  - useful for weaning off ventilator
- high-frequency oscillatory ventilation (HFOV)
  - very high breathing rate (up to 900 breaths/min in an adult), very low tidal volumes
  - used commonly in neonatal and pediatric respiratory failure
  - used in adults when conventional mechanical ventilation is failing.
- noninvasive positive pressure ventilation (NPPV)
  - achieved without intubation by using a nasal or face mask with:
    - BiPAP: increased pressure (like PSV) on inspiration and lower constant pressure on expiration
    - CPAP: delivers constant pressure on both inspiration and expiration

Complications of Mechanical Ventilation
- airway complications
  - tracheal stenosis, laryngeal edema
- alveolar complications
  - ventilator-induced lung injury, ventilator-associated pneumonia (nosocomial pneumonia), barotrauma, volutrauma, inflammation, auto-PEEP, patient-ventilator asynchrony
- cardiovascular complications
  - reduced venous return, reduced cardiac output, hypotension
- neuromuscular complications
  - muscle atrophy
  - increased intracranial pressure

Monitoring Ventilatory Therapy
- used with all invasive modes of ventilation

A Comparison of Four Methods of Weaning Patients from Mechanical Ventilation

Study: Prospective, randomized, multicenter trial.
Participants: 130 of 546 patients who received mechanical ventilation and were considered ready for weaning but had respiratory distress during a 2 h trial of spontaneous breathing.
Intervention: One of four weaning techniques following standardized protocol.
Outcome: Median duration of weaning.
Results: The median duration of weaning for intermittent mandatory ventilation, pressure-support ventilation, intermittent (multiple) trials of spontaneous breathing, and once-daily trial of spontaneous breathing was 5.4, 4.4, and 3.0 days respectively. The rate of successful weaning was higher with once-daily trial of spontaneous breathing than with intermittent mandatory ventilation (rate ratio 2.83; 95% CI 1.36 to 5.89; p<0.006) or pressure-support ventilation (rate ratio 2.05; 95% CI 1.04 to 4.04; p<0.04). There was no significant difference in the rate of success between once-daily trials and multiple trials of spontaneous breathing.
Conclusions: Once-daily or multiple trials of spontaneous breathing led to extubation more quickly than intermittent mandatory or pressure-support ventilation.

Tracheostomy
- Tracheostomy should be considered in patients who require ventilator support for extended periods of time
- Shown to improve patient comfort and give patients a better ability to participate in rehabilitation activities

Positive End Expiratory Pressure (PEEP)
- Positive pressure applied at the end of ventilation which opens up collapsed alveoli decreasing V/Q mismatch
- Used with all invasive modes of ventilation

Management of pneumothorax in patients on mechanical ventilation → chest tube.

Neoplasms

Lung Cancer

Classification
- lung tumours can be classified as primary or secondary, benign or malignant, endobronchial or parenchymal
- bronchogenic carcinoma (epithelial lung tumours) are the most common type of primary lung tumour (other types make up less than 1%)
  - small cell lung cancer (SCLC)
  - non-small-cell lung cancer (NSCLC)
    - squamous cell carcinoma: arise from the proximal respiratory epithelium
    - bronchioalveolar carcinoma: grows along the alveolar wall in the periphery; may arise at sites of previous lung scarring
    - large cell undifferentiated cancer: diagnosis of exclusion
- benign epithelial lung tumours can be classified as papillomas or adenomas
### Table 27. Characteristics of Bronchogenic Cancer

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Incidence</th>
<th>Correlation with Smoking</th>
<th>Location</th>
<th>Histology</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>35%</td>
<td>Weak</td>
<td>Peripheral</td>
<td>Glandular, mucin producing</td>
<td>Early, distant</td>
</tr>
<tr>
<td>Squamous cell carcinoma (SCC)</td>
<td>30%</td>
<td>Strong</td>
<td>Central</td>
<td>Keratin, intercellular bridges</td>
<td>Local invasion and distant spread, may cavitate</td>
</tr>
<tr>
<td>SCLC</td>
<td>25%</td>
<td>Strong</td>
<td>Central</td>
<td>Oat cell, neuroendocrine</td>
<td>Disseminated at presentation</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>10-15%</td>
<td>Strong</td>
<td>Peripheral</td>
<td>Anaplastic, undifferentiated</td>
<td>Early, distant</td>
</tr>
</tbody>
</table>

### Risk Factors
- cigarette smoking: the relative risk of developing lung cancer is 10-30 times higher for smokers than for nonsmokers
- other risk factors include cigar smoking, pipe smoking, second-hand smoke, asbestos without smoking (relative risk is 5), asbestos with smoking (relative risk is 92), metals (e.g. chromium, arsenic, nickel), radon gas, ionizing radiation, genetics

### Signs and Symptoms
- may be due to primary lesion, metastasis, or paraneoplastic syndrome
  - primary lesion:
    - cough (75%): beware of chronic cough that changes in character
    - dyspnea (60%)
    - chest pain (45%)
    - hemoptysis (35%)
    - other pain (25%)
    - clubbing (21%)
    - constitutional symptoms: anorexia, weight loss, fever, anaemia
  - metastasis
    - lung, hilum, mediastinum, pleura: pleural effusion, atelectasis, wheezing
    - pericardium: pericarditis, pericardial tamponade
    - esophageal compression: dysphagia
    - phrenic nerve: paralyzed diaphragm
    - recurrent laryngeal nerve: hoarseness
    - superior vena cava syndrome:
      - obstruction of SVC causing neck and facial swelling, as well as dyspnea and cough
      - other symptoms: hoarseness, tongue swelling, epistaxis, and hemoptysis
      - physical findings: dilated neck veins, increased number of collateral veins covering the anterior chest wall, cyanosis, edema of the face, arms, and chest, Pemberton's sign (facial flushing, cyanosis, and distension of neck veins upon raising both arms above head)
    - milder symptoms if obstruction is above the azygos vein
    - lung apex (Pancoast tumour): Horner's syndrome, brachial plexus palsy (most commonly C8 and T1 nerve roots)
    - rib and vertebral: erosion
    - distant metastasis to brain, bone, liver, adrenal
  - paraneoplastic syndromes (see Table 28)
    - a group of disorders associated with malignant disease, not related to the physical effects of the tumour itself
    - most often associated with SCLC

### Table 28. Paraneoplastic Syndromes

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical Presentation</th>
<th>Associated Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal</td>
<td>Clubbing, hypertrophic pulmonary osteoarthropathy (HPOA)</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Acanthosis nigricans</td>
<td>Bronchogenic cancer</td>
</tr>
<tr>
<td></td>
<td>Dermatomyositis</td>
<td>Bronchogenic cancer</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypercalcemia (osteolyis of PTHrP)</td>
<td>Squamous cell cancer</td>
</tr>
<tr>
<td></td>
<td>Hypophosphatemia</td>
<td>Squamous cell cancer</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
<td>Sarcoma</td>
</tr>
<tr>
<td></td>
<td>Cushing's syndrome (ACTH)</td>
<td>SCLC</td>
</tr>
<tr>
<td></td>
<td>Somatostatinoma syndrome</td>
<td>Bronchial carcinoid</td>
</tr>
<tr>
<td></td>
<td>SIADH</td>
<td>SCLC</td>
</tr>
<tr>
<td>Neuromyopathic</td>
<td>Lambert-Eaton syndrome</td>
<td>SCLC</td>
</tr>
<tr>
<td></td>
<td>Polymyositis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subacute cerebellar degeneration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sponcomelicellar degeneration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td></td>
</tr>
<tr>
<td>Vascular/</td>
<td>Nonbacterial endocarditis</td>
<td>Bronchogenic cancer</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Troussseau's syndrome (migratory thrombophlebitis)</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Renal</td>
<td>Nephrotic syndrome</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions**: Screening with low-dose CT reduces mortality from lung cancer.

### Summary of Recommendations on Screening for Lung Cancer

- **Canadian Task Force on Preventive Health Care (2003)**
  - Screening with CXR: Not recommended
  - Screening with low-dose CT: Insufficient evidence to make recommendation
- **American College of Chest Physicians (2013)**
  - Screening with CXR: Not recommended
  - Screening with low-dose CT: Recommended for high-risk patients (current or former smokers quit within last 15 y, aged 55-74, ≥30 pack-yr smoking Hx)
- **American Lung Association (2013)**
  - Screening with CXR: Not recommended
  - Screening with low-dose CT: Recommended for high-risk patients (current or former smokers aged 55-74, ≥30 pack-yr smoking Hx, no Hx of lung cancer)

### Reduced Lung-cancer Mortality with Low-dose CT Screening

- Rate of positive screening test: 24.2% vs 6.9%
- False positives: 96.4% vs 94.5%
- Incidence of lung cancer: 645/100K vs 572/100K
- Deaths from lung cancer: 247/100K vs 308/100K

**Conclusions**: Screening with low-dose CT reduces mortality from lung cancer.

**Malignant lung tumours are the most common cause of cancer mortality throughout the world in both men and women.**

### Endobronchial Ultrasound (EBUS):
- Allows visualization of peri-bronchial structures and distal peripheral lung lesions
- Provides detailed assessment of the airway wall layers
- Allows for guided biopsies of lymph nodes and tumours
- Used for diagnosis and staging
Investigations

- initial diagnosis
  - imaging: CXR, CT chest + upper abdomen, PET scan, bone scan
  - cytology: sputum
  - biopsy: bronchoscopy, percutaneous mediastinoscopy

- staging work-up
  - TMN staging system: T – primary tumour (size); N – regional lymph nodes; M – distant metastasis
  - blood work: electrolytes, LFTs, calcium, ALP
  - imaging: CXR, CT thorax and upper abdomen, bone scan, neuroimaging
  - invasive: bronchoscopy (EBUS), mediastinoscopy, mediastinotomy, thoracotomy

Table 29. SCLC vs. NSCLC

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Treatment</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCLC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited stage</td>
<td>Confined to single radiation port (one hemithorax and regional lymph nodes)</td>
<td>Radiation ± chemo</td>
<td>1-2 yr (12 wk without treatment)</td>
</tr>
<tr>
<td>Extensive stage</td>
<td>Extension beyond a single radiation port</td>
<td>Chemotherapy</td>
<td>6 mo (5 wk without treatment)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>IA</td>
<td>T1a-T1bN0M0</td>
<td>1st line is complete surgical resection with possible post-op adjuvant chemotherapy with stage IB and stage II. Radiotherapy for non-surgical candidates.</td>
</tr>
<tr>
<td></td>
<td>IB</td>
<td>T2aN0M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IIA</td>
<td>T1a-T2a,N1A0M0 or T2bN0M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IIB</td>
<td>T2bN1M0 or T3N0M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IIIA</td>
<td>T1a-T2b,N2M0 or T3bN0M0 or T4N0-1M0</td>
<td>Combined modality approach (concurrent chemotherapy followed by surgery)</td>
</tr>
<tr>
<td></td>
<td>IIIB</td>
<td>T4N2M0 or T1-4N3M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>T1-4N0-3M1a-1b</td>
<td>Systemic therapy or molecularly targeted therapy or symptom-based palliative management (radiation). Isolated metastasis may be resected.</td>
</tr>
</tbody>
</table>

* Depends on clinical vs. pathologic stage

Refer to AJCC Cancer Staging Manual, 7th ed. (2010) for complete TNM classification

Treatment

- options include surgery, radiotherapy, chemotherapy, and palliative care for end-stage disease (see Table 29)
- surgery not usually performed for SCLC since it is generally non-curable
- contraindications for surgery:
  - spread to contralateral lymph nodes or distant sites
  - patients with potentially resectable disease must undergo mediastinal node sampling since CT thorax is not accurate in 20-40% of cases
  - poor pulmonary status (e.g. unable to tolerate resection of lung)
- chemotherapy (used in combination with other treatments)
  - common agents: etoposide, platinum agents (e.g. cisplatin), ifosfamide, vincristine, anthracyclines, paclitaxel, irinotecan, gefitinib (an endothelial growth factor receptor inhibitor)
  - complications:
    - acute: tumour lysis syndrome, infection, bleeding, myelosuppression, hemorrhagic cystitis (cyclophosphamide), cardiotoxicity (doxorubicin), renal toxicity (cisplatin), peripheral neuropathy (vincristine)
    - chronic: neurologic damage, leukemia, additional primary neoplasms

Prognosis

- 5 yr survival rates for different subtypes:
  - squamous cell carcinoma 25%
  - adenocarcinoma 12% (60% for bronchoalveolar carcinoma, a subtype of adenocarcinoma, with a resectable solitary lesion)
  - large cell carcinoma 13%
  - SCLC 1% (poorest prognosis)
  - NSCLC (see Table 29)

Prevention

- smoking cessation
- avoidance of exposures
- early detection
Approach to the Solitary Pulmonary Nodule

- also see Medical Imaging, MI7

Definition
- a round or oval, sharply circumscribed radiographic lesion up to 3-4 cm, which may or may not be calcified, and is surrounded by normal lung
- can be benign or malignant

Table 30. Differential Diagnosis for Benign vs. Malignant Solitary Nodule

<table>
<thead>
<tr>
<th>Benign (70%)</th>
<th>Malignant (30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious granuloma (histoplasmosis, coccidiomycosis, TB, atypical mycobacteria)</td>
<td>Bronchogenic carcinoma</td>
</tr>
<tr>
<td>Benign neoplasms (hamartoma, lipoma, fibroma)</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Vascular (AV malformation, pulmonary varix)</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Developmental (bronchogenic cyst)</td>
<td>Large cell carcinoma</td>
</tr>
<tr>
<td>Inflammatory (granulomatosis with polyanthiasis, rheumatoi d nodules, sarcoidosis)</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>Other (hematoma, infarct, pseudotumour, rounded atelectasis, lymph nodes, amyloidoma, hamartoma)</td>
<td>Metastatic lesions</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
</tr>
<tr>
<td></td>
<td>Head and neck</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>Colon</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
</tr>
<tr>
<td></td>
<td>Sarcoma</td>
</tr>
<tr>
<td></td>
<td>Germ cell tumours</td>
</tr>
<tr>
<td></td>
<td>Pulmonary carcinoid</td>
</tr>
</tbody>
</table>

Investigations (see Figure 11)
- CXR: always compare with previous CXR (see Table 31)
- CT densitometry and contrast enhanced CT of thorax
- sputum cytology: usually poor yield
- biopsy (bronchoscopic or percutaneous) or excision (thoracoscopy or thoracotomy): if clinical and radiographic features do not help distinguish between benign or malignant lesion
  - if at risk for lung cancer, biopsy may be performed regardless of radiographic features
  - if a biopsy is non-diagnostic, whether to observe, re-biopsy or resect will depend on the level of suspicion
- watchful waiting: repeat CXR and/or CT scan at 3, 6, 12 mo
- PET scan can help distinguish benign from malignant nodules

Table 31. CXR Characteristics of Benign vs. Malignant Solitary Nodule

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>&lt;3 cm, round, regular</td>
<td>&gt;3 cm, irregular, spiculated</td>
</tr>
<tr>
<td>Margins</td>
<td>Smooth margin</td>
<td>Ill-defined or notched margin</td>
</tr>
<tr>
<td>Features</td>
<td>Calcified pattern: central, “popcorn” pattern if hamartoma, usually no cavitation; if cavitated, wall is smooth and thin, no other lung pathology</td>
<td>Usually not calcified; if calcified, pattern is eccentric, no satellite lesions, cavitation with thick wall, may have pleural effusions, lymphadenopathy</td>
</tr>
<tr>
<td>Doubling Time</td>
<td>Doubles in &lt;1 mo or &gt;2 yr</td>
<td>Doubles in &gt;1 mo or &lt;2 yr</td>
</tr>
</tbody>
</table>

Figure 11. Evaluation of a solitary pulmonary nodule
Sleep-Related Breathing Disorders

Hypoventilation Syndromes

- primary alveolar hypoventilation: idiopathic
- obesity-hypoventilation syndrome (Pickwickian syndrome)
- respiratory neuromuscular disorders

Sleep Apnea

Definition
- episodic decreases in airflow during sleep
- quantitatively measured by the Apnea/Hypopnea Index (AHI) = # of apneic and hypopneic events per hour of sleep
- sleep apnea generally accepted to be present if AHI >15

Classification
- obstructive (OSA)
  - caused by transient, episodic obstruction of the upper airway
  - absent or reduced airflow despite persistent respiratory effort
- central (CSA) (see Neurology, N42)
  - caused by transient, episodic decreases in CNS drive to breathe
  - no airflow because no respiratory effort
  - Cheyne-Stokes Respiration: a form of CSA in which central apneas alternate with hyperpneas to produce a crescendo-decrescendo pattern of tidal volume; seen in severe LV dysfunction, brain injury, and other settings (Figure 2)
- mixed (MSA)
  - features of both OSA and CSA
  - loss of hypoxic and hypercapnic drives to breathe secondary to "resuscitative breathing": overcompensatory hyperventilation upon awakening from OSA induced hypoxia

Risk Factors
- for OSA: obesity, upper airway abnormality, neuromuscular disease, hypothyroidism, alcohol/sedative use, nasal congestion, sleep deprivation
- for CSA: LV failure, brainstem lesions, encephalitis, encephalopathy, myxedema, high altitude

Signs and Symptoms
- obtain history from spouse/partner
- secondary to repeated arousals and fragmentation of sleep: daytime somnolence, personality and cognitive changes, snoring
- secondary to hypoxemia and hypercapnia: morning headache, polycythemia, pulmonary/systemic HTN, cor pulmonale/CHF, nocturnal angina, arrhythmias
- the typical presentation for OSA is a middle-aged obese male who snores
- CSA can be due to neurological disease

Investigations
- sleep study (polysomnography)
  - evaluates sleep stages, airflow, ribcage movement, ECG, SaO2, limb movements
  - indications
    - excessive daytime sleepiness
    - unexplained pulmonary HTN or polycythemia
    - daytime hypercapnia
    - titration of optimal nasal CPAP
    - assessment of objective response to other interventions

Treatment
- modifiable factors: weight loss, decreased alcohol/sedatives, nasal decongestion, treatment of underlying medical conditions
- OSA or MSA: nasal CPAP, postural therapy (i.e. no supine sleeping), dental appliance, uvulopalatopharyngoplasty, tonsillectomy
- CSA or hypoventilation syndromes: nasal BiPAP/CPAP, respiratory stimulants (e.g. progesterone) in select cases
- tracheostomy rarely required and should be used as last resort for OSA

Complications
- depression, weight gain, decreased quality of life, workplace and vehicular accidents, cardiac complications (e.g. HTN), reduced work/social function
Introduction to Intensive Care

• goal is to provide stabilization for critically ill patients: hemodynamic, respiratory or cardiac instability, or need for close monitoring

ICU Basics

Lines and Catheters

• arterial lines
  • monitor beat-to-beat blood pressure variations, obtain blood for routine ABGs
  • common sites are the radial and femoral arteries

• central venous catheter (central line)
  • administer IV fluids, monitor CVP, insert pulmonary artery catheters
  • administer TPN and agents too irritating for peripheral line
  • common sites: internal jugular vein, subclavian vein, femoral vein

• pulmonary arterial catheter
  • balloon guides the catheter from a major vein to the right heart
  • measures pulmonary capillary wedge pressure (PCWP) via a catheter wedged in distal pulmonary artery
  • PCWP reflects the LA and LV diastolic pressure (barring pulmonary venous or mitral valve disease)

• indications (N.B. now used infrequently due to associated complications):
  • diagnosis of shock states, primary pulmonary HTN, valvular disease, intracardiac shunts, cardiac tamponade, PE
  • assessment of hemodynamic response to therapies
  • differentiation of high- versus low-pressure pulmonary edema
  • management of complicated MI, multiorgan system failure and/or severe burns, or hemodynamic instability after cardiac surgery

• absolute contraindications:
  • tricuspid or pulmonary valve mechanical prosthesis
  • right heart mass (thrombus or tumour)
  • tricuspid or pulmonary valve endocarditis

Table 32. Useful Equations and Cardiopulmonary Parameters

<table>
<thead>
<tr>
<th>Equation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSA = (Ht (cm) + Wt (kg) – 60)/100</td>
<td>Body surface area</td>
</tr>
<tr>
<td>PCWP = LVEDP</td>
<td>Left ventricular end diastolic pressure</td>
</tr>
<tr>
<td>SV = CO / HR</td>
<td>Cardiac index</td>
</tr>
<tr>
<td>CI = CO / BSA</td>
<td>Stroke volume index</td>
</tr>
<tr>
<td>SVRI = [(MAP – RAP) 80]/CI</td>
<td>Systemic vascular resistance index</td>
</tr>
<tr>
<td>PP = sBP – dBP</td>
<td>Pulse pressure</td>
</tr>
<tr>
<td>P:F ratio = PaO2 / FiO2</td>
<td>Partial pressure of oxygen in arterial blood / fraction of inspired oxygen</td>
</tr>
</tbody>
</table>

Organ Failure

Table 33. Types of Organ Failure

<table>
<thead>
<tr>
<th>Type of Failure</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Failure (see Respiratory Failure, R24)</td>
<td>Hypoxemia, Hypercapnia</td>
<td>Treat underlying cause (e.g. lung disease, shunt, V/Q mismatch, drug-related, cardiac) Manage mechanical ventilation settings Supplemental oxygen</td>
</tr>
<tr>
<td>Cardiac Failure (see Cardiology, C30)</td>
<td>Hypertension, Decreased urine output, Acyanotic</td>
<td>Treat underlying cause (e.g. bradycardia, tachycardia, blood loss, adrenal insufficiency) Volume resuscitation Vasopressors Inotropes Intra-aortic balloon pump</td>
</tr>
<tr>
<td>Coagulopathy (see Hematology, H34)</td>
<td>Increased INR or PT, Low platelet count, Bleeding, bruising</td>
<td>Treat underlying cause (e.g. thrombocytopenia, drug-related, immune-related, DIC) Transfusion of blood product, clotting factors</td>
</tr>
<tr>
<td>Liver Failure (see Gastroenterology, G36)</td>
<td>Elevated transaminases, bilirubin, Jaundice, Mental alteration (encephalopathy)</td>
<td>Treat underlying cause (e.g. viral hepatitis, drug related, metabolic) Liver transplant Lactulose</td>
</tr>
<tr>
<td>Renal Failure (see Nephrology, NP35)</td>
<td>Elevated creatinine, Reduced urine output, Signs of volume overload (e.g. CHF, effusions)</td>
<td>Treat underlying cause (e.g. shock, drug-related, obstruction) Correct volume and electrolyte status, eliminate toxins Dialysis</td>
</tr>
</tbody>
</table>

ICU Psychosis

A form of delirium or acute brain failure that occurs in ICU patients. Signs and symptoms may include anxiety, agitation, paranoia, hallucinations, and disorientation in time and place. Treatment varies with cause.

Intensive Insulin Therapy in Critically Ill Patients

NEJM 2001;345:1359-1367

Study: Prospective, randomized controlled clinical outcome study.

Patients: 1548 patients admitted to the ICU.

Intervention: At admission, patients were randomly assigned to either intensive insulin therapy or conventional therapy. Those in the intensive group had an infusion started if BG exceeded 6.1 mmol/L, and maintained to keep BG between 4.4 to 6.1 mmol/L. Those in the conventional group were started on insulin only if BG exceeded 11.9, and the infusion was adjusted for a target between 10.0 and 11.1 mmol/L.

Primary Outcome: Death from any cause during ICU stay.

Results: 35 patients (4.6%) died in the intensive group in the ICU, versus 63 patients (8.0%) in the conventional group. This represents a 32% mortality reduction (p<0.04). Intensive insulin therapy also reduced overall in-hospital mortality, lowered deaths due to sepsis, multi-organ failure. Most of the mortality benefit was seen in long stay patients (</>5 d).

Conclusion: Intensive insulin therapy in the ICU reduces mortality by 32%, and improves in-hospital mortality and morbidity.
Shock

- see Emergency Medicine, ER3
- inadequate tissue perfusion potentially resulting in end organ injury
  - categories of shock:
    - hypovolemic: hemorrhage, dehydration, vomiting, diarrhea, interstitial fluid redistribution
    - cardiogenic: myopathic (myocardial ischemia ± infarction), mechanical, arrhythmic, pharmacologic
    - obstructive: massive PE (saddle embolus), pericardial tamponade, constrictive pericarditis, increased intrathoracic pressure (e.g. tension pneumothorax)
    - distributive: sepsis, anaphylactic reaction, neurogenic, endocrinologic, toxic

Table 34. Changes Seen in Different Classes of Shock

<table>
<thead>
<tr>
<th></th>
<th>Hypovolemic</th>
<th>Cardiogenic</th>
<th>Obstructive</th>
<th>Distributive</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>↑</td>
<td>↑, N, or ↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>BP</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>JVP</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Extremities</td>
<td>Cold</td>
<td>Cold</td>
<td>N or Cold</td>
<td>Warm</td>
</tr>
<tr>
<td>Other</td>
<td>Look for visible hemorrhage or signs of dehydration</td>
<td>Bilateral crackles on chest exam</td>
<td>Depending on cause, may see pulsus paradoxus, Kussmaul’s sign, or tracheal deviation</td>
<td>Look for obvious signs of infection or anaphylaxis</td>
</tr>
</tbody>
</table>

- treat underlying cause
- treatment goal is to return critical organ perfusion to normal (e.g. normalize BP)
- common treatment modalities include:
  - fluid resuscitation
  - inotropes (e.g. dobutamine), vasopressors (e.g. norepinephrine), vasopressin
  - revascularization or thrombolitics for ischemic events

Sepsis

- the leading cause of death in noncoronary ICU settings is multi-organ failure due to sepsis
- the predominant theory is that sepsis is attributable to uncontrollable immune system activation

Definitions
- sepsis: the presence of both infection and SIRS (see Table 35)
- severe sepsis: sepsis associated with organ dysfunction, hypoperfusion or hypotension
- septic shock: sepsis with arterial hypotension despite adequate fluid resuscitation
- multitorgan dysfunction syndrome: sepsis in the presence of altered organ function such that homeostasis cannot be maintained without intervention

Signs and Symptoms

Table 35. Clinical Manifestations of Sepsis

<table>
<thead>
<tr>
<th>General Variables</th>
<th>Organ Dysfunction Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (&gt;38°C) or hypothermia (&lt;36°C)</td>
<td>Arterial hypoxemia (P&lt;sub&gt;O2&lt;/sub&gt;/F&lt;sub&gt;IO2&lt;/sub&gt; &lt; 300)</td>
</tr>
<tr>
<td>Heart rate &gt;90/min</td>
<td>Acute oliguria (urine output &lt; 0.5 mL/kg/h)</td>
</tr>
<tr>
<td>sBP &lt;90 mmHg, MAP &lt;70, or a sBP decrease &gt;40 mmHg</td>
<td>Creatinine increase &gt; 0.5 mg/dl</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>Congestion abnormalities (INR &gt; 1.5 or aPTT &gt; 60 s)</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>Thrombocytopenia (platelet count &lt; 100,000/L)</td>
</tr>
<tr>
<td>Positive fluid balance (&gt;20 mL/kg over 24 h)</td>
<td>Hyperbilirubinemia (plasma total bilirubin &gt; 4 mg/dL or 70 mmol/L)</td>
</tr>
<tr>
<td>Hyperglycemia (BG &gt; 7.7 mmol/L) in the absence of diabetes</td>
<td>Leukocytosis (WBC &gt; 12,000/L)</td>
</tr>
<tr>
<td>Leukopenia (WBC &lt;4,000/L)</td>
<td>Tissue Perfusion Variables</td>
</tr>
<tr>
<td>Normal WBC count with &gt;10% immature forms</td>
<td>Hypernatremia (&gt;110 mmol/L)</td>
</tr>
<tr>
<td>Plasma C-reactive protein &gt;2 SD above the normal value</td>
<td>Decreased capillary refill or mottling</td>
</tr>
</tbody>
</table>


Treatment
- identify the cause and source of infection: blood, sputum, urine Gram stain and C&S
- initiate empiric antibiotic therapy
- monitor, restore and maintain hemodynamic function

Early Goal Directed Therapy
- adjustments of cardiac preload, afterload and contractility to balance oxygen delivery with demand
- should be started immediately and completed within 6 h of recognition of severe sepsis or septic shock

Shock: Clinical Correlation
- Hypovolemic: patients have cool extremities due to peripheral vasoconstriction.
- Cardiogenic: patients usually have signs of left-sided heart failure.
- Obstructive: varied presentation.
- Distributive: patients have warm extremities due to peripheral vasodilation.

Causes of SHOCK
- Spinal (neurogenic), Septic
- Hemorrhagic
- Obstructive (e.g. tension pneumothorax, cardiac tamponade, PE)
- Cardiogenic (e.g. arrhythmia, MI)

Systemic Inflammatory Response Syndrome (SIRS): generalized inflammatory reaction caused by infectious and noninfectious entities, manifested by two or more of:
- Body temperature >38.5°C or <35°C
- Heart rate >90/min
- Respiratory rate >20/min or P<sub>CO2</sub> < 32 mmHg
- WBC >12000 cells/mL or <4000 cells/mL or >10% bands

Corticosteroids for Treating Severe Sepsis and Septic Shock
- Cochrane DB Syst Rev 2010;CD002243
- Study: Meta-analysis of 25 RCTs and quasi-RCTs examining the efficacy of corticosteroids on death at one month in patients with severe sepsis and septic shock.
- Results: Overall, there was no difference in 28-d all-cause mortality but there was significant heterogeneity in dosing strategy between the studies. Treatment with long course of low dose corticosteroids significantly reduced 28-d mortality, increased the proportion of shock reversal by day 7 and day 28, reduced the sepsis-related organ failure assessment score by day 7, and survivors’ length of stay in the ICU, without inducing gastroduodenal bleeding, superinfection, or neuromuscular weakness. Corticosteroids increased the risk of hyperglycemia and hypernatremia.
- Conclusion: Corticosteroids did not change mortality in severe sepsis and septic shock. A long course of low dose corticosteroids reduced 28-d mortality without major complications.
• patient should meet SIRS criteria and sBP <90 mmHg or lactate >4 mmol/L
  1. supplemental oxygen ± intubation and mechanical ventilation
  2. central venous and arterial catheterization
  3. maintain CVP 8-12 mmHg with IV crystalloids/colloids
  4. MAP maintained 65-90 mmHg with the use of vasoactive agents
  5. SaO2 <70% then
    • transfusion of red cells until Hct >30%
    • if SaO2 <70% after transfusion then use inotropes agents

• supportive oxygenation and ventilation using lung-protective regime
• early nutritional support: enteral route is used to preserve function of intestinal mucosal barrier
• control hyperglycemia with insulin to decrease infectious complications
• physiologic dose corticosteroid replacement therapy in patients with relative adrenal insufficiency (nonresponders to corticotropin stimulation test)
• consider in mechanically ventilated septic shock patients with organ dysfunction requiring vasopressors, despite early goal-directed therapy and appropriate antibiotic therapy
• recombinant activated protein C may be considered in patients with severe sepsis or septic shock with an APACHE II score >25 despite early goal-directed therapy and appropriate antibiotic therapy
• DVT/PE prophylaxis
• advanced care planning, including the communication of likely outcomes and realistic goals of treatment with patients and families

## Common Medications

### Table 36. Common Medications for Respiratory Diseases

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Adult Dose</th>
<th>Indications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β2-AGONISTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting sabutolol/ibuterol (&lt;Ventolin®&gt; (light blue/navy), terbutaline (&lt;Bricanyl®&gt;)</td>
<td>1-2 puffs q4-6h pm</td>
<td>Bronchodilator in acute reversible airway obstruction</td>
<td>CV (angina, flushing, palpitations, tachycardia, can precipitate AFB), CNS (dizziness, headache, insomnia, anxiety), GI (diarrhea, nausea, vomiting), rash, hypokalemia, pancreas y bromochondraspam</td>
</tr>
<tr>
<td>Long-acting salmeterol (&lt;Serevent®&gt;, formoterol (&lt;Oxane®&gt;) indacaterol (&lt;Onbre®&gt;)</td>
<td>1-2 puffs bid</td>
<td>Maintenance treatment (prevention of bronchospasm) in COPD, asthma</td>
<td></td>
</tr>
<tr>
<td>Combination fluticasone and salmeterol (&lt;Advar®&gt; (purple MDI or diskus), Budesonide and formoterol (&lt;Zymabatic®&gt; (red turbuhaler), Mometasone and formoterol (&lt;Zenhal®&gt; (blue MDI))</td>
<td>1 puff bid</td>
<td>COPD and asthma</td>
<td>Common: CNS, headache, dizziness Resp: URTI, GI (N/V, diarrhea, pain/discomfort, oral candidiasis)</td>
</tr>
<tr>
<td><strong>ANTICHOLINERGICS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ipratropium bromide (&lt;Atrovent®&gt; (clear/green), itrotopium bromide (&lt;Spiriva®&gt; (light blue/navy), glycopyrrolate bromide</td>
<td>2-3 puffs qid</td>
<td>Bronchodilator used in COPD, bronchitis and emphysema</td>
<td>Palpitations, anxiety, dizziness, fatigue, headache, nausea, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drugs</td>
</tr>
<tr>
<td>1 puff qam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 puff daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CORTICOSTEROIDS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled fluticasone (&lt;Flovent®&gt; (orange/pach), budesonide (&lt;Pulmicort®&gt; (albesia), beclometasone (&lt;QVAR®, Vanceril®) Mometasone (&lt;Asmanex®&gt;</td>
<td>2-4 puffs bid</td>
<td>Maintenance treatment of asthma</td>
<td>Headache, fever, N/V, N/SK pain, URI, throat irritation, growth velocity reduction in children/adolescents, HPA axis suppression, increased pneumonia risk in COPD</td>
</tr>
<tr>
<td>2 puffs bid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4 puffs (0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4 puffs bid (40 µg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 puffs bid (80 µg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 puff daily or bid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic prednisone (&lt;Depo-prednisone®, Deltasone®&gt; methylprednisolone (&lt;Depo-Medrol®, Solu-Medrol®)</td>
<td>Typically 40-60 mg per day PO 125 mg q6h IV (sodium succinate) loading dose 2 mg/kg then 0.5-1 mg/kg q6h for 5 d</td>
<td>Acute exacerbation of COPD; severe, persistent asthma, PGP Status asthmatus</td>
<td>Endocrine (hirsutism, DM/glucose intolerance, Cushing’s syndrome, HPA axis suppression), GI (increased appetite, indigestion, nausea, vomiting), pancreatic, CV (tachycardia, palpitations, GI upset, abdominal discomfort), respiratory (cough, wheezing, bronchospasm), dermatologic (acne, dermatitis, hair loss), GI (diarrhea, nausea, vomiting), endocrine (hirsutism, DM/glucose intolerance, Cushing’s syndrome, HPA axis suppression), GI (increased appetite, indigestion, nausea, vomiting), pancreatic, CV (tachycardia, palpitations, GI upset, abdominal discomfort), respiratory (cough, wheezing, bronchospasm), dermatologic (acne, dermatitis, hair loss), skin (rash, pruritus)</td>
</tr>
<tr>
<td><strong>ADJUNCT AGENTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>theophylline (&lt;Uniphy®&gt;</td>
<td>400-600 mg OD</td>
<td>Treatment of symptoms of reversible airway obstruction due to COPD</td>
<td>GI upset, diarrhea, N/V, anxiety, headache, insomnia, muscle cramp, tremor, tachycardia, PVS, arrhythmias, Toxicity: persistent, repetitive vomiting, seizures</td>
</tr>
<tr>
<td><strong>LEUKOTRIENE ANTAGONISTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>montelukast (&lt;Singular®&gt;</td>
<td>10 mg PO qhs, now only available as once daily slow release 20 mg bid</td>
<td>Prophyaxis and chronic treatment of asthma</td>
<td>Headache, dizziness, fatigue, fever, rash, dyspnea, cough, flu-like symptoms</td>
</tr>
<tr>
<td>zafirlukast (&lt;Accolate®&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MONOCLONAL ANTIBODIES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>omalizumab (&lt;Xolar®&gt;</td>
<td>150-375 mg SC q2-4wk</td>
<td>Moderate-severe persistent asthma</td>
<td>Headache, sinusitis, pharyngitis, URI, viral infection, thrombocytopenia, anaphylaxis</td>
</tr>
</tbody>
</table>
### Table 36. Common Medications for Respiratory Diseases (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Adult Dose</th>
<th>Indications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PDE5 INHIBITORS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roflumilast (Daxas®)</td>
<td>500 µg PO OD</td>
<td>Severe emphysema, with frequent exacerbations</td>
<td>Weight loss, suicidal ideation</td>
</tr>
<tr>
<td><strong>ANTIBIOTICS – COMMUNITY ACQUIRED PNEUMONIA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Macrolide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>erythromycin</td>
<td>250-500 mg PO tid x 7-10 d</td>
<td>Alternate to doxycycline or fluoroquinolone</td>
<td>GI (abdominal pain, diarrhea, N/V), headache, prolonged QT, ventricular arrhythmias, hepatic impairment Gl (diabetes, N/V, abdo pain), renal failure, deafness, heartburn, abdo pain, increased area</td>
</tr>
<tr>
<td>azithromycin</td>
<td>500 mg PO x 1 dose, then 250 mg OD x 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>clarithromycin</td>
<td>500 mg PO bid x 7-10 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Doxycycline</strong></td>
<td>100 mg PO bid x 7-10 d</td>
<td>Alternate to macrolide or fluoroquinolone</td>
<td>Photosensitivity, rash, urticaria, anaphylaxis, diarrhea, enterocolitis, tooth discolouration in children</td>
</tr>
<tr>
<td><strong>Fluoroquinolone</strong></td>
<td></td>
<td>Alternate to macrolide or doxycycline</td>
<td>CNS (dizziness, fever, H/A), Gl (N/V, diarrhea, constipation), prolonged QT</td>
</tr>
<tr>
<td>levofloxacin (Levaquin®)</td>
<td>500 mg PO OD x 7-10 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moxifloxacin (Avelox®)</td>
<td>400 mg PO OD x 7 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANTIBIOTICS – HOSPITAL ACQUIRED PNEUMONIA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd gen Cephalosporin</td>
<td></td>
<td>Combine with fluoroquinolone or macrolide</td>
<td>Rash, diarrhea, esinophilia, thrombocytosis, leukopenia, elevated transaminases</td>
</tr>
<tr>
<td>ceftriaxone (Rocephin®)</td>
<td>1-2 g IV OD x 7-10 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td></td>
<td>Combine with 3rd gen cephalosporin</td>
<td>See above</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>750 mg PO OD x 5 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400 mg PO OD x 7 d (5 d for AECOPD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Piperacillin/Tazobactam</strong></td>
<td>4.5 g IV q6-8h x 7-10 d</td>
<td>Suspect Pseudomonas</td>
<td>CNS (confusion, convulsions, drowsiness), rash, Hematologic (abnormal platelet aggregation, prolonged PT, positive Coombs)</td>
</tr>
<tr>
<td>(Tazocin®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin (Vancocin®)</td>
<td>1 g IV bid x 7-10 d</td>
<td>Suspect MRSA</td>
<td>CNS (chills, drug fever), hematologic (esinophilia), rash, red man syndrome, interstitial nephritis, renal failure, ototoxicity</td>
</tr>
<tr>
<td>Macrolide</td>
<td></td>
<td>Suspect Legionella</td>
<td>See above</td>
</tr>
<tr>
<td>azithromycin</td>
<td>500 mg IV OD x 2 d, then 500 mg PO OD x 5 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>clarithromycin</td>
<td>500 mg PO bid x 7-10 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ICU MEDICATIONS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pressors/Inotropes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>norepinephrine (Levophed®)</td>
<td>0.5-30 µg/min IV</td>
<td>Acute hypotension</td>
<td>Angina, bradycardia, dyspnea, hyper/hypotension, arrhythmias See above</td>
</tr>
<tr>
<td>phenylephrine</td>
<td>0.5 µg/kg/min IV</td>
<td>Severe hypotension</td>
<td>See above</td>
</tr>
<tr>
<td>dobutamine</td>
<td>2-20 µg/kg/min IV</td>
<td>Inotropic support</td>
<td>See above</td>
</tr>
<tr>
<td><strong>Sedatives/Analgesia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fentanyl (opioid class)</td>
<td>50-100 µg then 50-unlimited µg/h IV</td>
<td>Sedation and/or analgesia</td>
<td>Bradycardia, respiratory depression, drowsiness, hypotension</td>
</tr>
<tr>
<td>propofol (anesthetic)</td>
<td>1-3 mg/kg then 0.3-5 mg/kg/h IV</td>
<td>Sedation and/or analgesia</td>
<td>Apnea, bradycardia, hypotension (good for ventilator sedation)</td>
</tr>
</tbody>
</table>

See Infectious Diseases, ID23 – for the management of pulmonary tuberculosis

### Landmark Respirology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS Network</td>
<td>NEJM 2000; 342:1301-8</td>
<td>Mortality decreased in ARDS patients ventilated with a low tidal volume strategy</td>
</tr>
<tr>
<td>Berlin Criteria</td>
<td>JAMA 2012; 307:2526-33</td>
<td>The new definition of ARDS, better predicts mortality</td>
</tr>
<tr>
<td>CPAP and Apeema</td>
<td>NEJM 2005; 353:2025-33</td>
<td>CPAP ameliorates symptoms of sleep apnea but does not affect mortality in CHF</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>NEJM 2012; 366:1287-97</td>
<td>Fixed dose of rivoxabarin was non-inferior to standard therapy (Vit K antagonist) initial and long term treatment of PE</td>
</tr>
<tr>
<td>Emphysema Treatment Trial</td>
<td>NEJM 2003; 348:2059-73</td>
<td>Lung volume reduction surgery benefits patients with upper lobe disease and low exercise capacity</td>
</tr>
<tr>
<td>IELCAP</td>
<td>NEJM 2006; 355:1763-71</td>
<td>High survival rate with early stage lung cancer detected by low dose CT screening</td>
</tr>
<tr>
<td>Lung Health</td>
<td>JAMA 1994; 272:1497-505</td>
<td>Aggressive smoking intervention significantly decreases the age-related decline in FEV1 in middle-aged smokers with mild airways obstruction</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>NEJM 1978; 298:801-9</td>
<td>Interstitial lung disease subsets have different prognoses and response to treatment (e.g. desquamative but not usual interstitial pneumonia respond well to corticosteroids)</td>
</tr>
<tr>
<td>POET-COPD</td>
<td>NEJM 2011; 364:1093-103</td>
<td>Tiotropium decreases the number of moderate-to-severe exacerbations in comparison to salmeterol</td>
</tr>
<tr>
<td>ROLFLUMILAST</td>
<td>LANCET 2009; 374:695-703</td>
<td>Leukotriene inhibitors improve FEV1 when used as add-on therapy in COPD patients on botropium or salmeterol</td>
</tr>
<tr>
<td>TORCH</td>
<td>NEJM 2007; 356:775-89</td>
<td>Combination of inhaled steroids and long-acting β2-agonists improves COPD symptoms, reduces exacerbations and shows a trend to lowers mortality</td>
</tr>
<tr>
<td>UPLIFT</td>
<td>NEJM 2008; 359:1543-54</td>
<td>Tiotropium improves symptoms of COPD with fewer exacerbations, but does not affect FEV1 decline</td>
</tr>
</tbody>
</table>
Anatomy of Joint Pathology ............... 2
Basics of Immunology ..................... 2
  Immune Mechanisms of Disease
  Immunogenetics and Disease
Differential Diagnoses of Common
  Presentations .............................. 3
Synovial Fluid Analysis .................... 4
Septic Arthritis ............................ 5
Degenerative Arthritis:
  Osteoarthritis (OA) ....................... 5
SEROPOSITIVE RHEUMATIC DISEASE
Investigations ............................. 6
Connective Tissue Disorders ............... 8
  Rheumatoid Arthritis (RA)
  Systemic Lupus Erythematosus (SLE)
  Anti-phospholipid Antibody Syndrome (APLA)
  Scleroderma
  Idiopathic Inflammatory Myopathy
  Sjögren’s Syndrome (SS)
  Mixed Connective Tissue Disease (MCTD)/
    Overlap Syndrome
Vasculitides ................................ 17
  Small Vessel Non-ANCA Associated Vasculitis
  Small Vessel ANCA-Associated Vasculitis
  Medium Vessel Vasculitis
  Large Vessel Vasculitis

SERONEGATIVE RHEUMATIC DISEASE
Spondyloarthropathies ..................... 21
  Ankylosing Spondylitis (AS)
  Enteropathic Arthritis (EA)
  Psoriatic Arthritis (PsA)
  Reactive Arthritis (ReA)
Crystal-Induced Arthropathies ............ 24
  Gout
  Pseudogout (Calcium Pyrophosphate
    Dihydrate Disease)
Pediatric Rheumatology .................. P96
Non-Articular Rheumatism ................. 26
  Polymyalgia Rheumatica (PMR)
  Fibromyalgia
  Adult Onset Still’s Disease
Common Medications ....................... 29
Landmark Rheumatology Trials .......... 31
References .................................. 32

Acronyms

Ab  antibody
Ag  antigen
ANA  antinuclear antibody
Anti-Sm  anti-Smith antibodies
APLA  antiphospholipid antibody syndrome
AS  ankylosing spondylitis
BUN  blood urea nitrogen
CBC  complete blood count
CCP  cyclic citrullinated peptide
CGS  central nervous system
CRP  C-reactive protein
DIP  distal interphalangeal joint
EA  enteropathic arthritis
ESR  erythrocyte sedimentation rate
GC  Neisseria gonorrhoea/gonococcus
GCA  giant cell arthritis
H/A  headache
HA  hyaluronic acid
Hb  hemoglobin
HLA  human leukocyte antigen
IA  intra-articular
IBD  inflammatory bowel disease
IE  infective endocarditis
MCP  metacarpal phalangeal joint
MCTD  mixed connective tissue disease
MHC  major histocompatibility complex
OA  osteoarthritis
PIP  proximal interphalangeal joint
PMR  polymyalgia rheumatica
PsA  psoriatic arthritis
PTT  partial thromboplastin time
RA  rheumatoid arthritis
RBC  red blood cell
RA  reactive arthritis
RF  rheumatoid factor
ROM  range of motion
SLE  systemic lupus erythematosus
SS  Sjögren’s syndrome
ULN  upper limit of normal
VDRL  venereal disease research laboratory
WBC  white blood cell
Anatomy of Joint Pathology

Figure 1. Structure of normal, degenerative and inflammatory joint

Basics of Immunology

Table 1. Mechanisms of Immunologically Mediated Disorders

<table>
<thead>
<tr>
<th>Type</th>
<th>Pathophysiology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylactic (type I)</td>
<td>Formation of IgE → release of immunologic mediators from basophils/ mast cells → diffuse inflammation</td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>Cytotoxic (type II)</td>
<td>Formation of antibody (Ab) → deposit and bind to antigen (Ag) on cell surface → phagocytosis or lysis of target cell</td>
<td>Autoimmune hemolytic anemia, Goodpasture’s syndrome, Graves’ disease, pernicious anemia</td>
</tr>
<tr>
<td>Immune complex (type III)</td>
<td>formation of Ag-Ab complexes → activate complement → attract inflammatory cells and release of cytokines</td>
<td>SLE, PAN, post-streptococcal glomerulonephritis, serum sickness</td>
</tr>
<tr>
<td>Cell-mediated/delayed hypersensitivity (type IV)</td>
<td>Release of cytokines by sensitized T-cells and T-cell mediated cytotoxicity</td>
<td>Contact dermatitis</td>
</tr>
</tbody>
</table>

Immunogenetics and Disease

- cell surface molecules called human leukocyte antigen (HLA) play a role in mediating immune reactions
- major histocompatibility complex (MHC) are genes on the short arm of chromosome 6 that encode HLA molecules
- there are three classes of MHC (see Table 2)
- discrete domains of hypervariability within MHC molecules thought to represent "susceptibility determinants”
- certain HLA haplotypes are associated with increased susceptibility to autoimmune diseases (see Table 3)

Table 2. Classes of Major Histocompatibility Complexes (MHCs)

<table>
<thead>
<tr>
<th>MHC Class</th>
<th>Types</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>HLA-A, B, C</td>
<td>All cells</td>
<td>Recognized by CD8+ (cytotoxic) T-lymphocytes</td>
</tr>
<tr>
<td>II</td>
<td>HLA-DP, DQ, DR</td>
<td>Antigen presenting cells (mononuclear phagocytes, B cells, others)</td>
<td>Recognized by CD4+ (helper) T-lymphocytes</td>
</tr>
<tr>
<td>III</td>
<td>Some components of the complement cascade</td>
<td>In plasma</td>
<td>Chemotaxis, opsonization, lysis of bacteria and cells</td>
</tr>
</tbody>
</table>
**Table 3. HLA-Associated Rheumatic Disease**

<table>
<thead>
<tr>
<th>HLA Type</th>
<th>Associated Conditions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>B27</td>
<td>Ankylosing spondylitis (AS)</td>
<td>In AS, relative risk = 70-90 times In ReA, relative risk = 40 times</td>
</tr>
<tr>
<td></td>
<td>Reactive arthritis (ReA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enteropathic arthritis (EA)</td>
<td></td>
</tr>
<tr>
<td>DR4, DR1</td>
<td>Rheumatoid arthritis (RA)</td>
<td>In RA, relative risk = 2-10 times; found in 93% of patients</td>
</tr>
<tr>
<td>DR3</td>
<td>Sjögren’s syndrome</td>
<td>DR3 associated with many non-rheumatic conditions (celiac disease, Type 1 DM, Graves’ disease, chronic active hepatitis)</td>
</tr>
<tr>
<td></td>
<td>SLE</td>
<td></td>
</tr>
</tbody>
</table>

**Differential Diagnoses of Common Presentations**

**Figure 2. Clinical approach to joint pain**

**Table 4. Differential Diagnosis of Monoarthritis**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Crystal</th>
<th>Degenerative</th>
<th>Neoplastic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic arthritis (staph, gonococcal, fungi, TB)</td>
<td>Gout</td>
<td>Osteoarthritis</td>
<td>Hemarthrosis</td>
<td>Tumour</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Osteonecrosis</td>
<td>Systemic inflammatory disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Polyarthritis presenting with monoarticular symptoms first</td>
</tr>
<tr>
<td></td>
<td>Pseudogout</td>
<td>Hydroxyapatite</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 5. Differential Diagnosis of Oligoarthritis/Polyarthritis**

<table>
<thead>
<tr>
<th>Acute (&lt;6 weeks)</th>
<th>Chronic (&gt;6 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First presentation of inflammatory arthritis</td>
<td>Seropositive inflammatory arthritis</td>
</tr>
<tr>
<td>Post-viral (parvovirus B19)</td>
<td>Ankylosing spondylitis</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Infectious (GC, non-GC)</td>
<td>Scleroderma</td>
</tr>
<tr>
<td></td>
<td>Polymyositis/dermatomyositis</td>
</tr>
</tbody>
</table>

**Table 6. Symptoms of Inflammatory Arthritis vs. Degenerative Arthritis**

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Degenerative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at rest, relieved by motion</td>
<td>Pain with motion, relieved by rest</td>
</tr>
<tr>
<td>Morning stiffness &gt; 1 h</td>
<td>Morning stiffness &lt; ½ h</td>
</tr>
<tr>
<td>Warmth, swelling, erythema</td>
<td>Joint instability, buckling, locking</td>
</tr>
<tr>
<td>Malalignment/deformity</td>
<td>Bony enlargement, malalignment/deformity</td>
</tr>
<tr>
<td>Extra-articular manifestations</td>
<td></td>
</tr>
</tbody>
</table>
Table 7. Seropositive vs. Seronegative Rheumatic Diseases

<table>
<thead>
<tr>
<th></th>
<th>Seropositive</th>
<th>Seronegative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td>F&gt;M</td>
<td>M&gt;F</td>
</tr>
<tr>
<td><strong>Peripheral Arthritis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symmetrical</td>
<td>Usually asymmetrical (psoriatic arthritis may be the exception)</td>
<td></td>
</tr>
<tr>
<td>Small (PIP, MCP) and medium joints (wrist, knee, ankle, elbow) common DIP less involved</td>
<td>Usually larger joints, lower extremities</td>
<td></td>
</tr>
<tr>
<td>Pelvic/Axial Disease</td>
<td>No (except for C-spine)</td>
<td>Yes</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Extra-Articular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodules</td>
<td>Intis (= anterior uveitis)</td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Oral ulcers</td>
<td></td>
</tr>
<tr>
<td>Sicca</td>
<td>GI</td>
<td></td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>Dermatologic features</td>
<td></td>
</tr>
</tbody>
</table>

Common Investigations in Rheumatology
- general: CBC, electrolytes, Cr
- acute phase reactants: ESR, CRP, ferritin, albumin, fibrinogen
- complement (C3, C4)
- urinalysis to detect disease complications (proteinuria, active sediment)
- serology: autoimmune Abs (ANA, anti-dsDNA, anti-Jo-1, anti-Sm, anti-La, anti-Ro, RhF, and anti-CCP, etc.)
- synovial fluid analysis
- radiology (plain film, CT, MRI, U/S, bone densitometry, angiography, bone scan)

**Synovial Fluid Analysis**
- synovial fluid is an ultrafiltrate of plasma plus hyaluronic acid; it lubricates joint surfaces and nourishes articular cartilage

**Indications**
- diagnostic: mandatory if septic arthritis suspected; advised if crystal arthritis or hemorrhatis suspected; advised if unexplained effusion in accessible joint
- therapeutic: drainage of blood, purulent or tense effusions; corticosteroid injection

**Contraindications**
- absolute: open lesion or suspected infection of overlying skin or soft tissue
- relative: bleeding diathesis, thrombocytopenia, prosthetic joint

**Most Important Tests of Synovial Fluid (3 Cs)**
- ensure synovial fluid is described in terms of colour, clarity, viscosity, and quantity
  1. Cell count and differential
  2. Culture and Gram stain (bacteria, mycobacteria, fungi)
  3. Crystal examination (microscopy with polarized light)
    - gout (monosodium urate) → needle-shaped, negatively birefringent (bright yellow)
    - pseudogout (calcium pyrophosphate dihydrate) → rhomboid-shaped, positively birefringent (pale blue)

Table 8. Synovial Fluid Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Non-Inflammatory</th>
<th>Inflammatory</th>
<th>Infectious</th>
<th>Hemorrhagic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colour</strong></td>
<td>Pale yellow</td>
<td>Pale yellow</td>
<td>Pale yellow</td>
<td>Yellow to white</td>
<td>Red/brown</td>
</tr>
<tr>
<td><strong>Clarity</strong></td>
<td>Clear</td>
<td>Clear</td>
<td>Opaque</td>
<td>Opaque</td>
<td>Sanguinous</td>
</tr>
<tr>
<td><strong>Viscosity</strong></td>
<td>High (due to hyaluronic acid)</td>
<td>High</td>
<td>Low</td>
<td>Low or paradoxically high if purulent</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>WBC/mm³</strong></td>
<td>&lt;200</td>
<td>&lt;2000</td>
<td>&gt;2000</td>
<td>Higher cell counts (particularly &gt;50,000) suggestive</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>% PMN</strong></td>
<td>&lt;25%</td>
<td>&lt;25%</td>
<td>&gt;25%</td>
<td>&gt;75%</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Culture/ Gram stain</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Usually positive</td>
<td>–</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td>Trauma</td>
<td>Osteoarthritis</td>
<td>Seropositives</td>
<td>S. aureus</td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td>Neuropathy</td>
<td>Seronegatives</td>
<td>Crystal</td>
<td>Gram negative</td>
<td>Hemophilia</td>
</tr>
<tr>
<td></td>
<td>Hypertrophic – arthropathy</td>
<td>Arthropathies</td>
<td>artropathies</td>
<td>Gonococcal</td>
<td>difficult to culture</td>
</tr>
</tbody>
</table>
Septic Arthritis

- for any acute monoarticular arthritis, one must rule out septic etiology; consider empiric antibiotic treatment until septic arthritis is excluded by history, physical exam and synovial fluid analysis
- poor prognostic factors: older age, immunocompromised, delay in treatment, previously damaged joint, joint prosthesis
- see Infectious Diseases for Gonococcal Arthritis, ID15/Orthopedics, OR10

Degenerative Arthritis: Osteoarthritis (OA)

Definition
- progressive deterioration of cartilage and bone due to failed repair of joint damage caused by stresses on the joint

Classification (based on etiology)
- primary (idiopathic)
  - most common, unknown etiology
- secondary
  - post-traumatic or mechanical
  - post-inflammatory (e.g. RA) or post-infectious
  - heritable skeletal disorders (e.g. scoliosis)
  - endocrine disorders (e.g. acromegaly, hyperparathyroidism, hypothyroidism)
  - metabolic disorders (e.g. gout, pseudogout, hemochromatosis, Wilson's disease, ochronosis)
  - neuropathic (e.g. Charcot joints)
    - atypical joint trauma due to peripheral neuropathy (e.g. diabetes, syphilis)
    - avascular necrosis
    - other (e.g. congenital malformation)

Pathophysiology
- deterioration of articular cartilage due to local biomechanical factors and release of proteolytic and collagenolytic enzymes
  - OA develops when cartilage catabolism > synthesis
  - loss of proteoglycans and water exposes underlying bone
- abnormal local bone metabolism further damages joint
- altered joint function and damage
- synovitis is secondary to cartilage damage; therefore, may see small effusions in OA

Epidemiology
- most common arthropathy
- increased prevalence with increasing age (35% of 30 yr olds, 85% of 80 yr olds)

Risk Factors
- genetic predisposition, advanced age, obesity (for knee OA), female, trauma

Signs and Symptoms
- localized to affected joints (not a systemic disease)
- pain is often insidious, gradually progressive, with intermittent flares and remissions

<table>
<thead>
<tr>
<th>Table 9. Signs and Symptoms of OA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signs</strong></td>
</tr>
<tr>
<td>Joint line tenderness; stress pain ≤ joint effusion</td>
</tr>
<tr>
<td>Bony enlargement at affected joints</td>
</tr>
<tr>
<td>Malalignment/deformity (angulation)</td>
</tr>
<tr>
<td>Limited ROM</td>
</tr>
<tr>
<td>Crepitus on passive ROM</td>
</tr>
<tr>
<td>Inflammation (mild if present)</td>
</tr>
<tr>
<td>Periarticular muscle atrophy</td>
</tr>
</tbody>
</table>

Joint Involvement (see Figure 3)
- asymmetric
- hand (see Figure 4)
  - DIP (Heberden’s nodes = osteophytes → enlargement of joints)
  - PIP (Bouchard’s nodes)
  - CMC (usually thumb squaring)
  - 1st MCP (other MCPs are usually spared)
Seropositive Rheumatic Disease

- seropositive arthropathies are characterized by the presence of a serologic marker such as a positive rheumatoid factor or ANA
- the vasculitides are not seropositive diseases – some may be ANCA positive

![Treatment](https://example.com/image1.png)

![Investigations](https://example.com/image2.png)

![Treatment](https://example.com/image3.png)

![Treatment](https://example.com/image4.png)

![Treatment](https://example.com/image5.png)

![Treatment](https://example.com/image6.png)

![Treatment](https://example.com/image7.png)

![Treatment](https://example.com/image8.png)

![Treatment](https://example.com/image9.png)

![Treatment](https://example.com/image10.png)

Figure 5. Seropositive rheumatic diseases
Investigations

Bloodwork
- general: CBC, creatinine
- acute phase reactants: ESR, CRP, ferritin, albumin, complement (C3 and C4), fibrinogen,
- Note: C3, C4 often decrease in active SLE
- autoantibodies (see Table 10)

Urinalysis
- proteinuria, active sediment
- synovial fluid analysis (see Table 8)
- radiology (plain film, CT, MRI, ultrasound, bone densitometry, angiography, bone scan)

Table 10. Autoantibodies and their Prevalence in Rheumatic Diseases

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Disease</th>
<th>Normal</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF</td>
<td>RA 80%</td>
<td>&lt;5%</td>
<td>Autoantibodies (IgM&gt;IgG&gt;IgA) directed against Fc domain of IgG. Present in most seropositive diseases. Levels correlate with disease severity in RA. Non-specific; may be present in IE, TB, hepatitis C, silicosis, sarcoidosis.</td>
</tr>
<tr>
<td>SS 50%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLE 20%</td>
<td></td>
<td>&gt;65</td>
<td></td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>RA 80%</td>
<td></td>
<td>In RA: anti CCP more specific than RF. May be useful in early disease and to predict aggressive disease.</td>
</tr>
<tr>
<td>ANA</td>
<td>SLE 98%</td>
<td>&lt;5%</td>
<td>Antibodies against nuclear components (DNA, RNA, histones, centromere). 1:40 dilution found in 5-30% of the normal population. Sensitive but not specific for SLE.</td>
</tr>
<tr>
<td>MCTD 95%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SS 70-90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREST 80%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>SLE 50-70%</td>
<td>0%</td>
<td>Specific for SLE. Levels correlate with disease activity.</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td>SLE &lt;30%</td>
<td>0%</td>
<td>Specific but not sensitive for SLE.</td>
</tr>
<tr>
<td>Anti-Ro (SSA)</td>
<td>SS 40-95%</td>
<td>0.5%</td>
<td>Subacutus cutaneous SLE and mothers of babies with neonatal SLE 25%.</td>
</tr>
<tr>
<td>Anti-La (SSB)</td>
<td>SS 40%</td>
<td>0%</td>
<td>Usually occurs with anti-Ro.</td>
</tr>
<tr>
<td>Anti-RNP</td>
<td>MCTD</td>
<td>0%</td>
<td>Present in MCTD; present in many other CTD.</td>
</tr>
<tr>
<td>Anti-centromere</td>
<td>CREST &gt;80%</td>
<td>0%</td>
<td>Specific for CREST variant of systemic sclerosis.</td>
</tr>
<tr>
<td>Anti-topoisomerase I (formerly Scl-70)</td>
<td>Diffuse systemic sclerosis 28-76%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>c-ANCA</td>
<td>Active GPA (granulomatosis with polyangiitis) &gt;90%</td>
<td>0%</td>
<td>Specific and sensitive.</td>
</tr>
<tr>
<td>p-ANCA</td>
<td>GPA (granulomatosis with polyangiitis) 10%. Other vasculitis</td>
<td>0%</td>
<td>Nonspecific and poor sensitivity (found in ulcerative colitis, polyarteritis nodosa, microscopic polyangiitis, Churg-Strauss, rapidly progressive glomerulonephritis).</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>DM 15-20%</td>
<td>0%</td>
<td>Specific but not sensitive (not available in all centres).</td>
</tr>
<tr>
<td>Antibodies against RBCs, WBCs, or platelets</td>
<td>SLE</td>
<td></td>
<td>Perform direct Coomb’s test. Test hemoglobin, reticulocyte, leukocyte and platelet count, antplatelet Abs.</td>
</tr>
</tbody>
</table>

- note: some individuals in the normal population test positive for RF and/or ANA, but do not have the conditions listed.
### Connective Tissue Disorders

#### Table 11. Features of Seropositive Arthropathies

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>SLE</th>
<th>Scleroderma</th>
<th>Dermatomyositis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL FEATURES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>Symmetrical polyarthritis (small joint involvement)</td>
<td>Multisystemic disease: rash, photosensitivity, Raynaud’s, alopecia, cardiac and pulmonary serositis, CNS symptoms, glomerulonephritis</td>
<td>Skin tightness, stiffness of fingers, Raynaud’s, heartburn, dysphagia, pulmonary hypertension, renal dysfunction, dyspnea on exertion</td>
<td>Heliotrope rash (periarticular), Gottron’s papules (violaceous papules over knuckles and IP joints) ± poikiloderma, Shawl sign macular erythema over chest and shoulder, Proximal muscle weakness ± pain, Dyspnea on exertion</td>
</tr>
<tr>
<td><strong>Physical Examination</strong></td>
<td>Effused joints, Tenosynovitis, Nodules, Joint deformities, Bone-on-bone crepitus</td>
<td>Confirm historical findings (rash, serositis, renal, CVS, etc.) ± effused (typically small) joints (can be minimal, look for soft tissue swelling)</td>
<td>Skin tightness on dorsum of hand, facial skin tightening, telangiectasia, calcinosis, non-effused joint, inspiratory crackles</td>
<td>Rash, proximal muscle weakness, inspiratory crackles</td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-specific</strong></td>
<td>↑ ESR in 50-60%</td>
<td>↑ ESR in &gt;90%</td>
<td>↑ ESR Normal WBC</td>
<td>Possible increased ESR Normal WBC</td>
</tr>
<tr>
<td></td>
<td>↑ platelets</td>
<td>↑ Hb (autoimmune)</td>
<td>↓ Hb (autoimmune)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ Hb</td>
<td>↓ WBC (leukopenia, lymphopenia)</td>
<td>↑ WBC</td>
<td></td>
</tr>
<tr>
<td><strong>Specific</strong></td>
<td>RF + ve in ~80%</td>
<td>Anti-topoisomerase 1 (diffuse)</td>
<td>ANA + ve in &gt;90% Anti-topoisomerase 1 (diffuse)</td>
<td>CX elevated in 80% Anti-topoisomerase 1 (diffuse)</td>
</tr>
<tr>
<td></td>
<td>Anti-CCP + ve in ~80%</td>
<td>Anti-centromere (usually in CREST, see RH13)</td>
<td>Anti-CCP + ve in &gt;90% Anti-topoisomerase 1 (diffuse)</td>
<td>Muscle biopsy EMG MRI</td>
</tr>
<tr>
<td>Synovial Fluid</td>
<td>Inflammation</td>
<td>Mild inflammation with + ve ANA</td>
<td>Not specific</td>
<td>Not specific</td>
</tr>
<tr>
<td>Radiographs</td>
<td>Periarticular osteopenia</td>
<td>Non-erosive</td>
<td>± pulmonary fibrosis</td>
<td>± esophageal dysmotility</td>
</tr>
<tr>
<td></td>
<td>Joint space narrowing</td>
<td>± osteosclerosis</td>
<td>± esophageal dysmotility</td>
<td>± interstitial lung disease</td>
</tr>
<tr>
<td></td>
<td>Erosions</td>
<td>± soft tissue swelling</td>
<td>± calcifications</td>
<td>± calcifications</td>
</tr>
<tr>
<td></td>
<td>Absence of bone repair</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symmetric/concentric</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Rheumatoid Arthritis (RA)

**Definition**
- chronic, symmetric, erosive synovitis of peripheral joints (i.e. wrists, MCPs, MTPs)
- characterized by a number of extra-articular features

#### Table 12. Classification Criteria for RA

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Joint involvement (swollen or tender)</td>
<td></td>
<td>Total score of ≥6: definite RA Must have at least ≥1 joint with definite clinical swelling, not better explained by other disease</td>
</tr>
<tr>
<td>1 large joint (shoulders, elbows, hips, knees, and ankles)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2-10 large joints</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1-3 small joints (MCPs, PIPs, wrists, 2nd-5th MTPs)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4-10 small joints</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>&gt;10 joints (at least 1 small joint)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2. Serology Negative RF and negative Anti-CCP</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Low-positive RF or low-positive Anti-CCP (&lt;3x ULN)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>High-positive RF or high-positive Anti-CCP (&gt;3x ULN)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3. Acute phase reactants Normal CRP and normal ESR</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abnormal CRP and abnormal ESR</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4. Duration of symptoms &lt;6 wk</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≥6 wk</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Pathophysiology
- autoimmune disorder, unknown etiology
- hallmark of RA is hypertrophy of the synovial membrane
- activated rheumatoid synovium (pannus) grows into and over the articular surface; inflammatory mediators lead to release of metalloproteinas and collagenases resulting in destruction of articular cartilage and subchondral bone
- two theories attempt to explain chronic remissions and exacerbations seen in RA
  - sequestered Ag
    - during inflammation, immune complexes (ICs) are deposited at avascular cartilage-bone junction
    - ICs are released as further cartilage breaks down
    - triggers inflammatory cascade
  - molecular mimicry
    - cartilage damage → altered cartilage resembles undefined offending agent → triggers inflammatory cascade

Epidemiology
- prevalence 1% of adult population
- F:M = 3:1
- age of onset 20-40 yr
- genetic predisposition: HLA-DR4/DR1 association (93% of patients have either HLA type)

Signs and Symptoms
- variable course of exacerbations and remissions
- morning stiffness >1 h, improves with use, increases with rest
- may have joint pain with activity
- symmetric joint involvement (see Figure 6)
- joint swelling, tender joints
- signs of mechanical joint damage: loss of motion, instability, deformity, crepitus
- constitutional symptoms: profound fatigue; rarely myalgia or weight loss
- extra-articular features (EAF) (see Table 13)
- limitation of function and decrease in global functional status
- complications of chronic synovitis
  - signs of mechanical joint damage: loss of motion, instability, deformity, crepitus
  - joint deformities (see Figure 7)
    - swan neck deformity, boutonnière deformity
    - ulnar deviation of MCP, radial deviation of wrist joint
    - hammer toe, mallet toe, claw toe
    - flexion contractures
  - atlanto-axial and subaxial subluxation
    - C-spine instability
    - neurological impingement (long tract signs)
    - difficult/dangerous intubation: risk of worsening subluxation and damage to spinal cord
- limited shoulder mobility, spontaneous tears of the rotator cuff leading to chronic spasm
- tenosynovitis → may cause rupture of tendons
- carpal tunnel syndrome
- ruptured Baker’s cyst (outpouching of synovium behind the knee); presentation similar to acute DVT

<table>
<thead>
<tr>
<th>System</th>
<th>Vasculitic</th>
<th>Lymphocytic Infiltrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Periungual infarction, cutaneous ulcers, palpable purpura</td>
<td>Rheumatoid nodules (may have vasculitic component)</td>
</tr>
<tr>
<td>Ocular</td>
<td>Episcleritis, scleritis</td>
<td>Keratoconjunctivitis sicca (see sidebar)</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>Xerostomia (see sidebar), Hashimoto’s thyroiditis (see Endocrinology, E27)</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>Peri-/myocarditis, valvular disease, conduction defects</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pulmonary fibrosis, pleural effusion, pleuritis, pulmonary nodules</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Peripheral neuropathy: sensory stocking-glove, mononeuritis multiplex</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Splenomegaly, neutropenia (Felty’s, see sidebar)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Amyloidosis – caused by accumulation of abnormal proteins</td>
<td></td>
</tr>
</tbody>
</table>

Classification of Global Functional Status in RA (American College of Rheumatology, 1991)
- Class I: able to perform usual ADLs (self-care, vocational, avocational)
- Class II: able to perform self-care and vocational activities, restriction of avocational activities
- Class III: able to perform self-care, restriction of vocational and avocational activities
- Class IV: limited ability to perform self-care, vocational, avocational activities

Table 13. Extra-Articular Features of RA Classified by Underlying Pathophysiology

Figure 7. Joint deformities

Syndromes in RA
- Sjögren’s syndrome (common): keratoconjunctivitis sicca and xerostomia (dry eyes and mouth)
- Caplan’s syndrome (rare): multiple pulmonary nodules and pneumoconiosis
- Felty’s syndrome (rare): arthritis, splenomegaly, neutropenia
1. Disease Modifying Anti-Rheumatic Drugs (DMARDs) and Biologics (see Table 32)
   - DMARDs: standard of care and should be started as soon as possible
   - treatments guided by disease severity and prognostic features
   - methotrexate is the gold standard and is first-line unless contraindicated
   - delayed onset of action (may take 8-12 wk)
   - potential toxicities: GI, hematologic, hepatic (liver enzymes), pulmonary, teratogenic
   - if inadequate response (3-6 mo) → combine or switch
   - add-ons include: hydroxychloroquine, sulfasalazine, leflunomide
   - biologics: indicated if inadequate response to DMARDs
     - can be combined with DMARD therapy
     - agents include abatacept, rituximab, tocilizumab
     - reassess every 3-6 mo and monitor disease severity

2. Reducing Inflammation and Pain
   - NSAIDs
     - individualize according to efficacy and tolerability
     - contraindicated or cautioned in some patients (e.g. PUD, ischemic cardiac disease, pregnancy, see Table 31), add acetaminophen ± opioid prn for synergistic pain control
   - corticosteroids
     - local
       - intra-articular injections to control symptoms in a specific joint
     - systemic (prednisone)
       - low dose (5-10 mg/d) useful for short term to improve symptoms if NSAIDs ineffective, to bridge gap until DMARD takes effect
       - do baseline DEXA bone density scan and consider bone supportive pharmacologic therapy if using corticosteroids >3 mo at >7.5 mg/d
       - cautions/contraindications: active infection, TB, osteoporosis, hypertension, gastric ulcer, diabetes

3. Surgical Therapy
   - indicated for structural joint damage
   - surgical options include: synovectomy, joint replacement, joint fusion, reconstruction/tendon repair

Investigations
- bloodwork
  - RF sensitivity ~80% but non-specific (see Table 10); may not be present at onset of symptoms
  - anti-CCP (cyclic citrullinated peptide): sensitivity ~80% but more specific; may precede onset of symptoms
  - increased disease activity is associated with decreased Hb (anemia of chronic disease), increased platelets, ESR, CRP, and RF
- imaging
  - x-rays may be entirely normal at onset
  - first change is periarticular osteopenia, followed by erosions
  - ultrasound, MRI may be used to image hands to detect early synovitis and erosions

Treatment
- goals of therapy: remission or lowest possible disease activity
  - control disease activity
  - relieve pain and stiffness
  - maintain function and lifestyle
  - prevent or control joint damage
  - key is early diagnosis and early intervention with disease-modifying anti-rheumatic drugs (DMARDs)
- “window of opportunity” = early treatment within first 3 mo of disease may allow better control/remission

Education
- The Arthritis Society (Canada) and Arthritis Foundation (U.S.) for educational resources

Behavioral
- exercise program (isometrics and active, gentle ROM exercise during flares, aquatic/aerobic/strengthening exercise between flares), assistive devices as needed
- job modification may be necessary

Pharmacologic
1. Disease Modifying Anti-Rheumatic Drugs (DMARDs) and Biologics (see Table 32)
   - DMARDs: standard of care and should be started as soon as possible
   - treatments guided by disease severity and prognostic features
   - methotrexate is the gold standard and is first-line unless contraindicated
   - delayed onset of action (may take 8-12 wk)
   - potential toxicities: GI, hematologic, hepatic (liver enzymes), pulmonary, teratogenic
   - if inadequate response (3-6 mo) → combine or switch
   - add-ons include: hydroxychloroquine, sulfasalazine, leflunomide
   - biologics: indicated if inadequate response to DMARDs
     - can be combined with DMARD therapy
     - agents include abatacept, rituximab, tocilizumab
     - reassess every 3-6 mo and monitor disease severity

2. Reducing Inflammation and Pain
   - NSAIDs
     - individualize according to efficacy and tolerability
     - contraindicated or cautioned in some patients (e.g. PUD, ischemic cardiac disease, pregnancy, see Table 31), add acetaminophen ± opioid prn for synergistic pain control
   - corticosteroids
     - local
       - intra-articular injections to control symptoms in a specific joint
     - systemic (prednisone)
       - low dose (5-10 mg/d) useful for short term to improve symptoms if NSAIDs ineffective, to bridge gap until DMARD takes effect
       - do baseline DEXA bone density scan and consider bone supportive pharmacologic therapy if using corticosteroids >3 mo at >7.5 mg/d
       - cautions/contraindications: active infection, TB, osteoporosis, hypertension, gastric ulcer, diabetes

Surgical Therapy
- indicated for structural joint damage
- surgical options include: synovectomy, joint replacement, joint fusion, reconstruction/tendon repair

Side Effects of Steroids
- Weight gain
- Osteoporosis
- Avascular necrosis (AVN)
- Cataracts, glaucoma
- Peptic ulcer disease (PUD)
- Susceptibility to infection
- Easy bruising
- Acne
- Hypertension
- Hyperlipidemia
- Hypokalemia, hyperglycemia
- Mood swings

Comparison of Treatment Strategies in Early Rheumatoid Arthritis
Study: RCT of 508 patients comparing 4 different treatment strategies for early rheumatoid arthritis (known as the BEST trial).

Intervention:
- Group 1: Sequential Monotherapy with traditional DMARDs
- Group 2: Step-Up Combination Therapy
- Group 3: Initial Combination Therapy with prednisone (high dose)
- Group 4: Initial Combination Therapy with infliximab

Results: Patients in groups 3 and 4 responded faster and had significantly greater overall change in physical function scores after the first year of treatment. By end of the second yr, groups 1 and 2 had achieved a similar response to groups 3 and 4. Groups 3 and 4 also showed significantly less radiologic progression of their disease over 2 yr than groups 1 and 2. There were no significant differences in toxicity levels between the 4 groups.

Conclusions: Initial combination therapy with prednisone or infliximab results in faster response rates. Whether faster initial response rates leads to better long-term disease outcomes has not yet been studied.
Systemic Lupus Erythematosus (SLE)

- please see Nephrology, NP24 and Dermatology, D39 for additional details

Definition
- chronic inflammatory multi-system disease of unknown etiology
- characterized by production of autoantibodies and diverse clinical manifestations

Table 14. Diagnostic Criteria of SLE: 4 or more of 11 must be present serially or simultaneously

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL</td>
<td></td>
</tr>
<tr>
<td>Malar rash</td>
<td>Classic “butterfly rash”, sparing of nasolabial folds, no scarring</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>May cause scarring due to invasion of basement membrane</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Skin rash in reaction to sunlight</td>
</tr>
<tr>
<td>Oral/nasal ulcers</td>
<td>Usually painless</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Painless or non-erosive arthritis</td>
</tr>
<tr>
<td>Serositis</td>
<td>Pleuritis or pericarditis</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>Seizures or psychosis</td>
</tr>
<tr>
<td>LABORATORY</td>
<td></td>
</tr>
<tr>
<td>Renal disorder</td>
<td>Proteinuria (≥0.5 g/d or 3+), Cellular casts (RBC, Hb, granular, tubular, mixed)</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>Hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Immunologic disorder</td>
<td>Anti-dsDNA or anti-Sm or antiphospholipid antibodies (anticardiolipin Ab, lupus anticoagulant) or false positive VDRL with 6 mo confirmation that it’s negative</td>
</tr>
<tr>
<td>Antinuclear antibody (ANA)</td>
<td>Most sensitive test (98%), not specific</td>
</tr>
</tbody>
</table>

Note: “4, 7, 11” rule - 4 out of 11 criteria (4 lab, 7 clinical) for diagnosis
American College of Rheumatology, 1997 update

Etiology and Pathophysiology
- production of autoantibodies causing multi-organ inflammation
- multi-factorial etiology (see Figure 8)
- genetics
  - common association with HLA-B8/DR3; ~10% have positive family history
- estrogen
  - pre-pubertal and post-menopausal women have similar incidence to men
  - men with SLE have higher concentration of estrogenic metabolites
- infection
  - viral (non-specific stimulant of immune response)
- drug-induced
  - anti-hypertensives (hydralazine), anti-convulsants (phenytoin), anti-arrhythmics (procainamide), isoniazid, biologics, oral contraceptive pills
  - anti-histone antibodies are commonly seen in drug-induced lupus
  - symptoms resolve with discontinuation of offending drug

Epidemiology
- prevalence: 0.05% overall
- F:M = 10:1
- age of onset in reproductive yr (13-40)
- more common and severe in African-Americans and Asians
- bimodal mortality pattern
  - active SLE, active nephritis, infection secondary to steroid use
  - late (>10 yr)
  - inactive SLE, inactive nephritis, atherosclerosis likely due to chronic inflammation

Signs and Symptoms
- characterized by periods of exacerbation and remission

The Safety of Infliximab, Combined with Background Treatments, among Patients with Rheumatoid Arthritis and Various Comorbidities (START)
Arthritis Rheum 2006;54:1075-1086
Study: Multicenter RCT.
Patients: 1084 patients (mean age 52 yr, 80% female) with active moderate to severe rheumatoid arthritis despite treatment with methotrexate.
Intervention: Patients were randomized to receive infusions of placebo, infliximab dosed at 3 mg/kg, or infliximab dosed at 10 mg/kg at 0, 2, 6, and 14 wk, in addition to methotrexate.
Primary Outcome: Incidence of serious infection within 22 wk.
Results: Compared with the placebo group, the relative risk of developing serious infection at 3 mg/kg and 10 mg/kg of Infliximab was 1.0 (95% CI 0.3-3.1, p=0.995) and 3.1 (95% CI 1.2-7.9, p=0.013) respectively. In addition, 31% of patients receiving infliximab at 3 mg/kg and 32% of patients receiving infliximab at 10 mg/kg were able to achieve remission at 22 wk compared with only 14% of those receiving placebo (p=0.007, NNT=6).
Conclusions: Therapy with infliximab 3 mg/kg does not significantly increase the risk of serious infection in patients with active moderate to severe rheumatoid arthritis already receiving methotrexate. However, therapy with infliximab 10 mg/kg does significantly increase the risk of serious infection in this population.
Table 15. Symptoms of SLE

<table>
<thead>
<tr>
<th>System</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td>Fatigue, malaise, weight loss, fever, lymphadenopathy</td>
</tr>
<tr>
<td>Renal</td>
<td>Hypertension, peripheral edema, glomerulonephritis, renal failure</td>
</tr>
<tr>
<td>Derm</td>
<td>Photosensitivity, malar rash, discoid rash, oral ulcers, alopecia (hair loss), purpura,</td>
</tr>
<tr>
<td></td>
<td>panniculitis (inflammation of subcutaneous fat and muscle tissue), urticaria</td>
</tr>
<tr>
<td>MSK</td>
<td>Polyarthalgias, polyarthritis, myalgias, avascular necrosis. Reducible deformities of hand</td>
</tr>
<tr>
<td></td>
<td>= Jaccoud’s arthritis</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>Keratoconjunctivitis sicca, episcleritis, scleritis, cytoid bodies (cotton wool exudates</td>
</tr>
<tr>
<td></td>
<td>on fundoscopy = infarction of nerve cell layer of retina)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Pericarditis, coronary artery disease, non-bacterial endocarditis (Libman-Sachs)</td>
</tr>
<tr>
<td></td>
<td>Note: SLE is an independent risk factor for atherosclerosis and CV</td>
</tr>
<tr>
<td>Vascular</td>
<td>Raynaud’s phenomenon, livedo reticularis (mottled discoloration of skin due to narrowing</td>
</tr>
<tr>
<td></td>
<td>of blood vessels, characteristic lacy or net-like appearance), thrombosis, vasculitis</td>
</tr>
<tr>
<td>Resp</td>
<td>Pleuritis, interstitial lung disease, pulmonary hypertension, PE, alveolar hemorrhage</td>
</tr>
<tr>
<td>GI</td>
<td>Pancreatitis, lupus enteropathy, hepatitis, hepatomegaly</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Headache, depression, psychosis, seizures, cerebritis, transverse myelitis, peripheral</td>
</tr>
<tr>
<td></td>
<td>neuropathy, stroke</td>
</tr>
</tbody>
</table>

Investigations

- blood work: ANA (sensitivity 98%, but poor specificity → used as a screening test, ANA titres are not useful to follow disease course)
- anti-dsDNA and anti-Sm are specific (95-99%)
- anti-dsDNA titer and serum complement (C3, C4) are useful to monitor treatment response in patients who are clinically and serologically concordant
  - anti-dsDNA increases and C3 and C4 decrease with disease activity
- anti-phospholipid antibodies (anti-cardiolipin Ab and lupus anticoagulant), may cause increased risk of clotting and increased aPTT

Treatment

- goals of therapy
  - treat early and avoid long term steroid use, if unavoidable see Endocrinology, E42 for osteoporosis management
  - if high doses of steroids necessary for long-term control, add steroid-sparing agents and taper when possible
  - treatment is tailored to organ system involved and severity of disease
  - all medications used to treat SLE require periodic monitoring for potential toxicity
- dermatologic
  - sunscreen, avoid UV light and estrogens
  - topical steroids, hydroxychloroquine
- musculoskeletal
  - NSAIDs ± gastroprotective agent for arthritis (also beneficial for pleuritis and pericarditis)
  - hydroxychloroquine improves long term control and prevents flares
  - bisphosphonates, calcium, vitamin D to combat osteoporosis
- organ-threatening disease
  - high-dose oral prednisone or IV methylprednisolone in severe disease
  - steroid-sparing agents: azathioprine, methotrexate, mycophenolate
  - IV cyclophosphamide for serious organ involvement (e.g. cerebritis or SLE nephritis)

Antiphospholipid Antibody Syndrome (APLA)

Definition

- multi-system vasculopathy manifested by recurrent thromboembolic events, spontaneous abortions and thrombocytopenia
- often presents with migraine-type headaches
- circulating anti-phospholipid autoantibodies interfere with coagulation cascade
- primary APLA: occurs in the absence of other disease
- secondary APLA: occurs in the setting of a connective tissue disease (including SLE), malignancy, drugs (hyalurazine, procainamide, phenytoin, interferon, quinidine), and infections (HIV, TB, hepatitis C, infectious mononucleosis)
- catastrophic APLA: development within 1 wk of small vessel thrombotic occlusion in ≥3 organ systems with positive anti-phospholipid antibodies (high mortality)
Table 16. Classification Criteria of APLA: 1 clinical and 1 laboratory criteria must be present

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
</table>
| Vascular thrombosis | Arterial: stroke/TIA, multi-infarct dementia, MI, valvular incompetence, limb ischemia  
Venous: DVT, PE, renal and retinal vein thrombosis  
Must be confirmed by imaging or histopathology |
| Pregnancy morbidity | Fetal death (>10 wk GA), recurrent spontaneous abortions (<10 wk GA) or premature birth (<34 wk GA) |

<table>
<thead>
<tr>
<th>LABORATORY</th>
<th>Labs must be positive on 2 occasions, at least 12 wk apart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus anticoagulant</td>
<td>Anti-cardiolipin Ab IgG and/or IgM</td>
</tr>
<tr>
<td>Anti-β2 glycoprotein-I Ab IgG and/or IgM</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL</td>
<td></td>
</tr>
<tr>
<td>Vascular thrombosis</td>
<td></td>
</tr>
<tr>
<td>Pregnancy morbidity</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LABORATORY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus anticoagulant</td>
<td>Anti-cardiolipin Ab</td>
</tr>
<tr>
<td>Anti-β2 glycoprotein-I Ab</td>
<td></td>
</tr>
</tbody>
</table>

Signs and Symptoms
- see clinical criteria in Table 16
- hematologic
  - thrombocytopenia, hemolytic anemia, neutropenia
- dermatologic
  - livedo reticularis, Raynaud’s phenomenon, purpura, leg ulcers, and gangrene

Treatment
- thrombosis
  - lifelong anti-coagulation with warfarin
  - target INR 2.0-3.0 for first venous event, >3.0 for recurrent and/or arterial event
  - recurrent fetal loss
  - heparin/low molecular weight heparin ± Aspirin® during pregnancy
  - catastrophic APS
    - high-dose steroids, anti-coagulation, cyclophosphamide, plasmapheresis

Scleroderma

Definition
- a non-inflammatory autoimmune disorder characterized by widespread small vessel vasculopathy and fibrosis

| Scleroderma | Morphoea  
|-------------| Hard oval patches on the skin  
| Limited systemic sclerosis  
| Skin sclerosis restricted to hands, face, neck  
| 3rd to 4th decade  
| Pulmonary hypertension common  
| CREST (see sidebar) |
| Generalized (systemic sclerosis)  
| Diffuse systemic sclerosis  
| Widespread skin disease (proximal to wrist, can involve trunk), tendons  
| Early visceral involvement (renal, pulmonary fibrosis) |

| Localized (no involvement of internal organs)  
| Mostly children and young adults |
| Systemic sclerosis |

| Early viscerale involvement |
| Skin changes limited to digits |

Figure 9. Forms of scleroderma

Table 17. Classification Criteria of Systemic Sclerosis: 1 major or 2 minor criteria must be present

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
</table>
| Major | Scleroderma proximal to MCPs  
Skin tightness, thickening, non-pitting induration |
| Minor | Sclerodactyly  
Digital pitting scars or loss of substance from finger pad  
Ribosalar pulmonary fibrosis |

American Rheumatism Association, 1980

Etiology and Pathophysiology
- idiopathic vasculopathy (not vasculitis) leading to atrophy and fibrosis of tissues
  - intimal proliferation and media mucinous degeneration → progressive obliteration of vessel lumen → fibrotic tissue
  - resembles malignant hypertension

A Systematic Review of Secondary Thromboprophylaxis in Patients with Anti-phospholipid Antibodies

Arthritis Rheum 2007;57:1487-11495

Study: Review of RCTs, prospective and retrospective cohort studies, and subgroup analysis (n >15) that focused on the secondary thromboprophylaxis in patients with anti-phospholipid antibodies (aPL) were selected.

Results: Sixteen studies were selected. Patients with venous events and a single test for aPL showed a low recurrence rate while receiving oral anti-coagulation at a target INR of 2.0-3.0. Patients with stroke and a single positive aPL test had no increased risk compared with those without aPL. Recurrence rates in patients with definite anti-phospholipid syndrome (APLA) and previous venous thromboembolism were lower than in patients with arterial and/or recurrent events, both with and without therapy. Only 3.8% of recurrent events occurred at an actual INR >3.0. Mortality due to recurrent thrombosis was higher than mortality due to bleeding (18 patients versus 1 patient reported).

Conclusion: For patients with definite APLA, the authors recommend prolonged warfarin therapy at a target INR of 2.0-3.0. For patients with stroke and a single positive aPL test, the authors recommend further testing to determine if they have a persisting antibody. If they do not, the same therapy as for the general population should be used (warfarin at a target INR of 2.0-3.0 and low-dose Aspirin®, respectively).

CREST Syndrome
- Calcinoi: calcium deposits on skin  
- Raynaud’s phenomenon  
- Esophageal dysfunction: acid reflux  
- Sclerodactyly: tightening of skin on digits  
- Telangiectasia: superficial dilated blood vessels
Epidemiology
- F:M = 3-4:1, peaking in 5th and 6th decades
- associated with HLA-DR1
- associated with environmental exposure (silica, epoxy resins, toxic oil, aromatic hydrocarbons, polyvinyl chloride)
- limited systemic sclerosis has a higher survival prognosis (>70% at 10 yr) than diffuse systemic sclerosis (40-60% at 10 yr)

Signs and Symptoms

Table 18. Clinical Manifestations of Scleroderma

<table>
<thead>
<tr>
<th>System</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>Painless non-pitting edema → skin tightening</td>
</tr>
<tr>
<td></td>
<td>Ulcerations, calcinosis, periungual erythema, hypo/hyperpigmentation, pruritus, telangiectasias</td>
</tr>
<tr>
<td></td>
<td>Characteristic face: mask-like facies with tight lips, beard nose, radial perioral furrows</td>
</tr>
<tr>
<td>Vascular</td>
<td>Raynaud’s phenomenon → digital pits, gangrene</td>
</tr>
<tr>
<td>Gastrointestinal (~90%)</td>
<td>Distal esophageal hypomotility → dysphagia</td>
</tr>
<tr>
<td></td>
<td>Loss of lower esophageal sphincter function → GERD, ulcerations, strictures</td>
</tr>
<tr>
<td></td>
<td>Small bowel hypomotility → bacterial overgrowth, diarrhea, cramps, malabsorption, weight loss</td>
</tr>
<tr>
<td></td>
<td>Large bowel hypomotility → wide mouth diverticuli are pathognomonic radiographic finding on barium study</td>
</tr>
<tr>
<td>Renal</td>
<td>Mild proteinuria, creatinine elevation, hypertension</td>
</tr>
<tr>
<td></td>
<td>“Scleroderma renal crisis” (10-15%) may lead to malignant arterial hypertension, oliguria and microangiopathic hemolytic anemia</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Interstitial fibrosis, pulmonary HTN, pleurisy, pleural effusions</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Left ventricular dysfunction, pericarditis, pericardial effusion, arrhythmias</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Polyarthalgias</td>
</tr>
<tr>
<td></td>
<td>&quot;Resorption of distal tufts&quot; (radiological finding)</td>
</tr>
<tr>
<td></td>
<td>Proximal weakness 2nd to disuse, atrophy, low grade myopathy</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypothyroidism</td>
</tr>
</tbody>
</table>

Investigations
- bloodwork
  - CBC, Cr, ANA
  - anti-topoisomerase 1/anti-Scl-70: specific but not sensitive for diffuse systemic sclerosis
  - anti-centromere: favours diagnosis of CREST (limited systemic sclerosis)
- PFT
  - assess for pulmonary hypertension or interstitial lung disease
- imaging
  - CXR for fibrosis, echo for pulmonary HTN

Treatment
- dermatologic
  - good skin hygiene
  - low-dose prednisone (>20 mg may provoke renal crisis if susceptible), methotrexate (limited evidence)
- vascular
  - patient education on cold avoidance
  - vasodilators (CCBs, local nitroglycerine cream, systemic PGE2 inhibitors, PDE5 inhibitors)
- gastrointestinal
  - GERD: PPIs are first line, then H2-receptor agonists
  - small bowel bacterial overgrowth: broad spectrum antibiotics (tetracycline, metronidazole)
- renal disease
  - ACE inhibitors for hypertensive crisis
- pulmonary
  - early interstitial disease: cyclophosphamide
  - pulmonary hypertension: vasodilators e.g. bosentan (Tracleer®), epoprostenol (Flolan®), PDE5 inhibitors
- cardiac
  - pericarditis: systemic steroids
- musculoskeletal
  - arthritis: NSAIDs
  - myositis: systemic steroids
Idiopathic Inflammatory Myopathy

Definition
- autoimmune diseases characterized by proximal muscle weakness ± pain
- muscle becomes damaged by a non-suppurative lymphocytic inflammatory process
- classification
  - polymyositis (PM)/dermatomyositis (DM) (see Table 19)
  - adult and juvenile form
  - associated with malignancy
    - increased risk of malignancy: age >50, DM>PM, normal CK, refractory disease
    - 2.4-6.5 fold increased risk of underlying malignancy usually in internal organs
    - associated with other connective tissue disease
    - inclusion body myositis (IBM)
      - age >50, M>F , slowly progressive, vacuoles in cells on biopsy
      - suspect when patient unresponsive to treatment
      - distal as well as proximal muscle weakness
      - muscle biopsy positive for inclusion bodies

POLYMYOSITIS (PM)/DERMATOMYOSITIS (DM)

Table 19. Classification Criteria for PM/DM. Definite if 4 present, probable if 3 present.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symmetric proximal muscle weakness</td>
<td>Typical involvement of shoulder girdle and hip girdle</td>
</tr>
<tr>
<td>2. Elevated muscle enzymes</td>
<td>↑ CK, aldolase, LDH, AST, ALT</td>
</tr>
<tr>
<td>3. EMG changes</td>
<td>Short polyphasic motor units, high frequency repetitive discharge, insertion</td>
</tr>
<tr>
<td>4. Muscle biopsy</td>
<td>Segmental fibre necrosis, basophilic regeneration, perivascular inflammation</td>
</tr>
<tr>
<td>5. Typical rash of dermatomyositis</td>
<td>Required for diagnosis of DM (see below)</td>
</tr>
</tbody>
</table>

NEJM 1975;292:403-407

Etiology and Pathophysiology
- PM is CD8 cell-mediated muscle necrosis, found in adults
- DM is B-cell and CD4 immune complex-mediated peri-fascicular vascular abnormalities

Signs and Symptoms
- progressive symmetrical proximal muscle weakness (shoulder and hip) developing over weeks to months
- difficulty lifting head off pillow, arising from chair, climbing stairs
- dermatological
  - DM has characteristic dermatological features (F>M, children and adults)
    - Gottron’s papules
      - pink-violaceous, flat-topped papules overlying the dorsal surface of the interphalangeal joints
    - Gottron’s sign
      - erythematous, smooth or scaly patches over the dorsal IPs, MCPs, elbows, knees, or medial malleoli
    - heliotrope rash: violaceous rash over the eyelids; usually with edema
    -shawl sign: erythematous rash over neck, upper chest, and shoulders
    - mechanic’s hands: dark, dry, thick scale on palmar and lateral surface of digits
    - periungual erythema
- cardiac
  - dysrhythmias, CHF, conduction defect, ventricular hypertrophy, pericarditis
- gastrointestinal
  - oropharyngeal and lower esophageal dysphagia, reflux
- pulmonary
  - weakness of respiratory muscles, interstitial lung disease, aspiration pneumonia

Investigations
- bloodwork: CK, ANA, anti-Jo-1 (DM), anti-Mi-2, anti-SRP
- imaging: MRI may be used to localize biopsy site
- EMG, muscle biopsy

Treatment
- non-pharm: physical therapy and occupational therapy
- pharmacologic treatment:
  - high-dose corticosteroid (1-2 mg/kg/d) and slow taper
  - add immunosuppressive agents (azathioprine, methotrexate, cyclosporine)
  - intravenous immunoglobulin if severe or refractory
  - hydroxychloroquine for DM rash
Sjögren’s Syndrome (SS)

Definition
- autoimmune condition characterized by dry eyes (keratoconjunctivitis sicca/xerophthalmia) and dry mouth (xerostomia), caused by lymphocytic infiltration of salivary and lacrimal glands
- may evolve into systemic disorder with diminished exocrine gland activity in respiratory tract and skin
- primary and secondary form (associated with RA, SLE, DM and HIV)
- incidence estimated at 4/100,000 people
- 90% of cases are among females
- mean age of diagnosis is 40-60 yr

Table 20. Classification Criteria for SS. Need 4 present, one of which includes salivary gland biopsy or autoantibodies

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dry eye symptoms</td>
<td>Dry &gt;3 mo, foreign body sensation, or requiring tear substitutes</td>
</tr>
<tr>
<td>2. Dry mouth symptoms</td>
<td>Dry &gt;3 mo, swollen salivary glands, or requiring liquids to swallow food</td>
</tr>
<tr>
<td>3. Dry eye signs</td>
<td>Schirmer test (to assess tear flow) or slit lamp exam with Rose Bengal stain</td>
</tr>
<tr>
<td>4. Dry mouth signs</td>
<td>Low salivary flow, sialography</td>
</tr>
<tr>
<td>5. Salivary gland biopsy</td>
<td>Focal lymphocytic sialoadenitis</td>
</tr>
<tr>
<td>6. Autoantibodies</td>
<td>anti-Ro and/or anti-La, ANA, RF</td>
</tr>
</tbody>
</table>

Signs and Symptoms
- "sicca complex": dry eyes (keratoconjunctivitis sicca/xerophthalmia), dry mouth (xerostomia)
- staphylococcus blepharitis
- dental caries, oral candidiasis, angular chelitis (inflammation and fissuring at the labial commissures of the mouth)
- systemic complications
  - sinusitis, autoimmune thyroid dysfunction
  - arthralgias, arthritis
  - subclinical diffuse interstitial lung disease, xerotrachea leading to chronic dry cough
  - renal disease, glomerulonephritis
  - palpable purpura, vasculitis
  - peripheral neuropathy
  - lymphoma risk greatly increased

Treatment
- ocular
  - artificial tears or surgical punctal occlusion for dry eyes
- oral
  - good dental hygiene, hydration
  - agents that stimulate salivary flow (e.g. pilocarpine)
  - topical nystatin or clotrimazole x 4-6 wk for oral candidiasis
- systemic
  - e.g. hydroxychloroquine, corticosteroids

Mixed Connective Tissue Disease (MCTD)/Overlap Syndrome
- syndrome with features of 3 different CTD (e.g. SLE, scleroderma, PM)
- common symptoms: Raynaud’s phenomenon, swollen fingers
- bloodwork: anti-RNP (see Table 10)
- treatment is generally guided by the severity of symptoms and organ system involvement
- prognosis
  - 50-60% will evolve into SLE
  - 40% will evolve into scleroderma
  - only 10% will remain as MCTD for the rest of their lives
  - cardiac involvement (dysrhythmia) common, renal or lung involvement rare
## Vasculitides

- inflammation and subsequent necrosis of blood vessels leading to tissue ischemia or infarction
- any organ system can be involved
- keys to diagnosis
  - clinical suspicion: suspect in cases of unexplained multiple organ ischemia or systemic illness with no evidence of malignancy or infection
  - labs non-specific: anemia, increased WBC and ESR, abnormal urinalysis
  - biopsy if tissue accessible
  - angiography if tissue inaccessible
- treatment generally involves corticosteroids and/or immunosuppressive agents

### Table 21. Classification of Vasculitis and Characteristic Features

<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SMALL VESSEL</strong></td>
<td></td>
</tr>
<tr>
<td>• Non-ANCA-associated</td>
<td></td>
</tr>
<tr>
<td>Predominantly cutaneous vasculitis</td>
<td>Immune complex-mediated (most common mechanism)</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura (see Pediatrics, P99)</td>
<td>Also known as hypersensitivity/leukocytoclastic vasculitis</td>
</tr>
<tr>
<td>Essential cryoglobulenic vasculitis</td>
<td>Vascular deposition of IgA causing systemic vasculitis (skin, GI, renal), usually self-limiting; most common in childhood</td>
</tr>
<tr>
<td>• ANCA-associated</td>
<td></td>
</tr>
<tr>
<td>Granulomatosis with polyangiitis (GPA, formerly Wegener’s)</td>
<td>Granulomatous inflammation of vessels of respiratory tract and kidneys, initially have URTI symptoms; most common in middle age</td>
</tr>
<tr>
<td>PR3 (c-ANCA) &gt; MPO (p-ANCA)</td>
<td>Granulomatous inflammation of vessels with hyperesinophilia and eosinophilic tissue infiltration, frequent lung involvement (asthma, allergic rhinitis), can be associated with MPO or PR3, other manifestations include coronary arteritis, myocarditis and neuropathy, average age 40s</td>
</tr>
<tr>
<td>Eosinophilic granulomatosis with polyangiitis (EPGA or Churg-Strauss syndrome) (50% ANCA positive)</td>
<td>Pauci-immune necrotizing vasculitis, affecting kidneys (necrotizing glomerulonephritis), lungs (capillaritis and alveolar hemorrhage), skin, most common in middle age</td>
</tr>
<tr>
<td>Microangiopathic polyangiitis (70% ANCA positive, usually MPO)</td>
<td></td>
</tr>
<tr>
<td><strong>MEDIUM VESSEL</strong></td>
<td></td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Segmental, non-granulomatous necrotizing inflammation</td>
</tr>
<tr>
<td>Kawasaki’s (see Pediatrics, P100)</td>
<td>T lymphocyte response and granuloma formation</td>
</tr>
<tr>
<td><strong>LARGE VESSEL</strong></td>
<td></td>
</tr>
<tr>
<td>Giant cell arteritis (GCA) / Temporal Arteritis</td>
<td>Inflammation predominantly of the aorta and arteries originating from it</td>
</tr>
<tr>
<td>Takayasu’s arteritis</td>
<td>“Pulseless disease”, unequal peripheral pulses; chronic inflammation, most often the aorta and its branches</td>
</tr>
<tr>
<td>Usually young adults of Asian descent, F&gt;M; risk of aortic aneurysm</td>
<td></td>
</tr>
<tr>
<td><strong>OTHER VASCULITIDES</strong></td>
<td></td>
</tr>
<tr>
<td>Buerger’s disease (“Thromboangiitis Obliterans”)</td>
<td>Inflammation secondary to pathological clotting, affects small and medium-sized vessels of distal extremities, may lead to distal claudication and gangrene, most important etiologic factor is cigarette smoking</td>
</tr>
<tr>
<td>Most common in young Asian males</td>
<td></td>
</tr>
<tr>
<td>Behçet’s disease</td>
<td>Leukocytoclastic vasculitis, multi-system disorder presenting with ocular involvement (uveitis), recurrent oral and genital ulceration, venous thrombosis, skin and joint involvement, more common in Mediterranean and Asia, average age 30s, M&gt;F</td>
</tr>
<tr>
<td>Vasculitis mimicry</td>
<td>Cholesterol emboli, atrial myxoma</td>
</tr>
</tbody>
</table>

### c-ANCA:
- circulating anti-neutrophil cytoplasmic antibody associated with anti PR3.

### p-ANCA:
- perinuclear anti-neutrophil cytoplasmic antibody associated with multiple antigens, e.g. lactoferrin (IBD), myeloperoxidase (microscopic polyangiitis).

### Features of Small Vessel Vasculitis
- Palpable purpura
- Vesicles
- Chronic urticaria
- Superficial ulcers

### Churg-Strauss Triad
- Allergic rhinitis and asthma (often quiescent at time of vasculitis)
- Eosinophilic infiltrative disease resembling pneumonia
- Systemic vasculitis often mononeuritis multiplex/peripheral neuropathy and peripheral eosinophilia

### Features of Medium Vessel Vasculitis
- Livedo reticularis
- Erythema nodosum
- Raynaud’s phenomenon
- Nodules
- Digital infarcts
- Ulcers
Small Vessel Non-ANCA Associated Vasculitis

PREDOMINANTLY CUTANEOUS VASCULITIS
- subdivided into
  - drug-induced vasculitis
  - serum sickness reaction
  - vasculitis associated with other underlying primary diseases

Etiology and Pathophysiology
- cutaneous vasculitis following
  - drug exposure (allopurinol, gold, sulfonamides, penicillin, phenytoin)
  - viral or bacterial infection
  - idiopathic causes
- small vessels involved (post-capillary vessels most frequently)
- usually causes a leukocytoclastic vasculitis: debris from neutrophils around vessels
- sometimes due to cryoglobulins which precipitate in cold temperatures

Signs and Symptoms
- palpable purpura ± vesicles and ulceration, urticaria, macules, papules, bullae, subcutaneous nodules

Investigations
- vascular involvement (both arteriole and venule) established by skin biopsy

Treatment
- stop possible offending drug
- corticosteroids ± immunosuppressive agents
- usually self-limiting

Small Vessel ANCA-Associated Vasculitis

GRANULOMATOSIS WITH POLYANGIITIS (formerly known as Wegener’s Granulomatosis)

Definition
- granulomatous inflammation of vessels that may affect the upper airways (rhinitis, sinusitis), lungs (pulmonary nodules, infiltrates), and kidneys (glomerulonephritis, renal failure)
- highly associated with c-ANCA
- incidence 5 per 100,000; more common in Northern latitudes

Table 22. Classification Criteria for GPA. Diagnosed if 2 or more of the following 4 criteria present.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nasal or oral involvement</td>
<td>Inflammation, ulcers, epistaxis</td>
</tr>
<tr>
<td>2. Abnormal findings on CXR</td>
<td>Nodules, cavitations, etc.</td>
</tr>
<tr>
<td>3. Urinary sediment</td>
<td>Protein, RBC casts</td>
</tr>
<tr>
<td>4. Biopsy of involved tissue</td>
<td>Lungs show granulomas, kidneys show necrotizing segmental glomerulonephritis</td>
</tr>
</tbody>
</table>

American College of Rheumatology, 1990
Etiology
- pathology is complex, possibly involving transformation from inflammatory prodrome (serous otitis media and sinusitis) to full-blown vasculitic syndrome

Signs and Symptoms
- systemic
  - malaise, fever, weakness, weight loss
- HEENT
  - sinusitis or rhinitis, nasal crusting and bloody nasal discharge, nasoseptal perforation, saddle nose deformity
  - proptosis due to: inflammation/vasculitis involving extra-ocular muscles, retrobulbar space occupying lesions or direct extension of masses from the upper respiratory tract
  - hearing loss due to involvement of CN VIII
- pulmonary
  - cough, hemoptysis
- renal
  - hematuria
- other
  - joint, skin, eye complaints, vasculitic neuropathy

Investigations
- bloodwork: anemia (normal MCV), increased WBC, increased Cr, increased ESR, ANCA pR3 > MPO
- urinalysis: proteinuria, hematuria, RBC casts
- CXR: pneumonitis, lung nodules, infiltrations, cavitary lesions
- biopsy: renal (segmental necrotizing glomerulonephritis), lung (granulomas, tracheobronchial erosion)
- possible decline in c-ANCA and ESR used to monitor response to treatment in some patients

Treatment
- prednisone 1 mg/kg/d PO for 3-6 mo ± cyclophosphamide 2 mg/kg/d PO for 3-6 mo followed by high dose methotrexate (20-25 mg PO/SC weekly) or azathioprine (2 mg/kg/d PO once daily)
- consider biologic agents (rituximab, IVIG) and plasmapheresis (PEXIVAS trial)
- RAVE trial (NEJM 2010; 363:221-232): rituximab equivalent or superior to cyclophosphamide with less toxicity

Medium Vessel Vasculitis

POLYARTERITIS NODOSA (PAN)

Definition
- systemic, necrotizing vasculitis of medium sized vessels
- ANCA negative
- often associated with hepatitis B positivity
- incidence 0.7 per 100,000; affects individuals between 40-60 yr; M:F = 2:1

Table 23. Classification Criteria for PAN. Diagnosed if 3 or more of the following 10 criteria present.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Weight loss</td>
<td>&gt;4 kg, not due to dieting or other factors</td>
</tr>
<tr>
<td>2. Myalgias, weakness or leg tenderness</td>
<td>Diffuse myalgias or weakness</td>
</tr>
<tr>
<td>3. Livedo reticularis</td>
<td>Mottled, reticular pattern over skin</td>
</tr>
<tr>
<td>4. Neuropathy</td>
<td>Mononeuropathy, mononeuropathy multiplex or polyneuropathy</td>
</tr>
<tr>
<td>5. Testicular pain or tenderness</td>
<td>Not due to infection, trauma or other causes</td>
</tr>
<tr>
<td>6. dBp &gt; 90 mmHg</td>
<td>Development of hypertension with dBp &gt; 90 mmHg</td>
</tr>
<tr>
<td>7. Elevated Cr or BUN</td>
<td>Cr &gt; 130 µmol/L (1.5 mg/dL), BUN &gt; 14.3 mmol/L (40 mg/dL)</td>
</tr>
<tr>
<td>8. Hepatitis B positive</td>
<td>Presence of Hepatitis B surface antigen or antibody</td>
</tr>
<tr>
<td>9. Arteriographic abnormality</td>
<td>Commonly aneurysms</td>
</tr>
<tr>
<td>10. Biopsy of artery</td>
<td>Presence of granulocytes and/or mononuclear leukocytes in the artery wall</td>
</tr>
</tbody>
</table>

American College of Rheumatology, 1990

Etiology and Pathophysiology
- focal panmural necrotizing inflammatory lesions in small and medium-sized arteries
- thrombosis, aneurysm, or dilatation at lesion site may occur
- healed lesions show proliferation of fibrous tissue and endothelial cells that may lead to luminal occlusion
Investigations
• bloodwork: CBC, ESR, Cr, BUN, p-ANCA, hepatitis B serology
• imaging: angiography
• arterial biopsy

Treatment
• prednisone 1 mg/kg/d PO and cyclophosphamide 2 mg/kg/d PO
• ± anti-viral therapy to enhance clearance of HBV

Large Vessel Vasculitis
• please see Neurology, N39 and Ophthalmology, OP38 for more details

GIANT CELL ARTERITIS (GCA)/TEMPORAL ARTERITIS

Table 24. Classification Criteria for GCA. Diagnosed if 3 or more of the following 5 criteria present.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age at onset &gt;50</td>
<td></td>
</tr>
<tr>
<td>2. New headache</td>
<td>Often temporal</td>
</tr>
<tr>
<td>3. Temporal artery abnormality</td>
<td>Temporal artery tenderness or decreased pulsations, not due to arteriosclerosis</td>
</tr>
<tr>
<td>4. Elevated ESR</td>
<td>ESR &gt;50 mm/h</td>
</tr>
<tr>
<td>5. Abnormal artery biopsy</td>
<td>Mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells</td>
</tr>
</tbody>
</table>

American College of Rheumatology, 1990

Epidemiology
• most frequent vasculitis in North America
• patients >50 yr
• F:M = 2:1
• North-South gradient (predominance in Northern Europe/US)
• affects extracranial arteries

Signs and Symptoms
• new onset temporal headache ± scalp tenderness due to inflammation of involved portion of the temporal or occipital arteries
• sudden, painless loss of vision and/or diplopia due to narrowing of the ophthalmic or posterior ciliary arteries (PCA more common); can affect both eyes
• tongue and jaw claudication (pain in muscles of mastication on prolonged chewing)
• polymyalgia rheumatica (proximal myalgia, constitutional symptoms, elevated ESR) occurs in 30% of patients
• aortic arch syndrome (involvement of subclavian and brachial branches of aorta result in pulseless disease), aortic aneurysm ± rupture are late complications

Investigations
• diagnosis made by clinical suspicion, increased ESR, increased CRP, temporal artery biopsy within 14 d of starting steroids, possible ultrasound

Treatment
• if suspect GCA, immediately start high dose prednisone 1 mg/kg in divided doses for approximately 4 wk, and then tapering prednisone as symptoms resolve; highly effective in treatment and in prevention of blindness and other vascular complications
• consider low dose ASA

Prognosis
• increased risk of thoracic aortic aneurysm and aortic dissection
• yearly CXR ± abdominal ultrasound as screening
SERONEGATIVE RHEUMATIC DISEASE

Spondyloarthropathies

Table 25. A Comparison of the Spondyloarthropathies (inflammatory joint disease of the vertebral column)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Ankylosing Spondylitis</th>
<th>Psoriatic Arthritis</th>
<th>Reactive Arthritis</th>
<th>Enteropathic Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>3:1</td>
<td>1:1</td>
<td>8:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Age of onset</td>
<td>20s</td>
<td>35-45</td>
<td>20s</td>
<td>Any</td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>25%</td>
<td>96%</td>
<td>90%</td>
<td>Common</td>
</tr>
<tr>
<td>Distribution</td>
<td>Axial, LE</td>
<td>Any</td>
<td>LE</td>
<td>LE</td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td>100%</td>
<td>40%</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>Uncommon</td>
<td>Occasional</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Less Common</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>Rare</td>
<td>100% Psoriasis eventually 70% at onset of arthritis</td>
<td>Common Keratoderma</td>
<td>Occasional Pyoderma, erythema nodosum</td>
</tr>
<tr>
<td>Uveitis</td>
<td>30%</td>
<td>Occasional</td>
<td>20%</td>
<td>Rare</td>
</tr>
<tr>
<td>Urethritis</td>
<td>Rare</td>
<td>Occasional</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>90%</td>
<td>40%</td>
<td>80%</td>
<td>30%</td>
</tr>
</tbody>
</table>

LE = lower extremities

Ankylosing Spondylitis (AS)

Definition
- chronic inflammatory arthritis involving the sacroiliac joints and vertebrae (see Figure 12)
- AS in women: more peripheral arthritis and upper spine spondylitis
- prototype of the spondyloarthropathies

Table 26. ASAS Classification Criteria for Axial Spondyloarthritis (for patients with ≥3 months back pain and age at onset <45 years)

| Sacroiliitis on imaging plus ≥1 SpA feature or HLA B-27 positive plus ≥2 SpA features |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| SpA features:                   | Sacroiliitis on imaging:        |                                 |                                 |
| • Inflammatory back pain        | • Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA |
| • Arthritis                     | • Definite radiographic sacroiliitis according to modified NY criteria |
| • Enthesitis (heel)             |                                 |                                 |                                 |
| • Uveitis                       |                                 |                                 |                                 |
| • Dactylitis                    |                                 |                                 |                                 |
| • Psoriasis                     |                                 |                                 |                                 |
| • Crohn’s disease/colitis       |                                 |                                 |                                 |
| • Good response to NSAIDs       |                                 |                                 |                                 |
| • Family history of SpA         |                                 |                                 |                                 |
| • HLA-B27 positive              |                                 |                                 |                                 |
| • Elevated CRP                  |                                 |                                 |                                 |

Etiology and Pathophysiology
- enthesitis (inflammation of tendon or ligament at site of attachment to bone)
- inflammation → osteopenia → erosion → ossification → osteoproliferation (syndesmophytes)

Epidemiology
- M:F = 5:1; females have milder disease which may be under-recognized
- 95% of patients have HLA-B27 (9% HLA-B27 positive in general population)
### Table 27. Types of Back Pain

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mechanical</th>
<th>Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past History</td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td>Family History</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Insidious</td>
</tr>
<tr>
<td>Age (years)</td>
<td>15-90</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Sleep Disturbance</td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td>Morning Stiffness</td>
<td>&lt;30 min</td>
<td>&gt;1 h</td>
</tr>
<tr>
<td>Involvement of Other Systems</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Exercise</td>
<td>Worse</td>
<td>Better</td>
</tr>
<tr>
<td>Rest</td>
<td>Better</td>
<td>Worse</td>
</tr>
<tr>
<td>Radiation of Pain</td>
<td>Anatomic (L5-S1)</td>
<td>Diffuse (thoracic, buttoc)</td>
</tr>
<tr>
<td>Sensory Symptoms</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Motor Symptoms</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

### Signs and Symptoms

- **axial**
  - mid and lower back stiffness, prolonged morning stiffness, night pain, persistent buttock pain, painful sacroiliac joint (+ Faber test) (see Table 27)
  - spinal restriction (decreased ROM): lumbar (decreased Schöber), thoracic (decreased chest wall expansion, normal >5 cm at T4), cervical (global decrease, often extension first)
  - postural changes: decreased lumbar lordosis + increased thoracic kyphosis + increased cervical flexion = increased occiput to wall distance (>5 cm)
- **peripheral**
  - asymmetrical large joint arthritis, most often involving lower limb
  - enthesitis: tenderness over tibial tuberosity, or Achilles tendon and plantar fascia insertions into the calcaneus
- **extra-articular manifestations**
  - ophthalmic: acute anterior uveitis is common (25-30% patients)
  - renal: amyloidosis (late and rare) and IgA nephropathy
  - gastrointestinal: inflammatory bowel disease
  - cardiac: aortitis, aortic regurgitation, pericarditis, conduction disturbances, heart failure (rare)
  - respiratory: apical fibrosis (rare)
  - neurologic: cauda equina syndrome (rare)
  - skin: psoriasis

### Investigations

- x-ray of SI joint: “pseudowidening” of joint due to erosion with joint sclerosis → bony fusion (late), symmetric sacroiliitis
- x-ray of spine: “squaring of edges” from erosion and sclerosis on corners of vertebral bodies (shiny corner sign) leading to ossification of outer fibres of annulus fibrosis (bridging syndesmophytes) → “bamboo spine” radiographically
- MRI of spine: assess activity in early disease; detection of cartilage changes, bone marrow edema, bone erosions, and subchondral bone changes. Best seen on T2 STIR images (suppress fat and see bone edema)

### Treatment

- **conservative/non-pharmacologic**
  - prevent fusion from poor posture and disability through: exercise (e.g. swimming), postural and deep breathing exercises, outpatient PT, smoking cessation
- **medical**
  - NSAIDs (first line of treatment)
  - glucocorticoids (topical eye drops, local injections)
  - DMARDs for peripheral arthritis (sulfasalazine, methotrexate)
  - biologics for axial and peripheral involvement
  - manage extra-articular manifestations
- **surgical**
  - hip replacement, vertebral osteotomy for marked deformity

### Prognosis

- spontaneous remissions and relapses are common and can occur at any age
- function may be excellent despite spinal deformity
- favourable prognosis if female and age of onset >40 yr
- early onset with hip disease may lead to severe disability; may require arthroplasty
Enteropathic Arthritis (EA)

- see Gastroenterology, Inflammatory Bowel Disease, G19
- MSK manifestations in the setting of either ulcerative colitis (UC) or Crohn’s disease (CD) include peripheral arthritis (large joint, asymmetrical), spondylitis, and hypertrophic osteoarthritis
- arthralgia, myalgia, osteoporosis and aseptic necrosis of bone 2° to steroid treatment of bowel inflammation
- NSAIDs should be used cautiously as they may exacerbate bowel disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Spondylitis</th>
<th>Peripheral Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B27 association</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Gender</td>
<td>M&gt;F</td>
<td>M=F</td>
</tr>
<tr>
<td>Onset before IBD</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Parallels IBD course</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Type of IBD course</td>
<td>UC=CD</td>
<td>CD</td>
</tr>
</tbody>
</table>

Psoriatic Arthritis (PsA)

Etiology and Pathophysiology
- unclear but many genetic, immunologic and some environmental factors involved (e.g. psoriatic plaque flora, particularly Group A Streptococcus, and trauma)

Epidemiology
- psoriasis affects 1% of population
- arthropathy in 10% of patients with psoriasis
- 15-20% of patients will develop joint disease before skin lesions appear

Signs and Symptoms
- dermatologic
  - well-demarcated erythematous plaques with silvery scale
  - nail involvement: pitting, transverse or longitudinal ridging, discoulouration, subungual hyperkeratosis, onycholysis, and oil drops
- musculoskeletal
  - 5 general patterns
    - asymmetric oligoarthritis (most common – 70%)
    - arthritis of DIP joints with nail changes
    - destructive (mutans) arthritis (5%)
    - symmetric polyarthritis (similar to RA)
    - sacroiliitis and spondylitis (usually older, male patients)
  - other findings: dactylitis, enthesopathy
- ophthalmic
  - conjunctivitis, iritis (anterior uveitis)
- cardiac and respiratory (late findings)
  - aortic insufficiency
  - apical lung fibrosis
- neurologic
  - cauda equina syndrome
- radiologic
  - floating syndesmophytes
  - pencil-in-cup appearance at IP joints
  - osteolysis, periostitis

Treatment
- treat skin lesions (e.g. steroid cream, salicylic and/or retinoic acid, tar, UV light)
- NSAIDs or intra-articular steroids
- DMARDs, biologic therapies to minimize erosive disease (use early if peripheral joint involvement)

Reactive Arthritis (ReA)

Definition
- two meanings
  1. Reactive arthritis: a sterile arthritis following an infection (e.g. rheumatic fever, post-viral arthritis, etc.), not used frequently by rheumatologists
  2. Reactive Arthritis (ReA): one of the seronegative spondyloarthropathies in which patients have a peripheral arthritis (≥1 mo duration) accompanied by one or more extra-articular manifestations that appears shortly after certain infections of the GI or GU tracts
Etiology
• onset following an infectious episode either involving the GI or GU tract
  - GI: *Shigella*, *Salmonella*, *Campylobacter*, *Yersinia* species
  - GU: *Chlamydia* (isolated in 16–44% of ReA cases), *Mycoplasma* species
• acute clinical course
  - 1-4 wk post-infection
  - lasts weeks to years
  - often recurring
  - spinal involvement persists

Epidemiology
• in HLA-B27 patients, axial > peripheral involvement
• M>F

Signs and Symptoms
• musculoskeletal
  - peripheral arthritis, asymmetric pattern, spondylitis, Achilles tendinitis, plantar fasciitis, dactylitis
• ophthalmic
  - iritis (anterior uveitis), conjunctivitis
• dermatomic
  - keratoderma blenorrhagicum (hyperkeratotic skin lesions on palms and soles) and balanitis cirinata (small, shallow, painless ulcers of glans penis and urethral meatus) are diagnostic
• gastrointestinal
  - oral ulcers, diarrhea
• urethritis and cervicitis
  - sterile cultures; presence not related to site of initiating infection

Investigations
• diagnosis is clinical plus laboratory
• bloodwork: normocytic, normochromic anemia and leukocytosis
• sterile cultures
• serology: HLA-B27 positive

Treatment
• antibiotics for non-articular infections
• NSAIDs, physical therapy, exercise
• local therapy
  - joint protection
  - intra-articular steroid injection
  - topical steroid for ocular involvement
• systemic therapy
  - corticosteroids, sulfasalazine, methotrexate (for peripheral joint involvement only)
  - TNF-α inhibitors for spinal inflammation

Prognosis
• self-limited, typically 3-5 mo, varies based on pathogen and patient’s genetic background
• chronic in 15-20% of cases

---

**Table 29. Gout vs. Pseudogout**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gout</th>
<th>Pseudogout</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>M&gt;F</td>
<td>M=F</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Middle-aged males, Post-menopausal females</td>
<td>Age &gt;60</td>
</tr>
<tr>
<td><strong>Onset of disease</strong></td>
<td>Acute</td>
<td>Acute/insidious</td>
</tr>
<tr>
<td><strong>Crystal type</strong></td>
<td>Monosodium urate (MSU), needle-shaped</td>
<td>Calcium pyrophosphate dihydrate (CPPD), rhomboid-shaped</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>First MTP classically, also midfoot, ankle, knee, or polyarticular</td>
<td>Knee, wrist; typically monoarticular</td>
</tr>
<tr>
<td><strong>Radiology (note findings are non-specific)</strong></td>
<td>Erosions</td>
<td>Chondrocalcinosis</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>NSAIDs, corticosteroids, colchicine, Allopurinol, febuxostat</td>
<td>NSAIDs, corticosteroids</td>
</tr>
</tbody>
</table>

---

*Clinical triad of reactive arthritis:*
- Arthritis
- Conjunctivitis
- Urethritis/cervicitis

*“Can’t see, can’t pee, can’t climb a tree”:* Triad of conjunctivitis, urethritis, and arthritis is 99% specific (but 51% sensitive) for ReA.
Gout

Definition
- derangement in purine metabolism resulting in hyperuricemia; monosodium urate crystal deposits in tissues (tophi) and synovium (microtophi)

Etiology and Pathogenesis
- sources of uric acid: diet and endogenous
  - synthesis
    - hypoxanthine $\rightarrow$ xanthine $\rightarrow$ uric acid
    - both steps catalyzed by xanthine oxidase
- hyperuricemia
  - primary or genetic
    - mostly due to idiopathic renal underexcretion (90%)
    - also idiopathic overproduction or abnormal enzyme production/function
  - secondary
    - dietary excess (particularly high consumption of beer, seafood, and meat)
    - underexcretion (>90%): renal failure, drugs, systemic conditions
    - overproduction (<10%): increased nucleic acid turnover states (e.g. malignancy, post-chemotherapy)
- sudden changes (increasing or decreasing) in uric acid concentration are more important than absolute values
- acute gout can occur with normal serum uric acid
- changes in pH, temperature or initiation of antihyperuricemics may precipitate an acute gouty attack
- common precipitants: alcohol, dietary excess, dehydration, drugs (e.g. thiazide and loop diuretics), trauma, illness, surgery, starting xanthine oxidase inhibitor therapy
- other associated conditions: hypertension, obesity, diabetes, starvation

Epidemiology
- most common in males >45 yr old
- extremely rare in premenopausal female

Signs and Symptoms
- single episode progressing to recurrent episodes of acute inflammatory arthritis
- acute gouty arthritis
  - severe pain, redness, joint swelling, usually involving lower extremities (see Figure 13)
  - joint mobility may be limited
  - attack will subside spontaneously within several days to weeks; may recur
- tophi
  - urate deposits on cartilage, tendons, bursae, soft tissues, and synovial membranes
  - common sites: first MTP, ear helix, olecranon bursae, tendon insertions (common in Achilles tendon)
- kidney
  - gouty nephropathy
  - uric acid calculi

Investigations
- joint aspirate: >90% of joint aspirates show crystals of monosodium urate (see Table 29) (negatively birefringent, needle-shaped)
- x-rays may show tophi as soft tissue swelling, punched-out lesions – erosion with "overhanging" edge

Treatment
- acute gout
  - NSAIDs: high dose, then taper as symptoms improve
  - corticosteroids: intra-articular, oral or intra-muscular (if renal, cardiovascular, or GI disease and/or if NSAIDs contraindicated or failed)
  - colchicine within first 12 h but effectiveness limited by narrow therapeutic range
  - allopurinol can worsen an acute attack (do not start during acute flare)
- chronic gout
  - conservative
    - avoid foods with high purine content (e.g. visceral meats, sardines, shellfish, beans, peas)
    - avoid drugs with hyperuricemic effects (e.g. pyrazinamide, ethambutol, thiazide, alcohol)
  - medical
    - antihyperuricemic drugs (allopurinol and febuxostat): decrease uric acid production by inhibiting xanthine oxidase
    - uricosuric drugs (probenecid, sulfinpyrazone): use if failure on or intolerant to allopurinol; do not use in renal failure
    - prophylaxis prior to starting antihyperuricemics drugs (colchicine/low-dose NSAID)
    - in renal disease secondary to hyperuricemia, use low-dose allopurinol and monitor creatinine
- indications for treatment with antihyperuricemic medications include:
  - recurrent attacks, tophi, bone erosions, urate kidney stones. Perhaps in renal dysfunction with very high urate load (controversial)

Precipitants of Gout
- Drugs are FACT
  - Furosemide
  - Aspirin®/Alcohol
  - Cytotoxic drugs
  - Thiazide diuretics
- Foods are SALT
  - Seafood
  - Alcohol (beer and spirits)
  - Liver and kidney
  - Turkey (meat)

Figure 13. Common sites of involvement in gout (asymmetric joint involvement)

An acute gout attack may mimic cellulitis. However, joint mobility is preserved in cellulitis. Gout often affects more than one joint (i.e. ankle, midfoot and MTPs).
Pseudogout (Calcium Pyrophosphate Dihydrate Disease)

Etiology and Pathophysiology
- acute inflammatory arthritis due to phagocytosis of IgG-coated calcium pyrophosphate dihydrate (CPPD) crystals by neutrophils and subsequent release of inflammatory mediators within joint space

Epidemiology
- more frequently polyarticular
- slower in onset in comparison to gout, lasts up to 3 wk but is self-limited

Risk Factors
- old age, advanced OA, neuropathic joints
- other associated conditions: hyperparathyroidism, hypothyroidism, hypomagnesemia, hypophosphatasia (low ALP), diabetes, hemochromatosis

Signs and Symptoms
- affects knees, wrists, MCPs, hips, shoulders, elbows, ankles, big toe (see Figure 14)
- multiple manifestations:
  - asymptomatic crystal deposition (seen on radiograph only)
  - acute crystal arthritis (self-limited flares of acute inflammatory arthritis resembling gout)
  - pseudo-osteoarthritis (progressive joint degeneration, sometimes with episodes of acute inflammatory arthritis)
  - pseudo-rheumatoid arthritis (symmetrical polyarticular pattern with morning stiffness and constitutional symptoms)
- acute may be triggered by dehydration, acute illness, surgery, trauma

Investigations
- must aspirate joint to rule out septic arthritis, gout
- CPPD crystals: present in 60% of patients, often only a few crystals
- x-rays show chondrocalcinosis in 75%: radiodensities in fibrocartilaginous structures (e.g. knee menisci) or linear radiodensities in hyaline articular cartilage

Treatment
- joint aspiration, rest, and protection
- NSAIDs: also used for maintenance therapy
- prophylactic colchicine PO (controversial)
- intra-articular or oral steroids to relieve inflammation

Pediatric Rheumatology
- see Pediatrics, P96

Non-Articular Rheumatism

Definition
- disorders that primarily affect soft tissues or periarticular structures
- includes bursitis, tendinitis, tenosynovitis, fibromyalgia, and polymyalgia rheumatica

Polymyalgia Rheumatica (PMR)

Definition
- characterized by pain and stiffness of the proximal extremities (girdle area)
- closely related to giant cell arteritis (15% of patients with PMR develop GCA)
- no muscle weakness
Table 30. PMR Classification Criteria Scoring Algorithm

| Required criteria: age ≥50, bilateral shoulder aching, and abnormal ESR/CRP |
|-----------------------------|-----------------------------|-----------------------------|
| Morning stiffness duration >45 min | 2 | 2 |
| Hip pain or limited ROM | 1 | 1 |
| Absence of RF or ACPA | 2 | 2 |
| Absence of other joint involvement | 1 | 1 |
| At least one shoulder with subdeltoid and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis on U/S | N/A | 1 |
| Both shoulders with subdeltoid bursitis, biceps tenosynovitis or gleno-humeral synovitis on U/S | N/A | 1 |

**A score of 4 or more is categorized as PMR in the algorithm without U/S and a score of 5 or more is categorized as PMR in the algorithm with U/S**

**Optional U/S criteria**

Epidemiology
- incidence 50 per 100,000 per year in those over age 50
- age of onset typically >50, F:M = 2:1

Signs and Symptoms
- constitutional symptoms prominent (fever, weight loss, malaise)
- pain and stiffness of symmetrical proximal muscles (neck, shoulder and hip girdles, thighs)
- gel phenomenon (stiffness after prolonged inactivity)
- physical examination reveals tender muscles, but no weakness or atrophy

Investigations
- bloodwork: often shows anemia, elevated platelets, elevated ESR and CRP; normal CK up to 5% of PMR reported with normal inflammatory markers

Treatment
- goal of therapy: symptom relief
- start with prednisone dose of 15-20 mg PO once daily
- taper slowly over 2-yr period monitoring ESR and symptoms closely
- treat relapses aggressively (50% relapse rate)
- monitor for steroid side effects, glucocorticoid-induced osteoporosis prevention, follow for symptoms of giant cell arteritis

Fibromyalgia

Definition
- chronic (>3 mo), widespread (axial, left- and right-sided, upper and lower segment), non-articular pain with characteristic tender points

Diagnosis

2010 Diagnostic Criteria for Fibromyalgia
1. Widespread pain index (WPI) ≥7 and symptom severity score (SS) ≥5 or WPI 3-6 and SS ≥9
2. Symptoms have been present at a similar level for ≥3 mo
3. The patient does not have a disorder that would otherwise explain the pain
   - WPI = number of areas in which the patient had pain over the last week (L and R: shoulder girdle, upper arm, lower arm, hip, upper leg, lower leg, jaw, chest, abdomen, upper and lower back, neck = max score 19)
   - SS = sum of a) severity of fatigue, b) waking unrefreshed, and c) cognitive symptoms over the past week, plus d) extent of somatic symptoms (IBS, headache, abdominal pain/cramps, dry mouth, fever, hives, ringing in ears, vomiting, heartburn, dry eyes, SOB, loss of appetite, rash, hair loss, easy bruising, etc.); all (a-d) rated on 0-3 scale: 0=no problem, 1 = mild, 2 = moderate, 3 = severe
- this clinical definition identified 88.1% of ACR classified fibromyalgia and can allow longitudinal assessment of symptom severity

Epidemiology
- F:M = 3:1
- primarily ages 25-45, some adolescents
- prevalence of 2-5% in general population
- overlaps with chronic fatigue syndrome and myofascial pain syndrome
- strong association with psychiatric illness
Signs and Symptoms
- widespread aching, stiffness
- easy fatigability
- sleep disturbance: non-restorative sleep, difficulty falling asleep, and frequent wakening
- symptoms aggravated by physical activity, poor sleep, emotional stress
- patient feels that joints are diffusely swollen although joint examination is normal
- neurologic symptoms of hyperalgesia, paresthesias
- associated with irritable bowel or bladder syndrome, migraines, tension headaches, restless legs syndrome, obesity, depression, and anxiety

Investigations
- bloodwork: includes TSH and ESR; all typically normal unless unrelated, underlying illness present
- serology: do not order ANA or RF unless there is clinical suspicion for a connective tissue disease
- laboratory sleep assessment

Differential Diagnosis
- diagnosis of exclusion
- rule out other disorders by history and physical exam

Treatment
- conservative
  - education
  - exercise program (walking, aquatic exercises), physical therapy (good posture, stretching, muscle strengthening, massage)
  - stress reduction, CBT
  - biofeedback, meditation, acupuncture may be helpful
- medical
  - low dose tricyclic antidepressant (e.g. amitriptyline)
  - for sleep restoration
  - select those with lower anticholinergic side effects
  - SNRI: duloxetine, milnacipran
  - anticonvulsant: pregabalin, gabapentin
  - analgesics may be beneficial for pain that interferes with sleep (NSAIDs, not narcotics)

Prognosis
- variable; usually chronic, unless diagnosed and treated early

Adult Onset Still’s Disease

Definition
- systemic inflammatory condition (ANA and RF negative) with fevers and characteristic rash, numerous systemic symptoms, may have severe arthritis

Etiology and Pathophysiology
- idiopathic; infectious triggers likely – various viruses and bacteria have been implicated
- stress increases risk

Epidemiology
- F>M; age of onset typically 16-40, approximately 1 per 100,000

Signs and Symptoms
- classic triad of symptoms:
  - high-spiking fevers (95.7% of patients, typically T 39°C, <4 h duration, quotidian pattern)
  - characteristic “salmon rash” (~72% of patients, on proximal limbs + trunk)
  - arthralgia/arthritis (64-100%)
- sore throat, myalgias and serositis may also occur
- arthritis is symmetric, typically affects large joints, i.e. wrists, knees and ankles, may involve PIP and DIPs, elbow, MTPs
- liver abnormalities ± hepatomegaly (50-75% patients)
- splenomegaly (44%)

Exercises for Treating Fibromyalgia Syndrome
- Cochrane DB Syst Rev 2008;CD003786
- Study: Systemic review of exercise training including cardiorespiratory endurance, muscle strengthening, and flexibility for global well-being and physical function in patients with fibromyalgia.
- Result: 24 studies were included (n = 2276).
- Aerobic-only exercises improve global well-being, physical function, and possibly pain and tender points. There was insufficient data to evaluate the effect of strength and flexibility on the primary outcomes.
- Conclusions: Moderate aerobic cardiorespiratory exercise improves function and well-being in patients with FM. Benefits from strength and flexibility require additional research to delineate benefits.

Fibromyalgia
- Study: Multicenter RCT. 750 patients with fibromyalgia with pain score of <40 mm on the visual analog scale (VAS) were assigned to placebo or pregabalin (300 mg, 450 mg, or 600 mg) daily for 12 wk.
- Primary Outcome: Change in the mean pain score derived from the subject’s daily pain diary as measured at the patient’s baseline to the end point of the study.
- Results: Patients treated with 450 and 600 mg/d pregabalin showed a statistically significant improvement in the end point mean pain score compared with placebo-treated subjects by -0.45 and -0.65 respectively.
- The 30% responder rate was 30%, 43%, 50%, and 48% in the placebo, 300 mg/d, 450 mg/d, an 600 mg/d respectively. The 50% responder rate was 15%, 24%, 27%, and 30% for placebo, 300 mg/d, 450 mg/d, and 600 mg/d respectively.
- Discontinuations due to adverse events were 12%, 16%, 22%, and 26% in placebo, 300 mg/d, 450 mg/d, and 600 mg/d respectively. The 450 and 600 mg/d groups were significantly different from placebo (P = 0001).
- Conclusions: Pregabalin at 300 mg/d, 450 mg/d, and 600 mg/d showed significantly greater response rates as compared to placebo although discontinuation rates for the 450 mg/d and 600 mg/d regimens were significantly higher as compared to placebo.
Classification
- Numerous classification systems proposed
- Yamaguchi’s criteria (J Rheumatol 1992;19:424-30) need 5 criteria to diagnose Still’s, at least 2 major
  - Major criteria
    - $T > 39^\circ C$, intermittent, > 1 wk
    - Typical rash
    - WBC > 10,000 (>80% granulocytes)
  - Minor criteria
    - Sore throat
    - Lymphadenopathy ± splenomegaly
    - Abnormal transaminases
    - Negative ANA and RF
  - Exclusion criteria: infection, malignancy, rheumatic disease

Investigations
- ANA and RF negative
- Markedly elevated ESR, CRP, ferritin (typically >1000 ng/mL, >2200 pmol/L)
  - Total ferritin >5 times ULN = 80% sensitive, 41% specific
- Anemia, thrombocytosis, leukocytosis may occur
- Transaminases, LDH may be elevated

Treatment
- 1st line therapy: methotrexate + low-dose glucocorticoids ± NSAIDs
- 2nd line therapy: other DMARDs (i.e. hydroxychloroquine, azathioprine, anti-IL1 and IL6 agents)

Common Medications

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing (PO)</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>acetaminophen</td>
<td>Tylenol®</td>
<td>500 mg tid q4h (4 g daily max)</td>
<td>1st line</td>
<td>Hepatotoxicity</td>
<td>Nausea, tinnitus, vertigo, rash, dyspepsia, GI bleed, PUD, hepatitis, renal failure, HTN, nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td>ECASA</td>
<td>Entrophen®</td>
<td>325-975 mg qid</td>
<td>2nd line</td>
<td>GI bleed</td>
<td>Nausea, tinnitus, vertigo, rash, dyspepsia, GI bleed, PUD, hepatitis, renal failure, HTN, nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td>ibuprofen</td>
<td>Advil®, Motrin®</td>
<td>200-600 mg tid</td>
<td>Renal impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>diclofenac</td>
<td>Voltaren®</td>
<td>25-50 mg tid</td>
<td>Allergy to ASA, NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>diclofenac/misoprostol</td>
<td>Antherate®, Aleve®</td>
<td>50-75/200 mg tid</td>
<td>Pregnancy (T3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>naproxen</td>
<td>Naprosyn®, Aleve®, Mobicox®</td>
<td>125-500 mg bid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>meloxicam</td>
<td>Mobicox®</td>
<td>7.5-15 mg OD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COX-2 INHIBITORS</td>
<td>celecoxib</td>
<td>Celebrex®</td>
<td>200 mg OD</td>
<td>High risk for GI bleed: age &gt; 65, hx of GI bleed, PUD</td>
<td>Renal impairment</td>
<td>Nausea, tinnitus, vertigo, rash, dyspepsia, GI bleed, PUD, hepatitis, renal failure, HTN, nephrotic syndrome</td>
</tr>
</tbody>
</table>

Other treatments

<table>
<thead>
<tr>
<th>Combination analgesics (acetaminophen + codeine, acetaminophen + NSAIDs)</th>
<th>Enhanced short term effect compared to acetaminophen alone</th>
<th>More adverse effects: sedation, constipation, nausea, GI upset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-articular corticosteroid injection</td>
<td>Short-term (weeks-months) decrease in pain and improvement in function</td>
<td>Used for management of an intraarticular inflammatory process when infection has been ruled out</td>
</tr>
<tr>
<td>Intra-articular hyaluronic acid q6mo</td>
<td>Used for mild-moderate OA of the knees, however little supporting evidence, and not considered to be effective</td>
<td>Precaution with chicken/egg allergy</td>
</tr>
<tr>
<td>Topical NSAIDs</td>
<td>1.5% wt/wt topical diclofenac (Pennsaid®)</td>
<td>May use for patients who fail acetaminophen treatment and who wish to avoid systemic therapy</td>
</tr>
<tr>
<td>Capsaicin cream</td>
<td>Mild decrease in pain</td>
<td></td>
</tr>
<tr>
<td>Glucosamine sulfate ± chondroitin</td>
<td>Limited clinical studies</td>
<td>No regulation by Health Canada</td>
</tr>
</tbody>
</table>
Table 32. Disease Modifying Anti-Rheumatic Drugs (DMARDs)

<table>
<thead>
<tr>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Contraindications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMMONLY USED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hydroxychloroquine $</td>
<td>Plaquenil®</td>
<td>400 mg PO OD initially 200-400 mg PO OD maintenance (6.5 mg/kg ideal body weight per day)</td>
<td>Retinal disease, G6PD deficiency</td>
<td>GI symptoms, skin rash, macular damage, neuropathy Requires regular ophthalmological screening to monitor for retinopathy</td>
</tr>
<tr>
<td>sulfasalazine $</td>
<td>Salazopyrin® Azulfidine® (US)</td>
<td>1000 mg PO bid-tid</td>
<td>Sulf/ASA allergy, kidney disease, G6PD deficiency</td>
<td>GI symptoms, rash, headache, leukopenia</td>
</tr>
<tr>
<td>methotrexate $</td>
<td>Rheumatrex® Folex/Mexate®</td>
<td>7.5-25 mg PO/IM/SC qweekly</td>
<td>Bone marrow suppression, liver disease, significant lung disease, immunodeficiency, pregnancy, EtOH abuse</td>
<td>Oral ulcers, GI symptoms, cirrhosis, myelosuppression, pneumonitis, tubular necrosis</td>
</tr>
<tr>
<td>leflunomide $</td>
<td>Arava®</td>
<td>10-20 mg PO OD</td>
<td>Liver disease</td>
<td>Alopecia, GI symptoms, liver dysfunction, pulmonary infiltrates</td>
</tr>
<tr>
<td><strong>NOT COMMONLY USED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyclosporine $</td>
<td>Neoral®</td>
<td>2.5-3 mg/kg/d divided and given in 2 doses PO</td>
<td>Kidney/liver disease, infection, hypertension</td>
<td>Hypertension, decreased renal function, hair growth, tremors, bleeding</td>
</tr>
<tr>
<td>gold (injectable) $</td>
<td>Solganal® Myocrysine®</td>
<td>50 mg IM q1wk after gradual introduction</td>
<td>IBD, kidney/liver disease</td>
<td>Rash, mouth soreness/ulcers, proteinuria, marrow suppression</td>
</tr>
<tr>
<td>azathioprine $</td>
<td>Imuran®</td>
<td>2.5 mg/kg/d PO once daily</td>
<td>Kidney/liver disease TPMT deficiency</td>
<td>Rash, pancytopenia (esp. ↓ WBC, ↑ AST, ALT), biliary stasis, vomiting, diarrhea</td>
</tr>
<tr>
<td>cyclophosphamide $</td>
<td>Cytoxan®</td>
<td>1 g/m²/mo IV as per protocol</td>
<td>Kidney/liver disease</td>
<td>Cardiotoxicity, GI symptoms, hemorrhagic cystitis, nephrotoxicity, bone marrow suppression, sterility</td>
</tr>
<tr>
<td><strong>NEWER DMARDs (Biologics)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>etanercept $$$</td>
<td>Enbrel®</td>
<td>25 mg biweekly or 50 mg weekly SC</td>
<td>Fusion protein of TNF receptor and Fc portion of IgG</td>
<td></td>
</tr>
<tr>
<td>infliximab $$$</td>
<td>Remicade®</td>
<td>3-5 mg/kg IV q8wk</td>
<td>Chimeric mouse/human monoclonal anti-TNF-α</td>
<td></td>
</tr>
<tr>
<td>adalimumab $$$</td>
<td>Humira®</td>
<td>40 mg SC q2wk</td>
<td>Monoclonal anti-TNF-α</td>
<td></td>
</tr>
<tr>
<td>abatacept $$$</td>
<td>Orencia®</td>
<td>IV infusion</td>
<td>Costimulation modulator of T-cell activation</td>
<td></td>
</tr>
<tr>
<td>rituximab $$$</td>
<td>Rituxan®</td>
<td>2 IV infusions, 2 wk apart</td>
<td>Causes B-cell depletion, binds to CD20</td>
<td></td>
</tr>
<tr>
<td>certolizumab $$$</td>
<td>Cimzia®</td>
<td>400 mg SC q2wk x3 then 200 mg SC q4wk</td>
<td>PEGylated monoclonal anti-TNF-α</td>
<td></td>
</tr>
<tr>
<td>golimumab $$$</td>
<td>Simponi®</td>
<td>50 mg SC q month</td>
<td>Monoclonal anti-TNF-α</td>
<td></td>
</tr>
<tr>
<td>tocilizumab $$$</td>
<td>Actemra®</td>
<td>4-8 mg/kg IV q4wk</td>
<td>Interleukin-6 receptor antagonist</td>
<td></td>
</tr>
</tbody>
</table>

**Risks of Biologics:**
- Reactivation of TB or hepatitis B. Patients require negative TB skin test, chest x-ray and negative HBV serology prior to starting any of these medications
- Increased risk of serious infections
- Worsening heart failure
# Landmark Rheumatology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RHUMATOID ARTHRITIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTEST</td>
<td>Ann Rheum Dis 2008; 67:1096-103</td>
<td>Abatacept and infliximab have similar efficacy in RA patients who have failed methotrexate</td>
</tr>
<tr>
<td>ATTRACT</td>
<td>Lancet 1999; 354:1932-9</td>
<td>Infliximab and methotrexate combined are more effective than methotrexate alone for patients with active RA</td>
</tr>
<tr>
<td>CIMESTRA</td>
<td>Arthritis Rheum 2006; 54:1401-9</td>
<td>Combination of methotrexate and sulfasalazine is superior to either alone</td>
</tr>
<tr>
<td>COMET</td>
<td>Lancet 2008; 372:375-82</td>
<td>Etanercept add-on therapy increases rates of remission in early RA</td>
</tr>
<tr>
<td>ERA</td>
<td>NEJM 2000; 343:1586-93</td>
<td>Etanercept more rapidly decreases symptoms in early RA compared to methotrexate</td>
</tr>
<tr>
<td>European Leflunomide Study Group</td>
<td>Lancet 1999; 353:259-66</td>
<td>Leflunomide is equal in efficacy to sulphasalazine</td>
</tr>
<tr>
<td>FIN-RAc</td>
<td>Lancet 1999; 353:1568-73</td>
<td>Combination therapy with DMARDs improves remission rates in early RA</td>
</tr>
<tr>
<td>Infliximab and methotrexate</td>
<td>NEJM 2000; 343:1594-602</td>
<td>Infliximab combined with methotrexate reduces joint damage in RA</td>
</tr>
<tr>
<td>Leflunomide Rheumatoid Arthritis Investigators Group</td>
<td>Arch Intern Med 1999; 159:2542-50</td>
<td>Leflunomide is equivalent to methotrexate therapy and superior to placebo</td>
</tr>
<tr>
<td>PREMIER</td>
<td>Arthritis Rheum 2006; 54:26-37</td>
<td>Combination therapy with adalimumab and methotrexate is superior to either alone in patients with early RA</td>
</tr>
<tr>
<td>Sveffot</td>
<td>Lancet 2009; 374:459-66</td>
<td>Anti-TNF agents are more effective second-line therapy than DMARDs in patients who fail methotrexate</td>
</tr>
<tr>
<td><strong>OSTEOARTHRITIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAIT</td>
<td>NEJM 2006; 343:795-808.</td>
<td>Glucosamine, chondroitin and the combination of both were no more effective than placebo in treatment of knee osteoarthritis</td>
</tr>
<tr>
<td><strong>LUPUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belimumab</td>
<td>Lancet 2011; 377:721-31</td>
<td>Treatment with belimumab reduces the incidence of BILAG A and B flares in patients with lupus compared to placebo</td>
</tr>
<tr>
<td>BILAG open-RCT</td>
<td>Rheumatology 2010; 49:723-32</td>
<td>Low dose cyclosporine and azathioprine are equivalent in efficacy as maintenance therapy for lupus</td>
</tr>
<tr>
<td>Mycophenylate mofetil or intravenous cyclophosphamide</td>
<td>NEJM 2005; 352:2219-28</td>
<td>Mycophenylate mofetil is more efficacious than cyclophosphamide in inducing remission of lupus nephritis</td>
</tr>
<tr>
<td><strong>CONNECTIVE TISSUE DISEASES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine or methotrexate maintenance for ANCA-associated vasculitis</td>
<td>NEJM 2008; 359:2790-803</td>
<td>Methotrexate and azathioprine are equally safe and effective as maintenance agents in ANCA vasculitis</td>
</tr>
<tr>
<td>Cyclophosphamide in scleroderma lung disease</td>
<td>NEJM 2006; 345:2805-6</td>
<td>Cyclophosphamide therapy led to transient improvements in lung function, skin scores, and overall health in patients with scleroderma</td>
</tr>
<tr>
<td>Etanercept plus standard therapy for granulomatosis with polyangiitis</td>
<td>NEJM 2005; 352:351-61</td>
<td>Etanercept is not effective in inducing remission in patients with ANCA vasculitis</td>
</tr>
<tr>
<td>Mycophenylate mofetil vs. azathioprine for maintenance in ANCA-associated vasculitis</td>
<td>JAMA 2010; 303:2391-8</td>
<td>Mycophenylate mofetil is less effective than azathioprine at inducing remission in ANCA-associated vasculitis</td>
</tr>
<tr>
<td>Rituximab versus cyclophosphamide for ANCA-associated vasculitis.</td>
<td>NEJM 2010; 363:222-32</td>
<td>Rituximab is not inferior to cyclophosphamide for induction of maintenance in ANCA vasculitis</td>
</tr>
<tr>
<td><strong>GOUT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febuxostat vs. allopurinol</td>
<td>NEJM 2005; 353:2450-61</td>
<td>Febuxostat is more effective than allopurinol at lowering serum urate, and has similar effectiveness on flare reduction</td>
</tr>
<tr>
<td>ANKYLOSING SPONDYLITIS</td>
<td>Reference</td>
<td>Results</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------</td>
<td>---------</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Arthritis Rheum 2006; 54:2136-46</td>
<td>Adalimumab induced partial remission in 22% of AS patients</td>
</tr>
<tr>
<td>ATLAS (adalimumab)</td>
<td>J Rheumatol 2008; 35:1348-53</td>
<td>Compared to placebo, adalimumab significantly reduces pain and fatigue in AS patients</td>
</tr>
<tr>
<td>ASSERT (rituximab)</td>
<td>Arthritis Rheum 2005; 52:582-91</td>
<td>Sixty percent of patients treated with rituximab had a clinical response to the medication</td>
</tr>
<tr>
<td>Infliximab in AS</td>
<td>Lancet 2002; 359:1167-93</td>
<td>Infliximab induces regression of symptoms in 50% of patients and is superior to placebo</td>
</tr>
<tr>
<td>SPINE (etanercept)</td>
<td>Ann Rheum Dis 2011; 70:799-804</td>
<td>ETN has short-term efficacy for patients with advanced AS and reduces disease severity</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Arthritis Rheum 1995; 38:618-27</td>
<td>Sulfasalazine is superior to placebo in treatment of patients with seronegative spondyloarthritis</td>
</tr>
</tbody>
</table>

References

CMAJ Clinical basics rheumatology series.
Kirkhof A. Diagnosis and management of inflammatory polyarthritis. CMAJ 2000;162:1833-1838.
Musculoskeletal Injury; (OPOT). Queen’s Printer of Ontario, June 2000. www.opot.org
Reid G, Esdaile JM. Getting the most out of radiology. CMAJ 2000;162:1318-1325.
Smetana, GW, Shmerling RH. Does this patient have temporal arteritis? JAMA 2002;287:227.
Acronyms ........................................... 2

Basic Anatomy Review .......................... 2
Abdominal Wall
Anatomy of Scrotum
Genito-Urinary Tract Anatomy
Penis Anatomy
Male Pelvis and Perineum

Urologic History ................................. 3

Common Presenting Problems ............... 4
Macroscopic (Gross) Hematuria
Microscopic Hematuria
Dysuria
Hydronephrosis

Voiding Dysfunction ............................. 6
Voiding
Failure to Store: Urinary Incontinence
Failure to Void: Urinary Retention
Benign Prostatic Hyperplasia (BPH)
Urethral Stricture
Neurogenic Bladder
Autonomic Dysreflexia
Post Obstructive Diuresis (POD)

Infectious and Inflammatory Diseases ...... 11
Urinary Tract Infection (UTI)
Recurrent/Chronic Cystitis
Interstitial Cystitis (Painful Bladder Syndrome)
Acute Pyelonephritis
Prostatitis/Prostatodynia
Epididymitis and Orchitis
Urethritis

Stone Disease ..................................... 16
Approach to Renal Stone

Urological Neoplasms .......................... 19
Approach to Renal Mass
Benign Renal Neoplasms
Malignant Renal Neoplasms
Carcinoma of the Renal Pelvis and Ureter
Bladder Carcinoma
Prostatic Carcinoma (CaP)
CaP Screening
Testicular Tumours
Penile Tumours

Scrotal Mass................................. 28
Penile Complaints ............................... 29
Peyronie’s Disease
Priapism
Paraphimosis
Phimosis
Erectile Dysfunction (ED)
Premature Ejaculation

Trauma ........................................... 32
Renal Trauma
Bladder Trauma
Urethral Injuries

Infertility ......................................... 34
Female Factors
Male Factors

Pediatric Urology ......................... 36
Congenital Abnormalities
Nephroblastoma (Wilms’ Tumour)
Cryptorchidism/Ectopic Testes
Disorders of Sexual Differentiation (DSD)
Circumcision
Enuresis

Selected Urological Procedures .......... 41
Bladder Catheterization
Cystoscopy
Radical Prostatectomy
Transurethral Resection of the Prostate (TURP)
Extracorporeal Shock Wave Lithotripsy (ESWL)

Common Medications ....................... 43
References ..................................... 45
## Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-hCG</td>
<td>beta-human chorionic gonadotropin</td>
</tr>
<tr>
<td>ABx</td>
<td>antibiotics</td>
</tr>
<tr>
<td>AFP</td>
<td>alpha-fetoprotein</td>
</tr>
<tr>
<td>AST</td>
<td>assisted reproductive technologies</td>
</tr>
<tr>
<td>AUA</td>
<td>American Urology Association</td>
</tr>
<tr>
<td>BPH</td>
<td>benign prostatic hyperplasia</td>
</tr>
<tr>
<td>CaP</td>
<td>prostatic carcinoma</td>
</tr>
<tr>
<td>CAH</td>
<td>congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>CBI</td>
<td>continuous bladder irrigation</td>
</tr>
<tr>
<td>CF</td>
<td>cystic fibrosis</td>
</tr>
<tr>
<td>CFU</td>
<td>colony-forming unit</td>
</tr>
<tr>
<td>CHF</td>
<td>congestive heart failure</td>
</tr>
<tr>
<td>CMG</td>
<td>cystometrogram</td>
</tr>
<tr>
<td>CIC</td>
<td>clean intermittent catheterization</td>
</tr>
<tr>
<td>CPPS</td>
<td>chronic pelvic pain syndrome</td>
</tr>
<tr>
<td>Cr</td>
<td>creatinine</td>
</tr>
<tr>
<td>CVA</td>
<td>costovertebral angle</td>
</tr>
<tr>
<td>CXR</td>
<td>chest x-ray</td>
</tr>
<tr>
<td>CSIS</td>
<td>culture and sensitivity</td>
</tr>
<tr>
<td>CVA</td>
<td>clean intermittent catheterization</td>
</tr>
<tr>
<td>DC</td>
<td>discharge</td>
</tr>
<tr>
<td>DHT</td>
<td>dihydrotestosterone</td>
</tr>
<tr>
<td>DRE</td>
<td>digital rectal exam</td>
</tr>
<tr>
<td>DSD</td>
<td>detrusor sphincter dyssynergia</td>
</tr>
<tr>
<td>EBRT</td>
<td>external beam radiation therapy</td>
</tr>
</tbody>
</table>

## Essential genito-urinary tract anatomy

- Figure 1. Midline cross-section of abdominal wall
- Figure 2. Anatomy of scrotum
- Figure 3. Essential genito-urinary tract anatomy

### Basic Anatomy Review

- Recall that the anatomical position of the penis is erect. Therefore, the anatomical ventral side of the penis appears to be the dorsal side of the flaccid penis.
Urologic History

- follow the OPQRSTUVW approach
  - note that pain may not be limited to the genital region (e.g., lower abdomen, CVA)
- inquire about risk factors: past urologic disease (e.g., UTI, stones, STI, cancers, anatomic abnormalities, family hx, medications, lifestyle factors, trauma, previous surgical procedures)
- constitutional symptoms: fever, chills, unintentional weight loss, night sweats, fatigue, malaise
- urinary output:
  - storage symptoms: frequency, nocturia, urgency, dysuria
  - voiding symptoms: straining, hesitancy, intermittency, post-void dribbling, reduced stream, feeling of incomplete voiding
  - hematuria: part of stream during which bleeding occurs, blood clots
  - incontinence: rushing to washroom (urge); leakage with coughing, sneezing, laughing (stress); constant dribbling (overflow)
- sexual function:
  - scrotal mass: see Scrotal Mass, U28
  - ED: see Erectile Dysfunction, U30
  - infertility: see Infertility, U34
- risk factors:
  - past urologic disease (e.g., UTI, stones, cancers, STI), anatomic abnormalities, trauma, previous surgical procedures, medications, family hx, lifestyle factors
- associated symptoms:
  - nausea/vomiting
- constitutional symptoms:
  - fever, chills, unintentional weight loss, night sweats, fatigue, malaise

Always ask about sexual function on history. Change in erectile function can be one of the first symptoms that there is concomitant coronary artery disease. If there is new onset ED, ask about chest pain with exertion.
Common Presenting Problems

Macroscopic (Gross) Hematuria

Definition
- blood in the urine that can be seen with the naked eye

Classification (see Nephrology, NP21)

Etiology

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-20</td>
<td>UTI, glomerulonephritis, congenital abnormalities</td>
</tr>
<tr>
<td>20-40</td>
<td>UTI, stones, bladder tumour</td>
</tr>
<tr>
<td>40-60</td>
<td>Male: bladder tumour, stones, UTI Female: UTI, stones, bladder tumour</td>
</tr>
<tr>
<td>&gt;60</td>
<td>Male: BPH, bladder tumour, UTI, RCC Female: bladder tumour, UTI, RCC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pseudohematuria</th>
<th>Pre-renal</th>
<th>Renal</th>
<th>Post-renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal bleeding</td>
<td>Anticoagulants, Coagulation defects, Sickle cell disease</td>
<td>Trauma, RCC (mainly in adult population), TCC, Wilms' tumour (mainly in pediatric population)</td>
<td>BPH, Stone</td>
</tr>
<tr>
<td>Dyes (beets, rhodamine B in candy and juices)</td>
<td>Hemoglobin (hemolytic anemia), Myoglobin (rhabdomyolysis)</td>
<td>Pyelonephritis, Glomerulonephritis, Interstitial nephritis, Tuberculosis</td>
<td>Neoplasms, Cystitis, Urethritis</td>
</tr>
<tr>
<td>Hemoglobin (hemolytic anemia)</td>
<td>Leukemia, Thromboembolism</td>
<td>Infarct, Polycystic kidneys, Arteriovenous malformation</td>
<td>Polyps, Foreign body</td>
</tr>
<tr>
<td>Myoglobin (rhabdomyolysis)</td>
<td>Drugs (rifampin, phenazopyridine, phenytoin)</td>
<td>Exercise-induced</td>
<td>Urethral stricture</td>
</tr>
<tr>
<td>Porphyria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laxatives (phenolphthalein)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

History
- if macroscopic, inquire about timing of hematuria in urinary stream
  - initial: anterior urethra
  - terminal: bladder neck and prostatic urethra
  - total: bladder and/or above

Investigations
- CBC (t/o anemia, leukocytosis), electrolytes, Cr, BUN
- urine studies:
  - U/A, C&S, cytology
- imaging:
  - CT (with contrast) has largely replaced IVP to investigate upper tracts (U/S alone is not sufficient)
  - cystoscopy to investigate lower tract (possible retrograde pyelogram)

Acute Management of Severe Bladder Hemorrhage
- manual irrigation via catheter with normal saline to remove clots
- CBI using large (22-26 Fr) 3-way Foley to help prevent clot formation
- cystoscopy if active bleeding:
  - identify resectable tumours
  - coagulate obvious sites of bleeding
- refractory bleeding:
  - continuous intravesical irrigation with 1% aluminum potassium sulfate solution as needed
  - intravesical instillation of 1% silver nitrate solution
  - intravesical instillation of 1-4% formalin (requires GA and pre-procedure cystogram to t/o reflux)
  - embolization or ligation of iliac arteries
  - cystectomy and diversion (rarely performed)

Upper Tract Imaging Options
- Intravenous Pyelogram (IVP): Traditional option but rarely used (replaced by CTU). Reasonable sensitivity for TCC, but poor sensitivity for RCC.
- U/S: Superior to IVP for evaluation of renal parenchyma and renal cysts. Limited sensitivity for TCC and small renal masses. U/S alone is not sufficient for upper tract imaging.
- CT Urogram (CTU): Optimal test for renal parenchyma, calculi, and infections. Involves exposure to radiation and IV contrast. Assess kidney function prior to use of contrast.
Microscopic Hematuria

Definition
• >2 RBCs/HPF on urinalysis of two separate samples

![Flowchart]

Figure 6. Workup of asymptomatic microscopic hematuria
Based on CUA Guidelines. AUA recommends cystoscopy and CT urogram for all patients with confirmed microscopic hematuria; follow-up for negative work-up is urinalysis yearly for two years, with repeat anatomic evaluation if microscopic hematuria persists

Dysuria

Definition
• painful urination

Etiology

Table 3. Differential Diagnosis of Dysuria

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Cystitis, urethritis, prostatitis, epididymitis/orchitis (if associated with lower tract inflammation), cervicitis, vulvovaginitis, perineal inflammation/infection, TB, vestibulitis</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>Kidney, bladder, prostate, penis, vagina/vulva, BPH</td>
</tr>
<tr>
<td>Calculi</td>
<td>Bladder stone, ureteral stone, kidney stone</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Seronegative arthropathies (reactive arthritis; arthritis, uveitis, urethritis), drug side effects, autoimmune disorders, chronic pelvic pain syndrome (CPPS), interstitial cystitis</td>
</tr>
<tr>
<td>Hormonal</td>
<td>Endometriosis, hypoestrogenism</td>
</tr>
<tr>
<td>Trauma</td>
<td>Catheter insertion, post-coital cystitis (honeymoon cystitis)</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>Somatization disorder, depression, stress/anxiety disorder</td>
</tr>
<tr>
<td>Other</td>
<td>Contact sensitivity, foreign body, radiation/chemical cystitis</td>
</tr>
</tbody>
</table>

Investigations
• focused hx and P/E to determine cause (fever, D/C, conjunctivitis, CVA tenderness, back/joint pain)
  • any D/C (urethral, vaginal, cervical) should be sent for gonococcus/chlamydia testing; wet mount if vaginal D/C
  • U/A and urine C&S
  • if suspect infection, may start empiric ABx treatment (see Table 8 in Infectious and Inflammatory Disease, U11, for ABx)
  • ± imaging of urinary tract (tumour, stones)
Hydronephrosis

Definition
- dilation of the renal pelvis and calyces caused by the backward pressure of trapped urine

Etiology
- mechanical:
  - congenital: see Congenital Abnormalities, U36
  - acquired:
    - intrinsic: trauma, inflammation and bleeding, calculi, urologic neoplasms, BPH, urethral stricture, phimosis
    - extrinsic: trauma, neoplasms (uterine fibroid; colorectal, uterine, and cervical malignancies; lymphoma), aortic aneurysm, pregnancy (gravid uterus)
- functional:
  - neurogenic: neurogenic bladder, diabetic neuropathy, spinal cord disease
  - pharmacologic: anticholinergics, α-adrenergic agonists
  - hormonal: pregnancy (progesterone decreases ureteral tone)

Investigations
- focused hx, inquiring about pain (flank, lower abdomen, testes, labia), U/O, medication use, pregnancy, trauma, fever, hx of UTIs, calculi and PID
- CBC, electrolytes, Cr, BUN, U/A, C&S
- imaging studies (U/S is >90% sensitive and specific)

Treatment
- aimed at relieving the cause of obstruction/stasis
- urgent treatment is required if associated with infection, acute renal failure, or severe pain
  - percutaneous nephrostomy tube or ureteral stenting to relieve pressure

Voiding Dysfunction

- see Gynecology, GY34 for relevant female topics

Voiding

- two phases of lower urinary tract function:
  1. storage phase (bladder filling and urine storage):
     - accommodation and compliance
     - no involuntary contraction
  2. voiding phase (bladder emptying):
     - coordinated detrusor contraction
     - synchronous relaxation of outlet sphincters
     - no anatomic obstruction
- voiding dysfunction can therefore be classified as:
  - failure to store: due to bladder or outlet
  - failure to void: due to bladder or outlet
- three types of symptoms
  - storage (formerly known as irritative)
  - voiding (formerly known as obstructive)
  - post-voiding

Failure to Store: Urinary Incontinence

Definition
- involuntary leakage of urine

Etiology
- urgency incontinence:
  - detrusor overactivity:
    - CNS lesion, inflammation/infection (cystitis, stone, tumour), bladder neck obstruction (tumour, stone), BPH, idiopathic
  - decreased compliance of bladder wall:
    - CNS lesion, fibrosis
    - sphincter/urethral problem
Clinical Features
- stress urinary incontinence (SUI):
  - common in women; seen in men after prostate cancer treatment or pelvic operations
  - urethral hypermobility:
    - weakened pelvic floor and musculofascial urethral and vaginal supporting mechanisms
    - associated with childbirth, pelvic surgery, aging, levator muscle weakness
    - intrinsic sphincter deficiency (ISD): weakness of the urethra and associated smooth and striated muscle elements
    - pelvic surgery, neurologic problem, aging and hypoestrogen state
  - ISD and urethral hypermobility can co-exist
  - mixed incontinence:
    - combination of stress and urgency incontinence
  - overflow incontinence:
    - is a term sometimes used to describe urinary incontinence as a complication of urinary retention; for causes of urinary retention see Failure to Void: Urinary Retention, below
  - the International Continence Society no longer recommends the use of this term as it is confusing and lacks a clear definition; if the term is used it should be accompanied by the associated pathophysiology (e.g. BPH with overflow incontinence)

Epidemiology
- variable prevalence in women: 25-45%
- F:M = 2:1
- more frequent in the elderly, affecting 5-15% of those living in the community and 50% of nursing home residents

Table 4. Urinary Incontinence: Types and Treatments

<table>
<thead>
<tr>
<th>Type</th>
<th>Urgency</th>
<th>Stress</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Involuntary leak of urine preceded by a strong, sudden urge to void</td>
<td>Involuntary leakage of urine with sudden increases in intra-abdominal pressure</td>
<td>Urinary leakage associated with urgency and increased intra-abdominal pressure</td>
</tr>
<tr>
<td>Etiology</td>
<td>Bladder (detrusor overactivity)</td>
<td>Urethra/sphincter weakness, post-partum pelvic musculature weakness</td>
<td>Combination of bladder and sphincter issues</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Hx Urodynamics</td>
<td>Hx</td>
<td>Hx Stress test</td>
</tr>
<tr>
<td>Therapy</td>
<td>Anticholinergics</td>
<td>Weight loss</td>
<td>Combination of management of urge and stress incontinence</td>
</tr>
<tr>
<td></td>
<td>Lifestyle changes</td>
<td>Kege exercises</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(fluid alterations, diet, etc.)</td>
<td>Bulking agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bladder habit training</td>
<td>Surgery (slings, tension-free vaginal tape, transobturator tape, artificial sphincters)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Botulinum toxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neuromodulation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Failure to Void: Urinary Retention

Table 5. Etiology of Urinary Retention

<table>
<thead>
<tr>
<th>Outflow Obstruction</th>
<th>Bladder Innervation</th>
<th>Pharmacologic</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder neck or urethra: calculus, clot, foreign body, neoplasm, neurological (DSD)</td>
<td>Intracranial: CVA, tumour, Parkinson's, cerebral palsy</td>
<td>Anticholinergics</td>
<td>GU: UTI, prostatitis, abscess, genital herpes</td>
</tr>
<tr>
<td>Prostate: BPH, prostate cancer</td>
<td>Spinal cord: injury, disc herniation, MS</td>
<td>Narcotics</td>
<td>Infected foreign body</td>
</tr>
<tr>
<td>Urethra: stricture, phimosis, traumatic disruption</td>
<td>DM</td>
<td>Antihypertensives (ganglionic blockers, methyl dopa)</td>
<td>Varicella zoster</td>
</tr>
<tr>
<td>Miscellaneous: constipation, pelvic mass</td>
<td>Post-abdominal or pelvic surgery</td>
<td>OTC cold medications containing ephedrine or pseudoephedrine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antihistamines</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychosomatic substances (e.g. eczasy)</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features
- suprapubic pain
- palpable and/or percussible bladder (suprapubic)
- possible purulent/bloody meatal D/C
- increased size of prostate or reduced anal sphincter tone on DRE
- neurologic: presence of abnormal or absent deep tendon reflexes, reduced “anal wink”, saddle anesthesia
Investigations
• CBC, electrolytes, Cr, BUN, U/A and urine C&S, U/S, cystoscopy, urodynamic studies, PVR

Treatment
• treat underlying cause
• catheterization:
  ▪ acute retention
    • immediate catheterization to relieve retention; leave Foley in to drain bladder; F/U to
determine cause; closely monitor fluid status and electrolytes (risk of POD)
  ▪ chronic retention
    • intermittent catheterization by patient is commonly used; definitive treatment depends
on etiology
  ▪ suprapubic tube placement
  ▪ for post-operative patients with retention:
    ▪ encourage ambulation
    ▪ α-blockers to relax bladder neck outlet
    ▪ may need catheterization
    ▪ definitive treatment will depend on etiology

Benign Prostatic Hyperplasia (BPH)

Definition
• periurethral hyperplasia of stroma and epithelium in prostatic transition zone (see Figure 7)
• prostatic smooth muscle cells play a role in addition to hyperplasia

Etiology
• etiology unknown
  ▪ DHT required (converted from testosterone by 5-a reductase)
  ▪ possible role of impaired apoptosis, estrogens, other growth factors

Epidemiology
• age-related, extremely common (50% of 50 yr olds, 80% of 80 yr olds)
• 25% of men will require treatment

Clinical Features
• result from outlet obstruction and compensatory changes in detrusor function
• voiding symptoms:
  ▪ hesitancy, straining, weak/interrupted stream, incomplete bladder emptying
• storage symptoms:
  ▪ urgency, frequency, nocturia, urgency incontinence
  ▪ thought to be due to detrusor overactivity and/or decreased compliance
• DRE
  ▪ prostate is smooth, rubbery and symmetrically enlarged
• complications:
  ▪ retention
  ▪ overflow incontinence
  ▪ hydronephrosis
  ▪ infection
  ▪ gross hematuria
  ▪ bladder stones

Investigations
• hx, assessing LUTS and impact on QOL
  ▪ may include self-administered questionnaires (IPSS or AUA symptom index for severity,
progression, and treatment response)
• P/E, including DRE
• U/A to exclude UTI
• Cr ± renal U/S to assess for hydronephrosis
• PSA to t/o malignancy (see CaP Screening, U25)
• uroflowmetry to measure flow rate (optional)
• PVR (optional)
• cystoscopy prior to potential surgical management
• biopsy if suspicious for malignancy

Patients with ascites may have a falsely elevated PVR measured by bladder scan.

Figure 7. Cross-section of prostate

Approximate Prostate Sizes
• 20 cc – chestnut
• 25 cc – plum
• 50 cc – lemon
• 75 cc – orange
• 100 cc – grapefruit

AUA Prostate Symptom Score

FUNWISE
F = Frequency
U = Urgency
N = Nocturia
W = Weak stream
I = Intermittency
S = Straining
E = Emptying, incomplete feeling of

Each symptom graded out of 5
0-7: Mildly symptomatic
8-19: Moderately symptomatic
20-35: Severely symptomatic

Note: dysuria not included in score but is commonly associated with BPH
Treatment

Table 6. Treatment of BPH

<table>
<thead>
<tr>
<th>When to use</th>
<th>Conservative</th>
<th>Medical</th>
<th>Surgical</th>
<th>Minimally Invasive Surgical Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Moderate to severe symptoms</td>
<td>Moderate to severe symptoms</td>
<td>Patients who wish to avoid or may not tolerate surgery</td>
<td></td>
</tr>
</tbody>
</table>

Options
- Watchful waiting: 50% of patients improve spontaneously
- Lifestyle modifications (e.g. evening fluid restriction, planned voiding)
- \(\alpha\)-adrenergic antagonists: reduce stromal smooth muscle tone
- 5-\(\alpha\) reductase inhibitor: block conversion of testosterone to DHT, act to reduce prostate size
- Combination is synergistic
- Anti-cholinergic agents (for storage LUTS, without elevated PVR)
- TURP (see U42)
- Laser ablation
- TUIP (prostate <30 g)
- Open prostatectomy
- Microwave therapy
- TUNA
- Prostatic stent

Urethral Stricture

Definition
- Decrease in urethral calibre due to scar formation in urethra (may also involve corpus spongiosum)
- M>F

Etiology
- Congenital
  - Failure of normal canalization (technically not a stricture)
- Trauma:
  - Instrumentation/catheterization (most common)
  - External trauma (e.g. burns, straddle injury)
- Foreign body
- Infection:
  - Long-term indwelling catheter
  - STI
- Inflammation:
  - Balanitis xerotica obliterans (lichen sclerosis or chronic progressive sclerosing dermatosis of the male genitalia) causing meatal stenosis

Clinical Features
- Voiding symptoms
- Urinary retention
- Hydronephrosis
- Related infections: recurrent UTI, secondary prostatitis/epididymitis

Investigations
- Laboratory findings:
  - Flow rates <10 mL/s (normal ~20 mL/s) on uroflowmetry
  - Urine culture usually negative, but U/A may show pyuria
- Radiologic findings:
  - RUG and VCU will demonstrate location
  - Cystoscopy

Treatment
- Urethral dilatation:
  - Temporarily increases lumen size by breaking up scar tissue
  - Healing will often reform scar tissue and recreate stricture
- Visual internal urethrotomy (VIU):
  - Endoscopically incise stricture
  - Cure rate 50-80% with single treatment, <50% with repeated courses
- Open surgical reconstruction:
  - Complete stricture excision with anastomosis, \(\pm\) urethroplasty depending on location and size of stricture
Neurogenic Bladder

Definition
• malfunctioning urinary bladder due to deficiency in some aspect of its innervation

Neurophysiology

Table 7. Efferent Sympathetic, Parasympathetic, and Somatic Nerve Supply

<table>
<thead>
<tr>
<th>Nerve Fibres</th>
<th>Nerve Roots</th>
<th>Neurotransmitter/Receptor</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic</td>
<td>T10-L2</td>
<td>NA/Adrenergic</td>
<td>Trigone, internal sphincter, proximal urethra</td>
</tr>
<tr>
<td></td>
<td>T10-L2</td>
<td></td>
<td>Bladder body</td>
</tr>
<tr>
<td>Somatic</td>
<td>S2-4</td>
<td>ACh/Nicotinic</td>
<td>External sphincter</td>
</tr>
<tr>
<td>Parasympathetic</td>
<td>S2-4</td>
<td>ACh/Muscarinic (M2, M3)</td>
<td>Detrusor</td>
</tr>
</tbody>
</table>

• stretch receptors in the bladder wall relay information to PMC and activate micturition reflex (normally inhibited by cortical input)
  ▪ micturition:
    ▪ stimulation of parasympathetic neurons (bladder contraction)
    ▪ inhibition of sympathetic and somatic neurons (internal and external sphincter relaxation, respectively)
  ▪ urine storage:
    ▪ opposite of micturition
• voluntary action of external sphincter ( pudendal nerve roots S2-S4) can inhibit urge to urinate
• cerebellum, basal ganglia, thalamus, and hypothalamus all have input at PMC in the brainstem

Classification of Neurologic Voiding Dysfunction
• neurogenic detrusor overactivity (formerly termed detrusor hyperreflexia):
  ▪ lesion above PMC (e.g. stroke, tumour, MS, Parkinson’s disease)
  ▪ loss of voluntary inhibition of voiding
  ▪ intact pathway inferior to PMC maintains coordination of bladder and sphincter
• detrusor sphincter dyssynergia (DSD):
  ▪ lesion of spinal cord (e.g. trauma, MS, arteriovenous malformation, transverse myelitis)
  ▪ loss of coordination between detrusor and sphincter (detrusor contracts on closed sphincter and vice versa)
  ▪ component of detrusor overactivity as well
• detrusor atony/areflexia:
  ▪ lesion of sacral cord or peripheral efferents (e.g. trauma, DM, disc herniation, MS, congenital spinal cord abnormality)
  ▪ flaccid bladder which fails to contract
  ▪ may progress to poorly compliant bladder with high pressures
• peripheral autonomic neuropathy:
  ▪ deficient bladder sensation → increasing residual urine → decompensation (e.g. DM, neurosyphilis, herpes zoster)
• muscular lesion:
  ▪ can involve detrusor, smooth/ striated sphincter

Neuro-Urologic Evaluation
• hx and P/E (urologic and general neurologic)
• U/A, renal profile
• imaging
  ▪ IVP (less used), U/S to r/o hydronephrosis and stones
• cystoscopy
• urodynamic studies:
  ▪ uroflowmetry to assess flow rate, pattern
  ▪ filling CMG to assess capacity, compliance, detrusor overactivity
  ▪ voiding CMG (pressure-flow study) to assess bladder contractility and extent of bladder outflow obstruction
  ▪ video study to visualize bladder/bladder neck/urethra during CMG using x-ray contrast
  ▪ EMG ascertains presence of coordinated or uncoordinated voiding, allows accurate diagnosis of DSD

Treatment
• goals of treatment:
  ▪ prevent renal failure
  ▪ prevent infections
  ▪ achieve social continence
• treatment options depend on status of bladder and urethra
  ▪ bladder hyperactivity → medications to relax bladder (see Urinary Incontinence, U6)
    • if refractory:
      – botulinum toxin injections into bladder wall
      – occasionally augmentation cystoplasty (enlarging bladder volume and improving compliance by grafting section of detubularized bowel onto the bladder)
      – occasionally urinary diversion (ileal conduit or continent diversion) if bladder management unsuccessful
  ▪ flaccid bladder → CIC

**Autonomic Dysreflexia**

• occurs in patients with spinal cord injury above T6/T7
• exaggerated sympathetic nervous system response to visceral stimulation below the lesion
• stimulation includes instrumentation or distension of bladder, urethra, or rectum
• symptoms include HTN, headache, reflex bradycardia, sweating, anxiety, piloerection
• vasoconstriction below lesion, vasodilation above lesion
• treatment: removal of noxious stimuli, parenteral ganglionic or α-blockers, nifedipine (prophylaxis during cystoscopy)

**Post-Obstructive Diuresis (POD)**

**Definition**

• polyuria resulting from relief of severe chronic obstruction
• >3 L/24 h or >200 cc/h over each of two consecutive hours

**Pathophysiology**

• physiologic POD secondary to excretion of retained urea, Na+, and H2O (high osmotic load) after relief of obstruction
  • self-limiting; usually resolves in 48 h with PO fluids but may persist to pathologic POD
• pathologic POD is a Na+-wasting nephropathy secondary to impaired concentrating ability of the renal tubules due to:
  ▪ decreased reabsorption of NaCl in the thick ascending limb and urea in the collecting tubule
  ▪ increased medullary blood flow (solute washout)
  ▪ increased flow and solute concentration in the distal nephrons

**Management**

• admit patient and closely monitor hemodynamic status and electrolytes (Na+ and K+ q6-12h and replace prn; follow Cr and BUN to baseline)
• monitor U/O q2h and ensure total fluid intake <U/O by replacing every 1 cc U/O with 0.5 cc 1/2 NS IV (PO fluids if physiologic POD)
• avoid glucose-containing fluid replacement (iatrogenic diuresis)

**Infectious and Inflammatory Diseases**

Table 8. Antibiotic Treatment of Urological Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethritis</td>
<td>non-gonococcal:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>azithromycin (1 g PO)</td>
<td>x 1</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>doxycycline (100 mg PO bid)</td>
<td>7 d</td>
</tr>
<tr>
<td></td>
<td>gonococcal:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ceftriaxone (250 mg IM) AND treat for Chlamydia trachomatis</td>
<td>x 1</td>
</tr>
<tr>
<td>Simple, Uncomplicated UTI</td>
<td>TMP-SMX (160 mg/800 mg PO bid)</td>
<td>3 d</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nitrofurantoin (100 mg PO bid)</td>
<td>5 d</td>
</tr>
<tr>
<td>Complicated UTI [see Classification for features]</td>
<td>ciprofloxacin (1 g PO daily OR 400 mg IV q12h)</td>
<td>up to 2-3 wk</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ampicillin (1 g IV q8h) + gentamicin (1 mg/kg IV q8h)</td>
<td>up to 2-3 wk</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ceftriaxone (1-2 g IV q24h)</td>
<td>up to 2-3 wk</td>
</tr>
<tr>
<td>Recurrent/Chronic Cystitis</td>
<td>continuous: TMP-SMX (40 mg/200 mg PO qd OR 3x/wk)</td>
<td>6-12 mo</td>
</tr>
<tr>
<td></td>
<td>post-coital: TMP-SMX (40 mg/200 mg-qd/400 mg)</td>
<td>within 2 h of coitus</td>
</tr>
</tbody>
</table>

Uncomplicated UTI in men <50 should be treated with 7 d courses of TMP-SMX.
Table 8. Antibiotic Treatment of Urological Infections (continued)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Prostatitis</td>
<td>ciprofloxacin (500-750 mg PO bid) OR</td>
<td>2-4 wk</td>
</tr>
<tr>
<td></td>
<td>TMP-SMX (160 mg/800 mg PO bid) OR</td>
<td>4 wk</td>
</tr>
<tr>
<td></td>
<td>IV therapy with gentamicin and ampicillin,</td>
<td>4 wk total (IV and oral step-down)</td>
</tr>
<tr>
<td></td>
<td>penicillin w/ β-lactamase inhibitor, 3rd gen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cephalosporin, OR a fluoroquinolone</td>
<td></td>
</tr>
<tr>
<td>Chronic Prostatitis</td>
<td>ciprofloxacin (500 mg PO bid)</td>
<td>4-6 wk</td>
</tr>
<tr>
<td>Epididymitis/Orchitis</td>
<td>ceftriaxone (200 mg IM) AND doxycycline (100 mg PO bid)</td>
<td>x 1</td>
</tr>
<tr>
<td></td>
<td>≥35 yr: ofloxacin (300 mg PO bid)</td>
<td>10 d</td>
</tr>
<tr>
<td>Acute Uncomplicated</td>
<td>ciprofloxacin (500 mg PO bid) OR</td>
<td>7 d</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>ceftriaxone (1 g IV) OR ciprofloxacin (400 mg IV)</td>
<td>x 1</td>
</tr>
<tr>
<td></td>
<td>IV therapy with a fluoroquinolone, gentamicin</td>
<td>14 d total (IV and oral step-down)</td>
</tr>
<tr>
<td></td>
<td>and ampicillin, extended spectrum cephalosporin, OR a carbapenem</td>
<td></td>
</tr>
</tbody>
</table>

Urinary Tract Infection (UTI)

- for UTIs during pregnancy, see Obstetrics, OB20

Definition
- symptoms suggestive of UTI (see Clinical Features below) + evidence of pyuria and bacteriuria on U/A or urine C&S
  - if asymptomatic + 100,000 CFU/mL = asymptomatic bacteriuria; only requires treatment in certain patients (e.g. pregnancy)

Classification
- uncomplicated: lower UTI in a setting of functionally and structurally normal urinary tract
- complicated: structural and/or functional abnormality, immunocompromised, iatrogenic complication, pregnancy, pyelonephritis, catheter-associated
- recurrent: see Recurrent/Chronic Cystitis, U13

Risk Factors
- stasis and obstruction:
  - residual urine due to impaired urine flow e.g. PUVs, reflux, medication, BPH, urethral stricture, cystocele, neurogenic bladder
- foreign body:
  - introduce pathogen or act as nidus of infection e.g. catheter, instrumentation
- decreased resistance to organisms:
  - DM, malignancy, immunosuppression, spermicide use, estrogen depletion, antimicrobial use
- other factors:
  - trauma, anatomic abnormalities, female, sexual activity, fecal incontinence

Clinical Features
- storage symptoms: frequency, urgency, dysuria
- voiding symptoms: hesitancy, post-void dribbling
- other: suprapubic pain, hematuria, foul-smelling urine
- pyelonephritis – if present: typically presents with more severe symptoms (e.g. fever/chills, CVA tenderness, flank pain)

Organisms
- typical organisms (see sidebar)
- atypical organisms:
  - tuberculosis (TB)
  - Chlamydia trachomatis
  - Mycoplasma (Ureaplasma urealyticum)
  - fungi (Candida)

Indications for Investigations
- pyelonephritis
- persistence of pyuria/symptoms following adequate therapy
- severe infection with an increase in Cr
- recurrent/persistent infections
- atypical pathogens (urea splitting organisms)
- hx of structural abnormalities/decreased flow

Antibiotic therapy should always be based on local resistance patterns and adjusted according to culture and sensitivity results.

IV antibiotics should be stepped down to oral when the patient is afebrile and clinically stable.

Acute uncomplicated pyelonephritis: suspected or confirmed enterococcus infection requires treatment with ampicillin.
Investigations
- U/A, urine C&S
  - UA: leukocytes ± nitrites ± hematuria
  - C&S: midstream, catheterized, or suprapubic aspirate
- if hematuria present, retest post-treatment, if persistent need hematuria workup (see Microscopic Hematuria, U5)
- CT scan if indicated

Treatment
- see Table 8 for approach to ABx therapy
- if febrile, consider admission with IV therapy and r/o obstruction

Recurrent/Chronic Cystitis

Definition
- ≥3 UTIs/12 mo

Etiology
- bacterial reinfection (80%) vs bacterial persistence (relapse)
  - bacterial reinfection:
    - recurrence of infection with either 1) a different organism, 2) the same organism if cultured >2 wk following therapy, or 3) with any organism with an intermittent sterile culture
  - bacterial persistence:
    - same organism cultured within 2 wk of sensitivity-based therapy

Investigations
- assess predisposing factors as described above
- investigations may include cystoscopy, U/S, CT

Treatment
- lifestyle changes (limit caffeine intake, increase fluid/H2O intake)
- ABx: continuous vs. post-coital (see Table 8)
- post-menopausal women: consider topical or systemic estrogen therapy
- no treatment for asymptomatic bacteriuria except in pregnant women or patients undergoing urinary tract instrumentation

Interstitial Cystitis
(Painful Bladder or Bladder Pain Syndrome)

Definition
- chronic urgency, frequency ± pain without other reasonable causation

Classification
- non-ulcerative (more common)
- ulcerative

Etiology
- unknown
  - theories: increased epithelial permeability, autoimmune, neurogenic, defective glycosaminoglycan (GAG) layer overlying mucosa
  - associations: severe allergies, IBS, fibromyalgia

Epidemiology
- prevalence: 20/100,000
- 90% of cases are in females
- mean age at onset is 40 yr (non-ulcerative tends to affect a younger to middle-aged population, while ulcerative tends to be seen in middle-aged to older)

Clinical Features
- pain associated with the bladder
- glomerulations (submucosal petechiae) or Hunner’s ulcers on cystoscopic examination
- urinary urgency
- negative U/A, urine C&S, and urine cytology

Differential Diagnosis
- UTI, vaginitis, bladder tumour
- radiation/chemical cystitis
- eosinophilic/TB cystitis
- bladder calculi

Prevention of UTIs
- Maintain good hydration (especially with cranberry juice)
- Wipe from front to back to avoid contamination of the urethra with feces from the rectum
- Avoid feminine hygiene sprays and scented douches
- Empty bladder immediately before and after intercourse

Cystoscopic evaluation is not necessary to make a diagnosis.
Treatment
• first-line: patient empowerment (diet, lifestyle, stress management), pain management
• second-line:
  ▪ oral: pentosan polysulfate sodium, amitriptyline, cimetidine, hydroxyzine
  ▪ intravesical: dimethylsulfoxide (DMSO), heparin, lidocaine
• third-line: cystoscopy with bladder hydrodistention (traditionally diagnostic) under GA, treat Hunner’s ulcers if present
• other: neuromodulation, cyclosporine A, intradetrusor botulinum toxin
• surgery (last resort): augmentation cystoplasty, or urinary diversion ± cystectomy

Acute Pyelonephritis

Definition
• infection of the renal parenchyma with local and systemic manifestations

Etiology
• ascending (usually GN bacilli) or hematogenous route (usually GP cocci)
• causative microorganisms:
  ▪ gram positives: *Enterococcus faecalis, S. aureus, S. saprophyticus*
  ▪ gram negatives: *E. coli* (most common), *Klebsiella, Proteus, Pseudomonas, Enterobacter*
• common underlying causes of pyelonephritis
  ▪ stones, strictures, prostatic obstruction, vesicoureteric reflux, neurogenic bladder, catheters, DM, sickle-cell disease, PCKD, immunosuppression, post-renal transplant, instrumentation, pregnancy

Clinical Features
• rapid onset (<24 h)
• LUTS including frequency, urgency, hematuria; NOT dysuria unless concurrent cystitis
• fever, chills, nausea, vomiting, myalgia, malaise
• CVA tenderness or exquisite flank pain

Investigations
• U/A, urine C&S
• CBC and differential: leukocytosis, left shift
• imaging indicated if suspicious of complicated pyelonephritis or symptoms do not improve with 48-72 h of treatment
  ▪ abdominal/pelvic U/S
  ▪ CT
• nuclear medicine: DMSA scan can be used to help secure the diagnosis
  ▪ a photopenic defect indicates active infection or scar; if normal alternative diagnoses should be considered

Treatment
• hemodynamically stable:
  ▪ outpatient oral ABx treatment ± single initial IV dose (see Table 8)
• severe or non-resolving:
  ▪ admit, hydrate, and treat with IV ABx (see Table 8)
• emphysematous pyelonephritis:
  ▪ consider emergent nephrectomy after IV ABx started and patient stabilized
• renal obstruction:
  ▪ admit for emergent stenting or percutaneous nephrostomy tube

Prostatitis/Prostatodynia

Epidemiology
• most common urologic diagnosis in men <50 yr
• prevalence 2-12%
Classification

Table 9. Comparison of the Three Types of Prostatitis

<table>
<thead>
<tr>
<th>Category I: Acute Bacterial Prostatitis</th>
<th>Category II: Chronic Bacterial Prostatitis</th>
<th>Category III: Chronic Pelvic Pain Syndrome (CPPS) (Abacterial)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Recurrent exacerbations of acute prostatitis-like signs and symptoms</td>
<td>Divided into inflammatory (IIA) and non-inflammatory (IIB)</td>
</tr>
<tr>
<td>Ascending urethral infection with KEEPS (see U12 sidebar): 80% E. coli</td>
<td>Recurrent UTI with same organism</td>
<td>Intraprostatic reflux of urine ± urethral hypertonia</td>
</tr>
<tr>
<td>Often associated with outlet obstruction, recent cystoscopy, prostatic biopsy</td>
<td></td>
<td>Multifactorial (immunological, neuropathic, neuroendocrine, psychosocial)</td>
</tr>
<tr>
<td>Most infections occur in the peripheral zone (see Figure 7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td>Pelvic pain, storage LUTS, ejaculatory pain, post-ejaculatory pain</td>
<td>Pelvic pain, storage LUTS, ejaculatory pain, post-ejaculatory pain</td>
</tr>
<tr>
<td>Acute onset fever, chills, malaise</td>
<td></td>
<td>Same as per Category II</td>
</tr>
<tr>
<td>Rectal, lower back and perineal pain</td>
<td></td>
<td>Consider psychological assessment</td>
</tr>
<tr>
<td>LUTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>PEx: Abdo, external genitalia, perineum, prostate</td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood CBC, C&amp;S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transrectal U/S if non-resolving/suspect prostatic abscess</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Supportive measures</td>
<td>Supportive measures</td>
</tr>
<tr>
<td>PO or IV ABx depending how sick (see Table 8)</td>
<td></td>
<td>Trial of ABx therapy if newly diagnosed</td>
</tr>
<tr>
<td>May consider catheterization in pts with severe obstructive LUTS or retention</td>
<td></td>
<td>Multi-modal Tx strategy may include:</td>
</tr>
<tr>
<td>If&amp;D of abscess if present</td>
<td></td>
<td>α-blocker</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>ABx (see Table 8)</td>
<td>Anti-inflammatories</td>
</tr>
<tr>
<td></td>
<td>Consider addition of an α-blocker</td>
<td>Phytotherapy (quercetin, cernilton)</td>
</tr>
</tbody>
</table>

*NIH-CPSI: National Institute of Health Chronic Prostatitis Symptom Index

Epididymitis and Orchitis

**Etiology**
- common infectious causes:
  - <35 yr: N. gonorrheae or Chlamydia trachomatis
  - ≥35 yr or penetrative anal intercourse: GI organisms (especially E. coli)
- other causes:
  - mumps infection may involve orchitis, post-parotitis
  - TB
  - syphilis
  - granulomatous (autoimmune) in elderly men
  - amiodarone (involves only head of epididymis)

**Risk Factors**
- UTI
- unprotected sexual contact
- instrumentation/catheterization
- reflux
- increased pressure in prostatic urethra (straining, voiding, heavy lifting) may cause reflux of urine along vas deferens → sterile epididymitis
- immunocompromise

**Clinical Features**
- sudden onset scrotal pain and swelling ± radiation along cord to flank
- scrotal erythema and tenderness
- fever
- storage symptoms, purulent D/C
- reactive hydrocele

**Investigations**
- U/A, urine C&S
- ± urethral D/C: Gram stain/culture
- if diagnosis uncertain, must do:
  - colour-flow Doppler U/S to r/o testicular torsion

**Treatment**
- r/o torsion (see Investigations and Table 23, U28)
- see Table 8 for ABx therapy
- scrotal support, bed rest, ice, analgesia

**Complications**
- if severe → testicular atrophy
- 30% have persistent infertility problems

Prehn’s sign: pain may be relieved with elevation of testicles in epididymitis but not in testicular torsion. Poor sensitivity, especially in children.

If unsure between diagnoses of epididymitis and torsion, always go to OR. Remember: torsion >6 h has poor prognosis

Inadequately treated acute epididymitis may lead to chronic epididymitis or epididymo-orchitis.
Urethritis

Etiology
• infectious or inflammatory (e.g. reactive arthritis)

Table 10. Infectious Urethritis: Gonococcal vs. Non-Gonococcal

<table>
<thead>
<tr>
<th></th>
<th>Gonococcal</th>
<th>Non-gonococcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causative organism</td>
<td>Neisseria gonorrhoeae</td>
<td>Usually Chlamydia trachomatis</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Hx of sexual contact, thick, profuse, yellow-grey purulent, D/C, LUTS</td>
<td>Hx of sexual contact, mucoid whitish purulent, D/C, ≥ storage LUTS</td>
</tr>
<tr>
<td></td>
<td>Gram stain (GN diplococci), urine PCR and/or culture from urethral specimen</td>
<td>Gram stain demonstrates &gt; 4 PMN/oil immersion field, no evidence of N. gonorrhoeae, urine PCR and/or culture from urethral specimen</td>
</tr>
<tr>
<td>Treatment</td>
<td>see Table 8</td>
<td>see Table 8</td>
</tr>
</tbody>
</table>

Stone Disease

Epidemiology
• prevalence of 2-3%
• male:female = 3:1
• peak incidence 30-50 yr of age
• recurrence rate: 10% at one yr, 50% at 5 yr, 60-80% lifetime

Risk Factors
• hereditary: RTA, G6PD, cystinuria, xanthinuria, oxaluria, etc.
• lifestyle: minimal fluid intake; excess vitamin C, oxalate, purines, calcium
• medications: loop diuretics (furosemide, bumetanide), acetazolamide, topiramate, and zonisamide
• medical conditions: UTI (with urea-splitting organisms), myeloproliferative disorders, IBD, gout, DM, hypercalcemia disorders (hyperparathyroidism, tumour lysis syndrome, sarcoidosis, histoplasmosis), obesity (BMI > 30)

Clinical Features
• urinary obstruction → upstream distention → pain
  ▪ flank pain from renal capsular distention (non-colicky)
  ▪ severe waxing and waning pain radiating from flank to groin, testis, or tip of penis due to stretching of collecting system or ureter (ureteral colic)
• writhing, never comfortable, nausea, vomiting, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
• occasionally symptoms of trigonal irritation (frequency, urgency)
• bladder stones result in: storage and voiding LUTS, terminal hematuria, suprapubic pain
• if fever, r/o concurrent pyelonephritis and/or obstruction

Table 11. Differential Diagnosis of Renal Colic

<table>
<thead>
<tr>
<th>GU</th>
<th>Abdominal</th>
<th>Neurological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyelonephritis</td>
<td>AAA</td>
<td>Radiculitis (L1): herpes zoster, nerve root compression</td>
</tr>
<tr>
<td>Ureteral obstruction from other cause: UPJ</td>
<td>Bowel ischemia</td>
<td></td>
</tr>
<tr>
<td>obstruction</td>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>clot colic secondary to gross hematuria, sloughed papillae</td>
<td>Other acute abdominal crisis</td>
<td></td>
</tr>
<tr>
<td>Gynecological: ectopic pregnancy, torsion/rupture of ovarian cyst, PID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>Struvite</td>
<td>Cystine</td>
</tr>
<tr>
<td>Struvite</td>
<td>Cystine</td>
<td>Uric acid</td>
</tr>
<tr>
<td>Cystine</td>
<td>Indinavir</td>
<td></td>
</tr>
<tr>
<td>Uric acid</td>
<td>Indinavir</td>
<td></td>
</tr>
</tbody>
</table>

Location of Stones
• calyx: may cause flank discomfort, persistent infection, persistent hematuria, or remain asymptomatic
• pelvis tend to cause obstruction at UPJ, may cause persistent infection
• ureter: <5 mm diameter will pass spontaneously in 75% of patients

Stone Pathogenesis
• supersaturation of stone constituents (at appropriate temperature and pH)
• stasis, low flow, and low volume of urine (dehydration)
• crystal formation and stone nidus
• loss of inhibitory factors:
  ▪ citrate (forms soluble complex with calcium)
  ▪ magnesium (forms soluble complex with oxalate)
  ▪ pyrophosphate
  ▪ Tamm-Horsfall glycoprotein
Approach to Renal Stone

Investigations

Table 12. Investigations for Renal Stones

<table>
<thead>
<tr>
<th>CBC, uric acid, U/A, urine C&amp;S</th>
<th>KUB x-ray</th>
<th>CT scan</th>
<th>Abdominal ultrasound</th>
<th>Cystoscopy</th>
<th>PTH, 24 h urine x 2 for volume, Cr, Ca²⁺, Na⁺, PO₄³⁻, Mg²⁺, oxalate, citrate, ± cystine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who gets it?</td>
<td>Everyone</td>
<td>Most</td>
<td>First episode renal colic</td>
<td>Pediatric cases or those concerning for obstruction</td>
<td>± Those concerning for bladder stone</td>
</tr>
<tr>
<td>Why is it done?</td>
<td>May show signs of infection, ± sensitivities</td>
<td>90% of stones are radiopaque, Good for follow-up</td>
<td>Distinguish radiolucent stone from soft tissue filling defect, X-ray comparison</td>
<td>No radiation, Visualize hydronephrosis</td>
<td>Visualize bladder</td>
</tr>
<tr>
<td>Cautions</td>
<td>–</td>
<td>Do not mistake phleboliths for stones!</td>
<td>Radiation</td>
<td>Must be a non-contrast scan</td>
<td>Not good at visualizing stones in ureter</td>
</tr>
</tbody>
</table>

Treatment – Acute

- medical
  - analgesic ± antiemetic
  - NSAIDs help lower intra-ureteral pressure
  - medical expulsions therapy (MET)
    - α-blockers: increase rate of spontaneous passage in distal ureteral stones
    - calcium channel blockers
  - ± Abx for bacteriuria
  - IV fluids if vomiting (note: IV fluids do not promote stone passage)
- interventional:
  - required if obstruction endangers patient, e.g. sepsis, renal failure
  - first line: ureteric stent (via cystoscopy)
  - second line: image-guided percutaneous nephrostomy
- admit if necessary:
  - see sidebar: Indications for Admission to Hospital

Treatment – Elective

- medical:
  - likely conservative if ureteral stone <10 mm or kidney stone <5 mm and no complications/symptoms well controlled
  - stones <5 mm especially likely to pass spontaneously
  - PO fluids to increase urine volume to >2 L/d (3-4 L if cystine) and MET
  - specific to stone type (see Table 13)
  - periodic imaging to monitor stone position and assess for hydronephrosis
  - progress to interventional stone removal methods if symptoms worsen or fail to improve (indicating stone passage)

Efficacy of α-Blockers for the Treatment of Ureteral Stones

J. Urol. 2007;177:983-987

Study: Meta-analysis of prospective randomized trials comparing α-blockers to conservative therapy.

Methods: MEDLINE, the Cochrane Central Search library, EMBASE, and the electronic database of abstracts presented at the Annual Meeting of the American Urological Association were searched for literature published in English. 11 studies met selection criteria (n=911). Treatment ranged from 8 d-6 wk. Outcome of interest was incidence of distal ureteral stone expulsion.

Results: Administration of an α-blocker with conservative therapy increases incidence of stone expulsion over conservative treatment alone by 44% (95% CI 1.31-1.59, p<0.001).

Conclusion: α-blocker therapy is associated with significantly increased rates of distal ureteral stone expulsion.

Indications for Admission to Hospital:
- Intractable pain
- Intractable vomiting
- Fever (suggests infection)
- Compromised renal function (including single kidney, bilateral obstructing stone)
- Pregnancy

Stones and Infection

If septic, urgent decompression via ureteric stent or percutaneous nephrostomy is indicated. Definitive treatment of the stone should be delayed until the sepsis has cleared.

Although hypercalciuria is a risk factor for stone formation, decreasing dietary calcium is NOT recommended to prevent stone formation. Low dietary calcium leads to increased GI oxalate absorption and higher urine levels of calcium oxalate.
interventional:
- kidney
  - may stent prior to ESWL if stone is 1.5-2.5 cm
  - ESWL if stone <2 cm
  - PCNL if stone >2 cm (see sidebar)
- ureteral stones >10 mm
  - ESWL and URS are both first line treatment modalities for all locations
    - URS has significantly greater stone-free rates for stones at all locations in ureter, but also has higher complication rates (ureter perforation, stricture formation, etc.)
  - PCNL is second line treatment
- laparoscopic or open stone removal (very rare)
- bladder
  - transurethral stone removal or cystolitholapaxy
  - remove outflow obstruction (TURP or stricture dilatation)

Prevention
- dietary modification:
  - increase fluid (>2 L/d), K+ intake
  - reduce animal protein, oxalate, Na+, sucrose, and fructose intake
  - avoid high-dose vitamin C supplements
- medications:
  - thiazide diuretics for hypercalciuria
  - allopurinol for hyperuricosuria
  - potassium citrate for hypocitraturia, hyperuricosuria

Table 13. Stone Classification

<table>
<thead>
<tr>
<th>Type of Stone</th>
<th>Calcium (75-85%)</th>
<th>Uric Acid (5-10%)</th>
<th>Struvite (5-10%)</th>
<th>Cystine (1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>Hyperuricosuria (25% of patients with Ca2+ stones)</td>
<td>Uric acid precipitates in low volume, acidic urine with a high uric acid concentration:</td>
<td>Infection with urea-splitting organisms (Proteus, Pseudomonas, Providencia, Klebsiella, Mycoplasma, Serratia, S. aureus) results in alkaline urinary pH and precipitation of struvite (magnesium ammonium phosphate)</td>
<td>Autosomal recessive defect in small bowel mucosal absorption and renal tubular absorption of dibasic amino acids results in “COLA” in urine (cystine, ornithine, lysine, arginine)</td>
</tr>
<tr>
<td>Hyperoxaluria</td>
<td>Hyperoxaluria (&lt;5% of patients) Hypocitraturia (12% of patients) Other causes:</td>
<td>Hyperuricosuria alone</td>
<td>Perpetuates UTI because stone itself harbours organism Stone and all foreign bodies must be cleared to avoid recurrence Associated with staghorn calculi Positive urine dip and cultures Note: E. coli infection does not cause struvite stones 3:1 (M:F), UTI more common in female</td>
<td>Aggressive stone disease seen in children and young adults Recurrent stone formation, family hx Often staghorn calculi Faintly radiopaque on KUB Positive urine sodium nitroprusside test, urine chromatography for cystine</td>
</tr>
<tr>
<td>Hypocitraturia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Key Features</strong></td>
<td>Radiopaque on KUB Reducing dietary Ca2+ is NOT an effective method of prevention/treatment</td>
<td>Radiopaque on KUB Acidic urine, pH &lt;5.5 (NOT necessarily elevated urinary uric acid)</td>
<td>Perpetuates UTI because stone itself harbours organism Stone and all foreign bodies must be cleared to avoid recurrence Associated with staghorn calculi Positive urine dip and cultures Note: E. coli infection does not cause struvite stones 3:1 (M:F), UTI more common in female</td>
<td>Aggressive stone disease seen in children and young adults Recurrent stone formation, family hx Often staghorn calculi Faintly radiopaque on KUB Positive urine sodium nitroprusside test, urine chromatography for cystine</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical if stone &lt;5 mm and no complications</td>
<td>Fluids to increase urine volume to &gt;2 L/d For calcium stones: cellulose phosphate, orthophosphate for absorptive causes Calcium oxalate: thiadiazides, ± potassium citrate, ± allopurinol Calcium struvite: Abx (stone must be removed to treat infection)</td>
<td>Increased fluid intake Alkalization of urine to pH 6.5 to 7 (bicarbonate, potassium citrate) ± allopurinol</td>
<td>Complete stone clearance Abx for 6 wk Regular F/U urine cultures</td>
<td>Increased fluid intake (3-4 L of urine/d) Alkalize urine (bicarbonate, potassium citrate), Penicillamine/ α-MPG or Captopril (form complex with cystine) ESWL not effective</td>
</tr>
<tr>
<td>Procedural/Surgical treatment if stone &gt;5 mm or presence of complications (see U17 for treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Urological Neoplasms

Approach to Renal Mass

Figure 9. Workup of a renal mass

*Imaging modality may be different in cases of contrast allergy or elevated creatinine

Benign Renal Neoplasms

CYSTIC KIDNEY DISEASE
- simple cysts: usually solitary or unilateral
  - very common: up to 50% at age 50
  - usually incidental finding on abdominal imaging
  - Bosniak Classification is used to stratify for risk of malignancy based on cyst features from contrast CT (see Table 14)
- polycystic kidney disease
  - autosomal recessive: multiple bilateral cysts, often leading to early renal failure in infants
  - autosomal dominant: progressive bilateral disease leading to HTN and renal failure
- medullary sponge kidney: cystic dilatation of the collecting ducts
  - usually benign course, but patients are predisposed to stone disease
- von Hippel-Lindau syndrome: multiple bilateral cysts or clear cell carcinomas (50% incidence of RCC)
  - renal cysts, cerebellar, spinal and retinal hemangioblastomas, pancreatic and epididymal cysts, pheochromocytomas

Table 14. Bosniak Classification of Renal Cysts

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Features</th>
<th>Risk of Malignancy</th>
<th>Management Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Simple cyst</td>
<td>Round, no septations, no calcifications, no solid component</td>
<td>Near zero</td>
<td>F/U usually not required</td>
</tr>
<tr>
<td>II</td>
<td>Simple cyst</td>
<td>A few thin septa, no true enhancement, well-marginated, uniform high attenuation, &lt;3 cm</td>
<td>Minimal</td>
<td>F/U usually not required</td>
</tr>
<tr>
<td>IIF</td>
<td>Minimally complex</td>
<td>Still well-marginated and non-enhancing, but now multiple thin septa or some thickening/calcification of septa/wall, &gt;3 cm</td>
<td>5-20%</td>
<td>Requires F/U with imaging q6-12 mo. If the lesion evolves, may require surgical resection</td>
</tr>
<tr>
<td>III</td>
<td>Complex cyst</td>
<td>Thicker or more irregular walls with measurable enhancement</td>
<td>&gt;50%</td>
<td>Requires surgical resection</td>
</tr>
<tr>
<td>IV</td>
<td>Clearly malignant</td>
<td>Class III + enhancing soft-tissue components</td>
<td>&gt;90%</td>
<td>Requires surgical resection</td>
</tr>
</tbody>
</table>
Table 15. Benign Renal Masses

<table>
<thead>
<tr>
<th>Angiomyolipoma (Renal Hamartoma)</th>
<th>Renal Oncocytoma</th>
<th>Renal Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1% of adult renal tumours</td>
<td>3-7% of renal tumours</td>
<td>Most common benign renal neoplasm</td>
</tr>
<tr>
<td>F&gt;M</td>
<td>M&gt;F</td>
<td>M:F = 3:1</td>
</tr>
<tr>
<td>20% associated with tuberous sclerosis (especially if multiple, recurrent)</td>
<td>Oncocytomas also found in adrenal, thyroid and parathyroid glands</td>
<td>Incidence increases with age</td>
</tr>
<tr>
<td></td>
<td>Found in 7-23% of all autopsies</td>
<td></td>
</tr>
<tr>
<td><strong>Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonal neoplasm consisting of blood vessels (angio-), smooth muscle (-myo-), and fat (-lipoma)</td>
<td>Spherical, capulsated with possible central scar</td>
<td>Small cortical lesions &lt; 1 cm</td>
</tr>
<tr>
<td>May extend into regional lymphatics and other organs and become symptomatic</td>
<td>Histologically organized aggregates of eosinophilic cells originating from intercalated cells of collecting duct</td>
<td>Majority are solitary but can be multifocal</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidental finding on CT</td>
<td>Incidental finding on CT</td>
<td>Incidental finding on CT</td>
</tr>
<tr>
<td>Negative attenuation (≤20 HU) on CT is pathognomonic</td>
<td>Difficult to distinguish from RCC on imaging – treated as RCC until proven otherwise</td>
<td>Rarely symptomatic</td>
</tr>
<tr>
<td>Rare presentation of hematuria, flank pain, and palpable mass (same as RCC)</td>
<td>Biopsy may be performed to rule out malignancy</td>
<td>Controversy as to whether this represents benign or pre-malignant neoplasm</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>May consider surgical excision or embolization if symptomatic (pain, bleeding) or higher risk of bleeding (e.g. pregnancy)</td>
<td>Partial/radical nephrectomy for large masses</td>
<td>If mass &gt;3 cm, likely not a benign adenoma; will require partial/radical nephrectomy due to increased likelihood of malignancy</td>
</tr>
<tr>
<td>Follow with serial U/S</td>
<td>HIFU or RFA for smaller masses</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Malignant Renal Neoplasms

RENAL CELL CARCINOMA (RCC)

**Etiology**
- cause unknown
- originates from proximal convoluted tubule epithelial cells in clear cell subtype (most common)
- hereditary forms seen with von Hippel-Lindau syndrome and hereditary papillary renal carcinoma

**Epidemiology**
- 8th most common malignancy (accounts for 3% of all newly diagnosed cancers)
- 85% of primary malignant tumours in kidney
- male:female = 3:2
- peak incidence at 50-60 yr of age

**Pathology**
- histological subtypes: clear cell (75-85%), papillary (10-15%), chromophobic (5-10%), collecting duct
- sarcomatoid elements in any subtype is a poor prognostic factor

**Risk Factors**
- top 3 risk factors: smoking, HTN, obesity
- miscellaneous: horseshoe kidney, acquired renal cystic disease

**Clinical Features**
- usually asymptomatic: frequently diagnosed incidentally by U/S or CT
- poor prognostic indicators: weight loss, weakness, anemia, bone pain
- classic “too late triad” found in 10-15%:
  - gross hematuria 50%  
  - flank pain <50%
  - palpable mass <30%
- was called the “internist’s tumour” because of paraneoplastic symptomatology (see sidebar) – now called the “radiologist’s tumour” because of incidental diagnosis via imaging
- metastases: seen in 1/3rd of new cases; additional 20-40% will go on to develop metastases
  - bone, brain, lung and liver most common sites

**Investigations**
- routine labs for paraneoplastic syndromes (CBC, ESR, LFTs, extended electrolytes)
- U/A (60-75% have hematuria)
- renal U/S: solid vs. cystic lesion
- CT: higher sensitivity than U/S for detection of renal masses and for staging purposes
- MRI: useful for evaluation of vascular extension
- FNA: to confirm diagnosis if considering observation or other non-surgical therapy

**Staging**
- involves CT, CXR, liver enzymes and LFTs, bone scan

RCC Systemic Effects: paraneoplastic syndromes (10-40% of patients)
- Hematopoietic disturbances: anemia, polycythemia, raised ESR
- Endocrinopathies: hypercalcemia (increased vitamin D hydroxylation), erythrocytosis (increased erythropoietin), HTN (increased renin), production of other hormones (prolactin, gonadotropins, TSH, insulin, and cortisol)
- Hepatic cell dysfunction or Stauffer syndrome: abnormal LFTs, decreased WBC count, fever, areas of hepatic necrosis; no evidence of metastases; reversible following removal of primary tumour
- Hemodynamic alterations: systolic HTN (due to AV shunting), peripheral edema (due to caval obstruction)
Table 16. 2010 TNM Classification of Renal Cell Carcinoma

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1: tumour &lt;7 cm, confined to renal parenchyma</td>
<td>N0: no regional nodes</td>
<td>M0: no evidence of metastasis</td>
</tr>
<tr>
<td>T1a: &lt;4 cm</td>
<td>N1: metastasis to a single node, &lt;2 cm</td>
<td>M1: presence of distant metastasis</td>
</tr>
<tr>
<td>T1b: 4-7 cm</td>
<td>N2: metastasis to a single node between 2 and 5 cm or multiple nodes &lt;2 cm</td>
<td></td>
</tr>
<tr>
<td>T2: tumour &gt;7 cm, confined to renal parenchyma</td>
<td>N3: node &gt;5 cm</td>
<td></td>
</tr>
<tr>
<td>T2a: tumour &gt;7 cm but ≤10 cm in greatest dimension, limited to the kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2b: tumour &gt;10 cm, limited to the kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3: tumour extends into major veins or perinephric tissues, but NOT into ipsilateral adrenal or beyond Gerota’s fascia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3a: into renal vein or sinus fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3b: into infradiaphragmatic IVC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3c: into supradiaphragmatic IVC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4: tumour extends beyond Gerota’s fascia including extension into ipsilateral adrenal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment

- surgical
  - radical nephrectomy: en bloc removal of kidney, tumour, ipsilateral adrenal gland (in upper pole tumours) and intact Gerota’s capsule and paraaortic lymphadenectomy
  - partial nephrectomy (parenchyma-sparing): <4 cm tumour or solitary kidney/bilateral tumours
  - surgical removal of solitary metastasis may be considered
- ablative techniques (cryoablation, RFA)
- palliative radiation to painful bony lesions
- therapy for advanced stage:
  - anti-angiogenesis/anti-VEGF (e.g. bevacizumab)
  - mTOR inhibitors (e.g. temsirolimus, everolimus)
  - high-dose IL-2 (high toxicity but able to induce long-term remission in 10% of patients)
  - IFN α: monotherapy has been largely replaced by molecularly targeted agents listed above
- tyrosine kinase inhibitors for metastatic disease (e.g. sunitinib, sorafenib)

Prognosis

- stage at diagnosis most important prognostic factor:
  - T1: 90-100% 5-yr survival
  - T2-T3: 60% 5-yr survival
  - metastatic disease: <5% 10-yr survival

Carcinoma of the Renal Pelvis and Ureter

Etiology

- risk factors include:
  - smoking
  - chemicals/dietary exposures (industrial dyes and solvents; aristolochic acid)
  - analgesic abuse (acetaminophen, ASA, and phenacetin)
  - Balkan nephropathy

Epidemiology

- rare: accounts for 5% of all urothelial cancers
- frequently multifocal, 2-5% are bilateral
- M:F = 3:1
- relative incidence: bladder:renal:ureter = 100:10:1

Pathology

- 85% are papillary urothelial carcinoma (TCC); others include SCC and adenocarcinoma
- TCC of ureter and renal pelvis are histologically similar to bladder TCC

Clinical Features

- gross/microscopic hematuria
- flank pain
- storage or voiding symptoms (dysuria only if lower urinary tract involved)
- flank mass ± hydronephrosis (10-20%)

Investigations

- IVP/CT urogram
- cystoscopy and retrograde pyelogram

Treatment

- radical nephroureterectomy with cuff of bladder
- distal ureterectomy for distal ureteral tumours

Differential Diagnosis of Filling Defect

- Urothelial cell carcinoma (differentiate via cytology and CT scan)
- Uric acid stone (differentiate via cytology and CT scan)
- Blood clot
- Pyelitis cystica
- Papillary necrosis
- Fungus ball
- Gas bubble from gas producing organisms

Sorafenib in Advanced Clear-Cell Renal Cell Carcinoma – TARGET Trial

NEJM 2007;356:125-134

Study: Phase III, double-blind RCT comparing multikinase inhibitor, sorafenib, with placebo in treatment of advanced clear-cell renal cell carcinoma.

Methods: Patients with clear cell renal cell carcinoma, resistant to standard therapy. The main intervention and outcome were sorafenib and overall survival, respectively.

Results: Progression-free survival in intervention group was 5.5 mo, compared with 2.8 mo in the placebo group. The survival improvement was associated with an increased number of adverse events.
Bladder Carcinoma

Etiology
- unknown, but environmental risk factors include:
  - smoking (main factor – implicated in 60% of new cases)
  - aromatic amines: naphthylamines, benzidine, tryptophan, phenacetin metabolites
  - cyclophosphamide
  - prior hx of radiation treatment to the pelvis
  - *Schistosoma hematobium* infection (associated with SCC)
  - chronic irritation: cystitis, chronic catheterization, bladder stones (associated with SCC)

Epidemiology
- 2nd most common urological malignancy
- male:female = 3:1, white:black = 4:1
- mean age at diagnosis is 65 yr

Pathology
- classification:
  - TCC >90%
  - SCC 5-7%
  - adenocarcinoma 1%
  - others <1%
- stages and prognoses of urothelial carcinoma at diagnosis:
  - non-muscle invasive (75%) → >80% overall survival
  - 15% of these will progress to invasive TCC
  - the majority of these patients will have recurrence
  - invasive (25%) → 50-60% 5-yr survival
  - 85% have no prior hx of superficial TCC (i.e. de novo)
  - 50% have occult metastases at diagnosis, and most of these will develop overt clinical evidence of metastases within 1 yr – lymph nodes, lung, peritoneum, liver
- carcinoma in situ → flat, non-papillary erythematous lesion characterized by dysplasia confined to urothelium
  - more aggressive, worse prognosis
  - usually multifocal
  - may progress to invasive TCC

Clinical Features
- asymptomatic (20%)
- hematuria (key symptom: 85-90% at the time of diagnosis)
- pain (50%) → location determined by size/extent of tumour (i.e. flank, suprapubic, perineal, abdominal, etc.)
- clot retention (17%)
- storage urinary symptoms → consider carcinoma in situ
- palpable mass on bimanual exam → likely muscle invasion
- obstruction of ureters → hydronephrosis and uremia (nausea, vomiting, and diarrhea)

Investigations
- U/A, urine C&S, urine cytology
- U/S
- CT scan with contrast or IVP → look for filling defect
- cystoscopy with bladder washings (gold standard)
- biopsy to establish diagnosis and to determine depth of penetration
- specific bladder tumour markers (e.g. NMP-22, BTA, Immunocyt, FDP)

Grading
- Grade 1: well-differentiated (10% invasive)
- Grade 2: moderately differentiated (50% invasive)
- Grade 3: poorly differentiated (80% invasive)

Staging
- for invasive disease: CT or MRI, CXR, LFTs, extended electrolytes (metastatic work-up)
Table 17. 2010 TNM Classification of Bladder Carcinoma (see Figure 11)

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta</td>
<td>N status: as for RCC</td>
<td>M status: as for RCC</td>
</tr>
<tr>
<td>Tis</td>
<td>carcinoma in situ (CIS); flat tumour</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>tumour invades submucosa/lamina propria</td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>tumour invades superficial muscle</td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>tumour invades deep muscle</td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>tumour invades perivesical tissue (microscopic)</td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>tumour invades perivesical tissue (macroscopic)</td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>adjacent organ involvement; prostate, uterus, or vagina</td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>adjacent organ involvement; pelvic wall or abdominal wall</td>
<td></td>
</tr>
</tbody>
</table>

Figure 11. Urothelial carcinoma of bladder

Treatment
- superficial (non-muscle invasive) disease: Tis, Ta, T1
  - TURBT ± single dose or 6-wk course of intravesical chemo/immuno-therapy (e.g. BCG, mitomycin C) to decrease recurrence rate
  - maintenance with intravesical chemotherapy with BCG may be continued for 2-3 yr
  - high grade disease: TURBT + maintenance BCG OR cystectomy in select patients
- invasive disease: T2a, T2b, T3
  - radical cystectomy + pelvic lymphadenectomy with urinary diversion (e.g. ileal conduit, Indiana pouch, ileal neobladder) or TURBT + chemo-radiation for small tumours
  - neo-adjuvant chemotherapy prior to cystectomy may also be done
  - use of adjuvant chemotherapy after definitive local treatment is controversial
- advanced/metastatic disease: T4a, T4b, N+, M+
  - initial combination of systemic chemotherapy ± irradiation ± surgery

Prognosis
- depends on stage, grade, size, number of lesions, recurrence and presence of CIS:
  - T1: 90% 5-yr survival
  - T2: 55% 5-yr survival
  - T3: 20% 5-yr survival
  - T4/N+/M+: <5% 5-yr survival

Prostatic Carcinoma (CaP)

Etiology
- not known
- risk factors
  - increased incidence in persons of African descent
  - high dietary fat = 2x risk
  - family hx
    - 1st degree relative = 2x risk
    - 1st and 2nd degree relatives = 9x risk

Epidemiology
- most prevalent cancer in males
- 3rd leading cause of male cancer deaths (following lung and colon)
- up to 50% risk of CaP at age 50
- lifetime risk of death from CaP is 3%
- 75% diagnosed between ages of 60 and 85; mean age at diagnosis is 72
Pathology
- adenocarcinoma
  - >95%, often multifocal
- urothelial carcinoma (4.5%)
  - associated with TCC of bladder; does NOT follow TNM staging below; not hormone-responsive
- endometrial (rare)
  - carcinoma of the utricle

Anatomy (see Figure 7)
- 60-70% of nodules arise in the peripheral zone
- 10-20% arise in the transition zone
- 5-10% arise in the central zone

Clinical Features
- usually asymptomatic
- most commonly detected by DRE, elevated PSA, or as an incidental finding on TURP
  - DRE: hard irregular nodule or diffuse dense induration involving one or both lobes
  - PSA: see CaP Screening, U25
- locally advanced disease
  - storage and voiding symptoms, ED (all uncommon without spread)
- metastatic disease:
  - bony mets to axial skeleton common
  - visceral mets are less common (liver, lung, and adrenal gland most common sites)
  - leg pain and edema with nodal mets obstructing lymphatic and venous drainage

Methods of Spread
- local invasion
- lymphatic spread to regional nodes
  - obturator > iliac > presacral/para-aortic
- hematogenous dissemination occurs early

Investigations
- DRE
- PSA elevated in the majority of patients with CaP
- TRUS-guided needle biopsy
- bone scan may be omitted in untreated CaP with PSA <10 ng/mL
- CT scanning to assess metastases
- MRI: being investigated for possible role in detection, staging, MRI-guided biopsying and active surveillance

<table>
<thead>
<tr>
<th>Table 18. 2010 TNM Classification of Prostate Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>T1: clinically undetectable tumour, normal DRE and TRUS</td>
</tr>
<tr>
<td>T1a: tumour incidental histologic finding in &lt;5% of tissue resected</td>
</tr>
<tr>
<td>T1b: tumour incidental histologic finding in &gt;5% of tissue resected</td>
</tr>
<tr>
<td>T1c: tumour identified by needle biopsy (because of elevated PSA level)</td>
</tr>
<tr>
<td>T2: palpable, confined to prostate</td>
</tr>
<tr>
<td>T2a: tumour involving ≤ one half of one lobe</td>
</tr>
<tr>
<td>T2b: tumour involving &gt; one half of one lobe, but not both lobes</td>
</tr>
<tr>
<td>T2c: tumour involving both lobes</td>
</tr>
<tr>
<td>T3: tumour extends through prostate capsule</td>
</tr>
<tr>
<td>T3a: extracapsular extension (unilateral or bilateral)</td>
</tr>
<tr>
<td>T3b: tumour invading seminal vesicle(s)</td>
</tr>
<tr>
<td>T4: tumour invades adjacent structures (besides seminal vesicles)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 19. Prostate Cancer Mortality Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
</tr>
<tr>
<td>PSA</td>
</tr>
<tr>
<td>&lt;10</td>
</tr>
<tr>
<td>Gleason Score</td>
</tr>
<tr>
<td>Stage</td>
</tr>
</tbody>
</table>
Costs:
- Medicare reimbursement for medical care.
- Weigh the costs and benefits of different treatment options.
- Consider the long-term consequences of treatment.

U25 Urology Urological Neoplasms Toronto Notes 2014

Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer (Scandinavian Prostate Cancer Group Study)
NEJM 2012;367:1708-1717
Study: Randomized clinical trial comparing surgical treatment with radical prostatectomy for localized prostate cancer.
Methods: 695 men from 14 centres in Finland, Sweden, and Iceland with newly diagnosed, localized prostate cancer were included in this study.
Main outcomes: Mortality, distant metastases, local progression.
Results: For men with low-risk prostate cancer (PSA<10, Gleason score<7), at 15 yr after treatment initiation, the relative risk of death due to prostate cancer in the radical prostatectomy group was 0.82 (p<0.01). The cumulative incidence of death from prostate cancer after radical prostatectomy was high as compared with other studies.
Conclusions: Radical prostatectomy was associated with reduced rate of death due to prostate cancer.

Radical Prostatectomy versus Observation for Localized Prostate Cancer. (Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group)
NEJM 2012;367:203-213
Study: Randomized clinical trial comparing observation with radical prostatectomy for localized prostate cancer.
Methods: 731 men at 52 United States centres with localized prostate cancer participated.
Main outcomes: Mortality, bone metastases, surgical morbidity.
Results: Radical prostatectomy did not reduce all-cause or prostate cancer mortality relative to observation (relative risk 0.80, p<0.09), through at least 12 yr of follow-up.
Conclusions: Observation is recommended for localized prostate cancer, especially in men with low PSA and low-risk disease.

CaP Screening
- PSA is specific to the PROSTATE, but NOT to prostate cancer.
- Causes of Increased PSA: BPH, prostatitis, prostatic ischemia/infarction, prostate biopsy/surgery, prostatic massage, acute urinary retention, urethral catheterization, cystoscopy, TRUS, strenuous exercise, perineal trauma, ejaculation, acute renal failure, coronary bypass graft, radiation therapy.

Table 20. Treatment Options for Localized Prostate Cancer

<table>
<thead>
<tr>
<th>Modality</th>
<th>Population Considered</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchful Waiting</td>
<td>Short life expectancy (&lt;5-10 yr); will likely only receive non-curative hormonal therapy if disease progresses</td>
<td>Disease progression</td>
</tr>
<tr>
<td>Active Surveillance (serial PSA, DRE, and biopsies)</td>
<td>Low grade disease, good F/U; is still considering more curative treatment if disease progresses</td>
<td>Disease progression; decrease in QOL associated with serial testing; risks associated with biopsies; no optimal monitoring schedule has been defined to date</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>Low volume, low PSA (&lt;10), low grade</td>
<td>ED (50%), long term effectiveness not well-established</td>
</tr>
<tr>
<td>EBRT</td>
<td>Locally advanced disease, older patients</td>
<td>Radiation proctitis (5%), ED (50%), risk of rectal cancer</td>
</tr>
<tr>
<td>RP</td>
<td>Young patients (&lt; 75 yr), high-risk disease</td>
<td>Incontinence (10%), ED (30-50%)</td>
</tr>
</tbody>
</table>

Notes: Other options include cryosurgery, HIFU, hormonal ablation.

Prognosis
- T1-T2: comparable to normal life expectancy
- T3-T4: 40-70% 10-yr survival
- N+ and/or M+: 40% 5-yr survival
- prognostic factors: tumour stage, tumour grade, PSA value, PSA doubling time

Digital Rectal Exam (DRE)
- should be included as part of initial screening
- suspicious findings: abnormal feeling, nodularity, focal lesion, discrete change in texture/fullness/symmetry

Prostate Specific Antigen (PSA)
- glycoprotein produced by epithelial cells of prostate gland
- leaks into circulation in settings of disrupted glandular architecture
- value of <4 ng/mL traditionally considered as cut-off to differentiate normal from pathologic value, but no single justifiable cutpoint
- measured serum PSA is a combination of free (15%) and bound PSA (85%)
- PSA velocity, PSA density, and free/total PSA: all intended to increase sensitivity and specificity of serum PSA values

Screening Recommendations
- conflicting evidence regarding mortality reduction with PSA-based screening and debate regarding overdiagnosis/ overtreatment
- Ontario Ministry of Health and Long-Term Care and United States Preventative Services Task Force both recommend against PSA testing as a population-wide screening tool
- serum PSA determination recommended in any man with >10 yr life-expectancy and any of the following:
  - suspicious finding on DRE (see above)
  - moderate-severe LUTS
  - investigating secondary carcinoma of unknown origin to r/o CaP as primary

Treatment
- T1/T2 (localized, low-risk)
  - if adequate life expectancy or no other significant co-morbidities, consider active surveillance vs. definitive local treatment (RP, brachytherapy, or EBRT)
  - no difference in cure rate between definitive treatment modalities
- T1/T2 (intermediate or high-risk)
  - definitive therapy over active surveillance
- T3, T4
  - EBRT + androgen deprivation therapy or RP + adjuvant EBRT
- N >0 or M >0
  - requires hormonal therapy/palliative radiotherapy for metastases; may consider combined androgen blockade
  - bilateral orchectomy – removes 90% of testosterone
  - GnRH agonists (e.g. leuprolide, goserelin)
  - estrogens [e.g. diethylstilbestrol (DES)]
  - antiandrogens (bicalutamide)
  - local irradiation of painful secondaries or half-body irradiation
  - hormone-refractory prostate cancer
  - chemotherapy: docetaxel, cabazitaxel, sipuleucel-T

NOTES:
- If suspicious finding on DRE (see above)
- chemotherapy: docetaxel, cabazitaxel, sipuleucel-T
Canadian Urological Association Guidelines (2011) re: CaP Screening
- harms and benefits of PSA testing must be explained to the patient and an informed, shared decision to test must be established
- initial screening should include both serum PSA and DRE
- all men should be offered screening at age 50 if >10 yr life-expectancy
- high-risk individuals (family hx of CaP or African ancestry) should be offered screening at age 40 if >10 yr life-expectancy
- standard has been annual screening, but q2-4 yr screening acceptable
- no strict cutpoint for when to biopsy. Decision to biopsy should be based on more than a single PSA value
*new guidelines under development, however, AUA guidelines recommend against universal routine PSA screening for CaP

Testicular Tumours

Etiology (Risk Factors)
- cryptorchidism, atrophy, sex hormones, HIV infection, infertility, family hx, past hx of testicular cancer

Epidemiology
- rare, but most common solid malignancy in young males 15-34 yr
- any solid testicular mass or acute hydrocele in young patient – must r/o malignancy
- slightly more common in right testis (corresponds with slightly higher incidence of right-sided cryptorchidism)
- 2-3% bilateral (simultaneously or successively)

Pathology
- primary:
  - 1% of all malignancies in males
  - cryptorchidism has increased risk (10-40x) of malignancy
  - 95% are germ cell tumours (all are malignant)
    - seminoma (35%) → classic, anaplastic, spermatocytic
    - NSGCT → embryonal cell carcinoma (20%), teratoma (5%), choriocarcinoma (<1%), yolk sac (<<1%), mixed cell type (40%)
  - 5% are non-germ cell tumours (usually benign) → Leydig (testosterone, precocious puberty), Sertoli (gynecomastia, decreased libido)
- secondary:
  - male >50 yr
  - usually lymphoma or metastases (e.g. lung, prostate, GI)

Clinical Features
- painless testicular enlargement (painful if intratesticular hemorrhage or infarction)
- dull, heavy ache in lower abdomen, anal area or scrotum
- associated hydrocele (10%)
- coincidental trauma (10%)
- infertility (rarely presenting complaint)
- gynecomastia due to secretory tumour effects
- supraclavicular and inguinal lymphadenopathy
- abdominal mass (retroperitoneal lymph node mets)

Methods of Spread
- local spread follows lymphatics:
  - right → medial, paracaval, anterior and lateral nodes
  - left → left lateral and anterior paraaortic nodes
  - “cross-over” metastases from right to left are fairly common, but no reports from left to right
  - hematogenous most commonly to lung, liver, bones, and kidney

Investigations
- diagnosis is established by radical inguinal orchidectomy
- tumour markers:
  - β-hCG and AFP are positive in 85% of non-seminomatous tumours
  - elevated marker levels return to normal post-operatively if no secondaries
  - β-hCG positive in 7% of seminomas, AFP never elevated with seminoma
  - testicular U/S (hypoechoic area within tunica albuginea = high suspicion of testicular cancer)
  - evidence of testicular microlithiasis is not a risk factor for testicular cancer
  - needle aspiration contraindicated

Management
- orchiectomy through inguinal ligament for all stages
- consider sperm banking
- adjuvant therapies (see Figure 13)
Table 21. 2010 TNM Classification of Testicular Carcinoma

| Tis: intratubular germ cell neoplasia | N status: same as RCC | M0: no distant mets |
| T1: limited to testis and epididymis w/o vascular/lymphatic invasion | | M1: distant mets |
| T2: limited to testis and epididymis w/ vascular/lymphatic invasion | | M1a: nonregional lymph node(s) or pulmonary mets |
| T3: invasion of the spermatic cord ± vascular/lymphatics | | M1b: distant mets other than to regional lymph nodes and lung |
| T4: invasion of the scrotum ± vascular/lymphatics | | |

Germ Cell Testis Tumour

- 50% Seminoma
  - 90% Stage I
  - 10% Stage II = III
- 50% Non-Seminoma
  - 40% Stage I
  - 20% Stage II
  - 20% Stage III

Surveillance ✓
Radiation ✓
RPLND ± ✓ ✓ ✓ (residual mass)
Chemotherapy ? ✓ ? ✓ ✓

Figure 13. Adjuvant management of testicular cancer post-orchiectomy
Adapted from Dr. MAS Jewett

Prognosis
- 99% cured with stage I and II disease
- 70-80% complete remission with advanced disease

Penile Tumours

Epidemiology
- rare (<1% of cancer in males in U.S.)
- most common in 6th decade

Benign
- cyst, hemangioma, nevus, papilloma

Pre-malignant
- balanitis xerotica obliterans, leukoplakia, Buschke-Lowenstein tumour (large condyloma)

Pre-invasive Cancer
- carcinoma in situ (CIS):
  - Bowen's disease → crusted, red plaques on the shaft
  - erythroplasia of Queyrat → velvet red, ulcerated plaques on the glans
  - treatment options: local excision, laser, radiation, topical 5-fluorouracil

Malignant
- risk factors:
  - chronic inflammatory disease
  - STI
  - phimosis
  - uncircumcised penis
- 2% of all urogenital cancers
- SCC (>95%), basal cell, melanoma, Paget's disease of the penis (extremely rare)
- definitive diagnosis requires full thickness biopsy of lesion
- lymphatic spread (superficial/deep inguinal nodes → iliac nodes) >> hematogenous

Treatment
- wide surgical excision with tumour-free margins (dependent on extent and area of penile involvement) ± lymphadenectomy
- consider less aggressive treatment modalities in CIS (cryotherapy, laser therapy, etc.) if available
## Scrotal Mass

### Table 22. Differentiating between Scrotal Masses

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pain</th>
<th>Palpation</th>
<th>Additional Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torsion</td>
<td>+</td>
<td>Diffuse tenderness</td>
<td>Absent cremaster reflex, negative Prehn’s sign</td>
</tr>
<tr>
<td>Epididymitis (U15)</td>
<td>+</td>
<td>Epididymal tenderness</td>
<td>Present cremaster reflex, positive Prehn’s sign</td>
</tr>
<tr>
<td>Orchitis (U15)</td>
<td>+</td>
<td>Diffuse tenderness</td>
<td>Present cremaster reflex, positive Prehn’s sign</td>
</tr>
<tr>
<td>Hematocele</td>
<td>+</td>
<td>Diffuse tenderness</td>
<td>No transillumination</td>
</tr>
<tr>
<td>Hydrocele</td>
<td>–</td>
<td>Testis not separable from hydrocele, cord palpable</td>
<td>Transillumination, hx of trauma</td>
</tr>
<tr>
<td>Spermatocele</td>
<td>–</td>
<td>Testis separable from spermatocele, cord palpable</td>
<td>Transillumination</td>
</tr>
<tr>
<td>Varicocele</td>
<td>–</td>
<td>Bag of worms</td>
<td>No transillumination, increases in size with Valsalva, decrease in size if supine</td>
</tr>
<tr>
<td>Indirect Inguinal</td>
<td>+</td>
<td>Testis separable from hernia, cord not palpable, cough impulse may transmit, may be reducible</td>
<td>No transillumination</td>
</tr>
<tr>
<td>Tumour</td>
<td>–</td>
<td>Bag of worms</td>
<td>Hard lump/nodule</td>
</tr>
<tr>
<td>Generalized/Dependant edema</td>
<td>–</td>
<td>Diffuse swelling</td>
<td>Often post-op or immobilized, check for liver dysfunction</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>–</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 23. Benign Scrotal Masses

<table>
<thead>
<tr>
<th>Type</th>
<th>Varicocele</th>
<th>Spermatocele</th>
<th>Hydrocele</th>
<th>Testicular Torsion</th>
<th>Inguinal Hernia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Dilatation and tortuosity of pampiniform plexus</td>
<td>A benign, sperm filled epididymal retention cyst</td>
<td>Collection of serous fluid that results from a defect or irritation in the tunica vaginalis</td>
<td>Twisting of the testicle causing venous occlusion and engorgement as well as arterial ischemia and infarction</td>
<td>Protrusion of abdominal contents through the inguinal canal into the scrotum</td>
</tr>
<tr>
<td>Etiology</td>
<td>15% of men Due to incompetent valves in the testicular veins 90% left sided</td>
<td>Multiple theories, including: Distant obstruction Aneurysmal dilations of the epididymis Agglutinated germ cells</td>
<td>Usually idiopathic Found in 5-10% testicular tumours Associated with trauma/ infection Communicating: patent processus vaginalis, changes size during day (peds) Non-communicating: non-patent processus vaginalis (adult)</td>
<td>Trauma Cryptoorchidism “Bell clapper deformity” Many occur in sleep (50%) Necrosis of glands in 5-6 h</td>
<td>Indirect (through internal ring, often into scrotum): congenital Direct (through external ring, rarely into scrotum): abdominal muscle weakness</td>
</tr>
<tr>
<td>Hx/P/E</td>
<td>“Bag of worms” Often painless Pulsates with Valsalva</td>
<td>Non-tender, cystic mass Transilluminates</td>
<td>Non-tender, intrascrotal mass Cystic Transilluminates</td>
<td>Acute onset severe scrotal pain, swelling GI upsets cases Retracted and transverse testicle (horizontal lie) Negative Phren’s sign Absent cremasteric reflex</td>
<td>A small bulge in the groin that may increase in size and disappear when lying down Can present as a swollen or enlarged scrotum Discomfort or sharp pain – especially when straining, lifting, or exercising</td>
</tr>
<tr>
<td>Investigations</td>
<td>P/E Valsalva</td>
<td>P/E U/S to r/o tumour</td>
<td>U/S to r/o tumour</td>
<td>U/S with colour flow Doppler probe over testicular artery Decrease uptake on 99mTc-pertechnetate scintillation scan (doughnut sign)</td>
<td>Hx, and P/E Invagination of the scrotum Valsalva</td>
</tr>
<tr>
<td>Treatment</td>
<td>Conservative Surgical ligation of testicular veins Percutaneous vein occlusion (balloon, sclerosing agents) Repair may improve sperm count/motility 50-75%</td>
<td>Conservative Avoid needle aspiration as it can lead to infection, reaccumulation and spilling of irritating sperm within scrotum Excise if symptomatic</td>
<td>Conservative Needle drainage Surgical</td>
<td>Emergency manual detorsion (rotate outward) with elective bilateral orchiopexy Failure of manual detorsion: surgical detorsion with orchiopexy Orchietomy if poor prognosis</td>
<td>Surgical repair</td>
</tr>
</tbody>
</table>
TORSION OF TESTICULAR APPENDIX
- twisting of testicular/epididymal vestigial appendix

Signs and Symptoms
- clinically similar to testicular torsion, but vertical lie and cremaster reflex preserved
  - “blue dot sign”:
    - blue infarcted appendage seen through scrotal skin (can usually be palpated as small, tender lump)

Treatment
- analgesia – most will subside over 5-7 d
- surgical exploration and excision if refractory pain

HEMATOCELE
- trauma with bleed into tunica vaginalis
- U/S helpful to exclude fracture of testis which requires surgical repair

Treatment
- ice packs, analgesics, surgical repair

Penile Complaints

Peyronie’s Disease

Definition
- benign curvature of penile shaft secondary to fibrous thickening of tunica albuginea
  - most commonly on dorsal surface resulting in upward curvature of erect penis

Etiology
- exact etiology unknown
- trauma/repeated microtrauma → inflammation → fibrosis
- familial predisposition
- associated with DM, vascular disease, autoimmunity, Dupuytren’s contracture, erectile dysfunction
- unclear role of vitamin E deficiency, β-blockade, elevated serotonin

Clinical Features
- penile curvature and/or pain with erection
- penile shortening and poor erection distal to plaque

Treatment
- limited evidence, depends on pain and interference with intercourse

Table 24. Treatment of Peyronie’s Disease

<table>
<thead>
<tr>
<th>Conservative</th>
<th>Medical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reassurance and education</td>
<td>Vitamin E, colchicine, potassium paraaminobenzoate, and carnitine have all been suggested</td>
<td>If stable disease, significant deformity AND failed medical therapy</td>
</tr>
<tr>
<td>Watchful waiting (spontaneous resolution in up to 50%)</td>
<td>Intrallesional or topical verapamil</td>
<td>Incision/excision of plaque</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shortening of less affected side</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± penile prosthesis</td>
</tr>
</tbody>
</table>

Priapism

Definition
- prolonged erection lasting >4 h in the absence of sexual excitement/desire
- tumescence (swelling) of corpora cavernosa with flaccid glans penis (no corpora spongiosum involvement)

Classification
- low-flow/ischemic (most common):
  - reduced/absent cavernosal blood flow → hypoxia, acidosis → ischemia
- high-flow/non-ischemic:
  - unregulated arterial flow with normal tissue oxygenation

Suspect a Retroperitoneal Mass/Process in a Patient with a Varicocele if:
- Acute onset
- Right sided (isolated)
- Palpable abdominal mass
- Doesn’t reduce while supine

Indications for Treatment of Varicocele
- Impaired sperm quality or quantity
- Pain or dull ache affecting QOL
- Affected testis fails to grow in adolescents
- Cosmetic indications (especially in adolescents)
Etiology

- primary: up to 50% idiopathic
- secondary:
  - thromboembolic: e.g. sickle cell, thalassemia, total parenteral nutrition, dialysis, leukemia, solid tumours
  - neurogenic: spinal cord injury, autonomic neuropathy
  - traumatic: cavernosal artery laceration, arterio-venous fistula
  - medication: intracavernosal vasoactive drug injection (e.g. triple mix), α-blockers, anticoagulants, antidepressants, antipsychotics, PDE-5 inhibitors
  - recreational drugs: cocaine, marijuana, heavy alcohol intake

Treatment

- treat reversible causes
- high-flow often self-limited, but arterial embolization may be considered
- low-flow:
  1. urgent decompression via needle aspiration
  2. phenylephrine injection into the corpora cavernosa q3-5min (in monitored setting)
  3. shunt creation between cavernosum and spongiosum if no response within 1 h

Complications

- ED due to corporal fibrosis if treatment delayed
  - 90% risk if >24 h

Paraphimosis

Definition

- foreskin caught behind glans leading to edema → inability to reduce foreskin

Treatment

- squeeze edema out of the glans with manual pressure (analgesia required)
- pull on foreskin with fingers while pushing on glans with thumbs
- if fails, perform dorsal slit or circumcision
- elective circumcision for definitive treatment (paraphimosis tends to recur)

Complications

- infection, glans ischemia, gangrene

Phimosis

Definition

- inability to retract foreskin over glans penis
- may be caused by balanitis (infection of glans), often due to poor hygiene or congenital

Treatment

- proper hygiene, topical corticosteroids, dorsal slit, circumcision

Complications

- balanoposthitis (inflammation of prepuce), paraphimosis, penile cancer

Erectile Dysfunction (ED)

Definition

- consistent (>3 mo duration) or recurrent inability to obtain or maintain an adequate erection for satisfactory sexual performance

Physiology

- erection involves the coordination of psychologic, neurologic, hemodynamic, mechanical, and endocrine components
- nerves: sympathetic (T11-L2), parasympathetic (S2-4), somatic [dorsal penile/pudendal nerves (S2-4)]
- erection ("POINT"):
  - parasympathetics → release of nitric oxide (NO) → increased cGMP levels within corpora cavernosa leading to:
    1. arteriolar dilation
    2. sinusoidal smooth muscle relaxation → increased arterial inflow and compression of penile venous drainage (decreased venous outflow)
• emission (“SHOOT”):
  ▪ sensory afferents from glans
  ▪ secretions from prostate, seminal vesicles, and ejaculatory ducts enter prostatic urethra (sympathetics)
• ejaculation (“SHOOT”)
  ▪ bladder neck closure (sympathetic)
  ▪ spasmotic contraction of bulbo-cavernosus and pelvic floor musculature (somatic)
• detumescence:
  ▪ sympathetic nerves, norepinephrine, endothelin-1 → arteriolar and sinusoidal constriction
  → penile flaccidity

Classification

Table 25. Classification of Erectile Dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Psychogenic</th>
<th>Organic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion</td>
<td>10%</td>
<td>90%</td>
</tr>
<tr>
<td>Onset</td>
<td>Sudden</td>
<td>Gradual</td>
</tr>
<tr>
<td>Frequency</td>
<td>Sporadic</td>
<td>All circumstances</td>
</tr>
<tr>
<td>Variation</td>
<td>With partner and circumstance</td>
<td>No</td>
</tr>
<tr>
<td>Age</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Organic risk factors</td>
<td>No organic risk factors</td>
<td>Risk factors present</td>
</tr>
<tr>
<td>(HTN, DM, dyslipidemia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturnal/AM erection</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Etiology (“IMPOTENCE”)  
• Iatrogenic: pelvic surgery, pelvic radiation  
• Mechanical: Peyronie’s, post-priapism  
• Psychological: depression, stress, anxiety, PTSD, widower syndrome  
• Occlusive vascular: arterial HTN, DM, smoking, hyperlipidemia, PVD, venous (impaired veno-occlusion)  
• Trauma: penile/pelvic, bicycling  
• Extra factors: renal failure, cirrhosis, COPD, sleep apnea, malnutrition  
• Neurogenic: CNS (e.g. Parkinson’s, MS, spinal cord injury, Guillain–Barré, spina bifida, stroke), PNS (e.g. DM, peripheral neuropathy)  
• Chemical: antihypertensives, sedatives, antidepressants, antipsychotics, anxiolytics, anticholinergics, antihistamines, anti-androgens (including 5-α reductase inhibitors), statins, GnRH agonists, illicit drugs  
• Endocrine: DM, hypogonadism, hyperprolactinemia, hypo/hyperthyroid

Diagnosis

• complete hx (include sexual, medical, and psychosocial aspects)  
• self-administered questionnaires (e.g. International Index of Erectile Function, Sexual Health Inventory for Men Questionnaire, ED Intensity Scale, ED Impact Scale)  
• focused P/E, including vascular and neurologic examinations, secondary sexual characteristics  
• lab investigations, dependent on clinical picture  
  ▪ risk factor evaluation: fasting blood glucose or HbA1c, cholesterol profile  
  ▪ optional: TSH, CBC, U/A, testosterone (free and total), prolactin, LH  
• specialized testing including nocturnal penile tumescence monitoring and evaluation of penile vasculature is usually unnecessary

Treatment

• can often be managed by family doctor, see sidebar for when to refer  
• must fully inform patient/partner of options, benefits and complications  
• non-invasive:  
  ▪ lifestyle changes (alcohol, smoking), psychological (sexual counseling and education)  
  ▪ change precipitating medications  
  ▪ treat underlying causes (diabetes, CVD, HTN, endocrinopathies)  
• minimally invasive:  
  ▪ oral medication (see Common Medications, U43)  
  ▪ sildenafil, tadalafil, vardenafil: inhibits PDE-5 to increase intracavernosal cyclic GMP levels  
    ▪ all three have similar effectiveness, but tadalafil has certain advantages: earlier onset, longer half-life, no cyanopsia, can be taken on empty or full stomach (others better on empty stomach)  
  ▪ vacuum devices: draw blood into penis via negative pressure, then put ring at base of penis once erect  
  ▪ MUSE: male urethral suppository for erection – vasoactive substance (PGE1) capsule inserted into urethra

Testosterone deficiency is an uncommon cause of ED.

When to Consider Referral

FAT PEN
  Failed medical therapy  
  penile Anatomic abnormality  
  pelvic/perineal Trauma  
  Psychogenic cause  
  Endocrinopathy  
  vascular/Neurologic assessment

PDE-5 inhibitors are contraindicated in patients on nitrates/nitroglycerin due to severe hypotension.
**Premature Ejaculation**

**Definition**
- occurrence of ejaculation prior to when one or both partners desire it, either before or soon after penetration
- often thought to be due to psychological factors
- primary premature ejaculation
  - never experienced sexual activity without the presence of premature ejaculation
- secondary premature ejaculation
  - the individual once had acceptable ejaculatory control, but now experiences premature ejaculation, not associated with a general medical condition

**Epidemiology**
- 3-30% prevalence (self-reporting is consistently higher than clinical prevalence)
- most common sexual dysfunction reported in men 18-30 yr, associated with secondary impotence in men 45-65 yr

**Investigations**
- indicated by hx and P/E
- testosterone levels if in conjunction with impotence

**Treatment**
- must r/o and treat any associated general medical conditions (e.g. fear of angina)
- referral to psychiatry, couples counseling or sex therapy
- SSRIs or clomipramine, either daily or on-demand dosing
- topical lidocaine and/or prilocaine

---

**Trauma**

- see Emergency Medicine, ER14

---

**Renal Trauma**

**Classification According to Severity**
- minor:
  - contusions and superficial lacerations/hematomas: 90% of all blunt traumas, surgical exploration seldom necessary
- major:
  - laceration that extends into medulla and collecting system, major renal vascular injury, shattered kidney

**Etiology**
- 80% blunt (MVC, assaults, falls) vs. 20% penetrating (stab wounds and gunshots)

**Clinical Features**
- mechanism of injury raises suspicion
- can be hemodynamically unstable secondary to renal vascular injury and/or other sustained injuries: ABCs
- upper abdominal tenderness, flank tenderness, flank contusions, lower rib/vertebral transverse process fracture

**Investigations**
- U/A:
  - hematuria: requires workup but degree does not correlate with the severity of injury
- imaging:
  - CT (contrast, triphasic) if patient stable: look for renal laceration, extravasation of contrast, retroperitoneal hematoma, and associated intra-abdominal organ injury
Staging (does not necessarily correlate well with clinical status)
- I: contusion/hematoma
- II: <1 cm laceration without urinary extravasation
- III: >1 cm laceration without urinary extravasation
- IV: urinary extravasation
- V: shattered kidney or avulsion of pedicle

Treatment
- microscopic hematuria + isolated well-staged minor injuries → no hospitalization
- gross hematuria + contusion/minor lacerations → hospitalize, bedrest, repeat CT if bleeding persists
- surgical intervention/minimally invasive angiography and embolization:
  - absolute indications:
    - hemorrhage and hemodynamic instability
  - relative indications:
    - non-viable tissue and major laceration
    - urinary extravasation
    - vascular injury
    - expanding or pulsating peri-renal mass
    - laparotomy for associated injury
- F/U with U/S or CT before D/C, and at 6 wk

Complications
- HTN in 5% of renal trauma

Bladder Trauma

Classification
- contusions: no urinary extravasation, damage to mucosa or muscularis
- intraperitoneal ruptures: often involve the bladder dome
- extraperitoneal ruptures: involve anterior or lateral bladder wall in full bladder

Etiology
- blunt (MVC, falls, and crush injury) vs. penetrating trauma to lower abdomen, pelvis, or perineum
- blunt trauma is associated with pelvic fracture in 97% of cases

Clinical Features
- abdominal tenderness, distention, peritonitis, and inability to void
- can be hemodynamically unstable secondary to pelvic fracture, other sustained injuries: ABCs
- suprapubic pain

Investigations
- U/A: gross hematuria in 90%
- imaging (including CT cystogram and post-drainage films for extravasation)

Treatment
- penetrating trauma → surgical exploration
- contusion → urethral catheter until hematuria completely resolves
- extraperitoneal bladder perforations → typically non-operative with foley insertion, and follow with cystograms
  - surgery if: infected urine, rectal/vaginal perforation, bony spike into bladder, laparotomy for concurrent injury, bladder neck involvement, persistent urine leak and failed conservative management
- intraperitoneal rupture usually requires surgical repair and suprapubic catheterization

Complications
- complications of bladder injury itself are rare
- mortality is around 20%, and is usually due to associated injuries rather than bladder rupture
Urethral Injuries

Etiology
- posterior urethra:
  - common site of injury is junction of membranous and prostatic urethra due to blunt trauma, MVCs, pelvic fracture
  - shearing force on fixed membranous and mobile prostatic urethra
- anterior urethra:
  - straddle injury can crush bulbar urethra against pubic rami
- other causes:
  - iatrogenic (instrumentation, prosthesis insertion), penile fracture, masturbation with urethral manipulation
- always look for associated bladder rupture

Clinical Features
- blood at urethral meatus
- high-riding prostate on DRE
- swelling and butterfly perineal hematoma
- penile and/or scrotal hematoma
- sensation of voiding without U/O
- distended bladder

Investigations
- must perform RUG or cystoscopy prior to catheterization

Treatment
- simple contusions:
  - no treatment
- partial urethral disruption:
  - very gentle attempt at catheterization by urologist
  - with no resistance to catheterization → Foley x 2-3 wk
  - with resistance to catheterization → suprapubic cystostomy or urethral catheter alignment in OR
- periodic flow rates/urethrograms to evaluate for stricture formation
- complete disruption:
  - immediate repair if patient stable, delayed repair if unstable (suprapubic tube in interim)

Complications
- stricture

Infertility

Definition
- failure to conceive after one year of unprotected, properly timed intercourse
- incidence:
  - 15% of all couples
  - ~ 35-40% female, 20% male, 25-30% combined problem

Female Factors
- see Gynecology, GY22

Male Reproduction
- hypothalamic-pituitary-testicular axis (HPTA):
  - pulsatile GnRH from hypothalamus acts on anterior pituitary stimulating release of LH and FSH
  - LH acts on Leydig (interstitial) cells → testosterone synthesis and secretion
  - FSH acts on Sertoli cells → structural and metabolic support to developing spermatogenic cells
  - FSH and testosterone support germ cells (responsible for spermatogenesis)
  - sperm route: epididymis → vas deferens → ejaculatory ducts → prostatic urethra
Etiology
- idiopathic (40-50% infertile males)
- testicular
  - varicocele (35-40% infertile males)
  - tumour
    - congenital (Klinefelter’s triad: small, firm testes, gynecomastia, and azoospermia)
    - post-infectious (epididymo-orchitis, STIs, mumps)
    - uncorrected torsion
    - cryptorchidism (<5% of cases)
- obstructive
  - iatrogenic (surgery: see below)
  - infectious (gonorrhea, chlamydia)
  - trauma
  - congenital (absence of vas deferens, CF)
  - bilateral ejaculatory duct obstruction, epididymal obstructions
  - Kartagener’s syndrome (autosomal recessive disorder causing defect in action of cilia)
- endocrine (see Endocrinology, E47)
  - HPTA (2-3%) e.g. Kallmann’s syndrome (congenital hypothalamic hypogonadism), excess prolactin, excess androgens, excess estrogens
- other
  - retrograde ejaculation secondary to surgery
  - medications (see below)
    - drugs: marijuana, cocaine, tobacco, alcohol
    - increased testicular temperature (sauna, hot baths, tight pants or underwear)
  - chronic disease: e.g. liver, renal
  - unexplained infertility

History
- age of both partners
- medical: past illness, DM, trauma, CF, genetic syndromes, STIs
- surgical: vasectomy, herniorrhaphy orchidopexy, cryptorchidism, prostate surgery
- fertility: pubertal onset, previous pregnancies, duration of infertility, treatments
- sexual: libido, erection/ejaculation, timing, frequency
- family hx
- medications: cytotoxic agents, GnRH agonists, anabolic steroids, nitrofurantoin, cimetidine, sulfasalazine, spironolactone, α-blockers
- social hx: alcohol, tobacco, cocaine
- occupational exposures: radiation, heavy metals

Physical Exam
- general appearance: sexual development, gynecomastia, obesity
- scrotal exam: size, consistency and nodularity of testicles; palpation of cord; DRE; Valsalva for varicocele

Investigations
- semen analysis (SA) at least 2 properly obtained specimens over several weeks
- hormonal evaluation:
  - indicated with abnormal SA (rare to be abnormal with normal SA)
  - testosterone and FSH
  - serum LH and prolactin are measured if testosterone or FSH are abnormal
- genetic evaluation:
  - chromosomal studies (Klinefelter’s syndrome – XXY)
  - genetic studies (Y-chromosome microdeletion, CF gene mutation)
  - immunologic studies (antisperm antibodies in ejaculate and blood)
  - testicular biopsy
  - scrotal U/S (varicocele, testicular size)
  - vasography (assess patency of vas deferens)

Treatment
- assessment of partner
- lifestyle
  - regular exercise, healthy diet
  - eliminate alcohol, tobacco and illicit drugs
- medical
  - endocrine therapy (see Endocrinology, E48)
  - treat retrograde ejaculation
  - discontinue anti-sympathomimetic agents, may start α-adrenergic stimulation (phenylpropanolamine, pseudoephedrine, orephedrine)
  - treat underlying infections
• surgical
  ▪ varicocelectomy (if indicated)
  ▪ vasovasostomy (vasectomy reversal)
  ▪ epididymovasostomy
  ▪ transurethral resection of blocked ejaculatory ducts
• assisted reproductive technologies (ART):
  ▪ refer to infertility specialist
  ▪ sperm washing + intrauterine insemination (IUI)
  ▪ in vitro fertilization (IVF)
  ▪ intracytoplasmic sperm injection (ICSI) after CF screening of patient and partner in patients
    with congenital bilateral absence of vas deferens

Figure 15. Infertility workup

**Pediatric Urology**

**Congenital Abnormalities**

• not uncommon; 1/200 have congenital abnormalities of the GU tract
• six common presentations of congenital urological abnormalities:

1. **ANTENATAL HYDRONEPHROSIS**

Epidemiology
• 1-5% fetal U/S, detectable as early as first trimester
• most common urological consultation in perinatal period and one of most common U/S
  abnormalities of pregnancy

Differential Diagnosis
• UPJ or UVJ obstruction
• multi-cystic dysplastic kidney
• VUR
• PUVs (only in boys)
• duplication anomalies
• ureterocele
• ectopic ureter

Treatment
• antenatal in utero intervention rarely indicated unless evidence of PUVs with oligohydramnios

2. **POSTERIOR URETHRAL VALVES (PUV)**

Epidemiology
• the most common congenital obstructive urethral lesion in male infants
Pathophysiology
- abnormal mucosal folds at the distal prostatic urethra causing varying degrees of obstruction

Clinical Presentation
- dependent on age:
  - antenatal: bilateral hydrourephrosis, distended bladder, oligohydramnios
  - neonatal (recognized at birth): palpable abdominal mass (distended bladder, hydrourephrosis), ascites (transudation of retroperitoneal urine), respiratory distress (pulmonary hypoplasia from oligohydramnios), weak urinary stream
  - neonatal (not recognized at birth): within weeks present with urosepsis, dehydration, electrolyte abnormalities, failure to thrive
  - toddlers: UTIs or voiding dysfunction
  - school-aged boys: voiding dysfunction → urinary incontinence
- associated findings include renal dysplasia and secondary VUR

Investigations
- most commonly recognized on prenatal U/S → bilateral hydrourephrosis, thickened bladder, dilated posterior urethra (“keyhole sign”), oligohydramnios in a male fetus
- VCUG → dilated and elongated posterior urethra, trabeculated bladder, VUR

Treatment
- immediate catheterization to relieve obstruction, followed by cystoscopic resection of PUV when baby is stable
- if resection of PUV is not possible, vesicostomy is indicated

3. URETEROPELVIC JUNCTION (UPJ) OBSTRUCTION

Etiology
- unclear: adynamic ureteral segment, stenosis, strictures, extrinsic compression, stenosis, strictures, aberrant blood vessels
- can be secondary to tumour, stone, etc.

Epidemiology
- the most common congenital defect of the ureter
- M:F = 2:1
- up to 40% bilateral, which may be associated with worse prognosis

Clinical Presentation
- symptoms depend on severity and age at diagnosis (mostly asymptomatic finding on antenatal U/S)
  - infants: abdominal mass, urinary infection
  - children: pain, vomiting, failure to thrive
- some cases are diagnosed after puberty and into adulthood
  - in adolescents and adults, the symptoms may be triggered by episodes of increased diuresis, such as following alcohol ingestion (Dietl’s crisis)

Investigations
- antenatal U/S most common, Doppler U/S (rare), IVP (rare), and renal scan ± furosemide

Treatment
- surgical correction (pyeloplasty), consider nephrectomy if <15% differential renal function

4. VESICOURETERAL REFUX (VUR)

Definition
- retrograde passage of urine from the bladder, through the ureterovesicular junction (UVJ), into the ureter

Classification
- primary reflux: incompetent or inadequate closure of UVJ
  - lateral ureteral insertion, short submucosal segment
- secondary reflux: abnormally high intravesical pressure resulting in failure of UVJ closure
  - often associated with anatomic (PUV) or functional (neurogenic) bladder obstruction

Epidemiology
- estimated ~1% of newborns, but not well known
- incidence and clinical relevance higher in children with febrile UTIs and prenatal hydrourephrosis
- risk factors: race (white > black), female gender, age (<2 yr), genetic predisposition
Investigations
- focused hx, particularly of voiding dysfunction (frequency, urgency, diurnal enuresis, constipation, encopresis)
  - also screen for signs of infection (UTI, pyelonephritis, urosepsis) and renal failure (uremia, HTN)
- initial evaluation of renal status, growth parameters, and blood pressure is warranted in any child with VUR due to high incidence of renal scarring
  - height, weight, blood pressure
  - Cr
  - U/A, C&S
  - renal U/S
  - DMSA renal scan if at high risk (greater sensitivity than U/S but entails radiation exposure)
- family screening is controversial

Treatment
- spontaneous resolution in 60% of primary reflux
  - in lower grades (I-III), goal is to prevent infection or renal damage via medical treatment and monitoring
- medical treatment: long-term ABx prophylaxis at half the treatment dose for half the treatment time (TMP/SMX, trimethoprim, amoxicillin, or nitrofurantoin)
- surgical treatment: ureteral reimplantation ± ureteroplasty, or subureteral injection with bulking agents (Deflux® or Macroplastique®)
  - indications include failure of medical management, renal scarring (e.g. renal insufficiency, HTN), breakthrough UTIs, persistent high grade (IV or V) reflux

5. HYPOSPADIAS

Definition
- a condition in which the urethral meatus opens on the ventral side of the penis, proximal to the normal location in the glans penis
- depending on severity, may result in difficulty directing urinary stream or infertility

Epidemiology
- very common; 1/300 live male births
- white >> black
- may be associated with ventral penile curvature, disorders of sexual differentiation, undescended testicles or inguinal hernia

Treatment
- early surgical correction; optimal repair before 2 yr
- neonatal circumcision should be deferred because the foreskin may be utilized in the correction

6. EPISPADIAS-EXTROPHY COMPLEX

Definition
- a spectrum of defects depending on the timing of the rupture of the cloacal membrane
  - bladder extrophy: congenital absence of a portion of lower abdominal and anterior bladder wall, with exposure of the bladder lumen
  - cloacal extrophy:
    - exposed bladder and bowel with imperforate anus
    - associated with spina bifida in >50%
  - epispadias (least severe)
    - urethra opens on dorsal aspect of the penis

Etiology
- represents failure of closure of the cloacal membrane, resulting in the bladder and urethra opening directly through the abdominal wall

Epidemiology
- rare: incidence 1/30,000, 3:1 male to female predominance
- high morbidity → incontinence, infertility, reflux

Treatment
- surgical correction at birth
- later corrections for incontinence, VUR, and bladder capacity may be needed
Nephroblastoma (Wilms’ Tumour)

Etiology
• arises from abnormal proliferation of metanephric blastema

Epidemiology
• 5% of all childhood cancers, 5% bilateral
• most common primary malignant renal tumour of childhood
• average age of incidence is 3 yr

Clinical Features
• abdominal mass: large, firm, unilateral (80%)
• HTN (25%)
• flank tenderness
• microscopic hematuria
• nausea/vomiting

Treatment
• always investigate contralateral kidney
• unilateral disease: radical nephrectomy ± radiation ± chemotherapy
• bilateral disease: nephron-sparing surgery following neoadjuvant chemotherapy

Prognosis
• 5-yr survival 80%

Cryptorchidism/Ectopic Testes

Definition
• abnormal location of testes somewhere along the normal path of descent (external inguinal ring > inguinal canal > abdominal)
• ectopic testis (testis found outside its normal path of descent) is most commonly located within a superficial pouch between the external oblique fascia and Scarpas fascia (Denis Browne pouch)
• differential diagnosis:
  ▪ retractile testes
  ▪ atrophic testes
  ▪ disorders of sexual differentiation (bilateral impalpable gonads)

Epidemiology
• 2.7% of full term newborns
• 0.7%-0.8% at 1 yr old

Treatment
• orchiopexy
• hormonal therapy not proven to be of benefit over standard surgical treatment

Prognosis
• reduction in fertility
  ▪ untreated bilateral cryptorchidism: ~100% infertility
  ▪ paternity rates: 53%, 90%, and 93% in formerly bilateral cryptorchid, formerly unilateral cryptorchid, and normal men, respectively
  ▪ increased malignancy risk
    ▪ intraabdominal > inguinal
  ▪ surgical correction facilitates testicular monitoring and may reduce malignancy risk
  ▪ increased risk of testicular torsion (reduced by surgical correction)

Disorders of Sexual Differentiation (DSD)

Definition
• formerly known as intersex disorders
• abnormal genitalia for chromosomal sex due to the undermasculinization of males or the virilization of females
• considered a social emergency

Classification
1. 46 XY DSD
  ▪ defect in testicular synthesis of androgens
  ▪ androgen resistance in target tissues
  ▪ palpable gonad
2. 46 XX DSD
   • most due to CAH (21-hydroxylase deficiency most common enzymatic defect) → shunt in steroid biosynthetic pathway leading to excess androgens
   • undiagnosed and untreated CAH can be associated with life-threatening electrolyte abnormalities in the newborn (salt-wasting CAH)
3. ovotesticular DSD
4. mixed gonadal dysgenesis (46 XY/45 XO most common karyotype)
   • presence of Y chromosome → partial testis determination to varying degrees

Diagnosis
• thorough family hx noting any consanguinity
• maternal hx, especially medication/drug use during pregnancy (maternal hyperandrogenemia)
• P/E: palpable gonad (= chromosomal male), hyperpigmentation, evidence of dehydration, HTN, stretched phallus length, position of urethral meatus
• laboratory tests:
  • plasma 17-OH-progesterone (after 36 h of life) → increased in 21-hydroxylase deficiency (CAH)
  • plasma 11-deoxycortisol → increased in 11-β-hydroxylase deficiency
  • basal adrenal steroid levels
  • serum testosterone and DHT pre- and post-hCG stimulation (2,000 IU/d for 4 d)
  • serum electrolytes
  • chromosomal evaluation including sex karyotype
• U/S of adrenals, gonads, uterus, and fallopian tubes
• P/E: palpable gonad (= chromosomal male), hyperpigmentation, evidence of dehydration, HTN, maternal hx, especially medication/drug use during pregnancy (maternal hyperandrogenemia)
• thorough family hx noting any consanguinity

Treatment
• steroid supplementation as indicated (e.g. CAH)
• sex assignment after extensive family consultation
  • must consider capacity for sexually functioning genitalia in adulthood, fertility potential, and psychological impact
• reconstruction of external genitalia between 6 and 12 mo
• long-term psychological guidance and support for both patient and family

Circumcision

Definition
• removal of some or all of the foreskin from the penis

Epidemiology
• 30% worldwide
• frequency varies depending on geographic location, religious affiliation, socioeconomic classification

Medical Indications
• phimosis and recurrent paraphimosis
• recurrent UTIs (particularly in infants and in association with other urinary abnormalities)
• balanitis xerotica obliterans or other chronic inflammatory conditions

Contraindications
• unstable or sick infant
• congenital genital abnormalities (hypospadias)
• family hx of bleeding disorders warrants laboratory investigation prior to circumcision

Complications
• bleeding
• infection
• penile entrapment, skin bridges
• fistula
• glans injury
• penile sensation deficits

Enuresis
• see Pediatrics, P9
**Bladder Catheterization**

- catheter size measured by the French (Fr) scale – circumference in mm
- each 1 mm increase in diameter = approximately 3 Fr increase (standard size 16-18 Fr)
- should be removed as soon as possible

**Continuous Catheterization**

- indications:
  - accurate monitoring of U/O
  - relief of urinary retention due to medication, neurogenic bladder, or intravesical obstruction
  - temporary therapy for urinary incontinence
  - perineal wounds
  - clot prevention (24-28 Fr) for CBI
  - post-operative

**Alternatives to Continuous Catheterization**

- intermittent catheterization:
  - PVR measurement
  - to obtain sterile diagnostic specimens for U/A, urine C&S
  - management of neurogenic bladder or chronic urinary retention
- condom catheter
- suprapubic catheter

**Causes of Difficult Catheterizations and Treatment**

- patient discomfort → use sufficient lubrication (± xylocaine)
- collapsing catheter → lubrication as above ± firmer catheter (silastic catheter)
- meatal/urethral stricture → dilate with progressively larger catheters/balloon catheter
- BPH → use coudé catheter as angled tip can help navigate around prostate
- urethral disruption/obstruction → filiform and followers or suprapubic catheterization
- anxious patient → anxiolytic medication

**Complications of Catheterization**

- infection: UTI
- meatal/urethral trauma

**Contraindications**

- urethral trauma: blood at the meatus of the urethra, scrotal hematoma, pelvic fracture, and/or high riding prostate

**Cystoscopy**

**Objective**

- endoscopic inspection of the lower urinary tract (urethra, prostate, bladder, and ureteral orifices), samples for cytology
- scopes can be flexible or rigid

**Indications**

- gross hematuria
- LUTS (storage or voiding)
- urethral and bladder neck strictures
- bladder stones
- bladder tumour surveillance
- evaluation of upper tracts with retrograde pyelography (ureteric stents, catheters)

**Complications**

- during procedure
  - bleeding
  - anesthetic-related
  - perforation (rare)
- post-procedure (short-term)
  - infections, e.g. epididymo-orchitis (rare)
  - urinary retention
- post-procedure (long-term)
  - stricture
Radical Prostatectomy (RP)

Objective
- the removal of the entire prostate and prostatic capsule via a lower midline abdominal incision, laparoscopically or robotically
  - internal iliac and obturator vessel lymph nodes may also be dissected and sent for pathology (dependent on risk: clinical stage, grade, PSA)
  - seminal vesicle vessels are also ligated or removed

Indications
- treatment for localized prostate cancer

Complications
- immediate (intraoperative):
  - blood loss
  - rectal injury
  - ureteral injury (extremely rare)
- perioperative:
  - lymphocele formation
- late:
  - moderate to severe urinary incontinence (3-10%)
  - mild urinary incontinence (20%)
  - ED (~50%, depending on whether one, both, or neither of the neurovascular bundles are involved in extracapsular extension of tumour)

Transurethral Resection of the Prostate (TURP)

Objective
- to partially resect the periurethral portion of the prostate (transition zone) to decrease symptoms of urinary tract obstruction
- accomplished via a transurethral (cystoscopic) approach using an electrocautery loop, irrigation (glycine), and illumination

Indications
- obstructive uropathy (large bladder diverticula, renal insufficiency)
- refractory urinary retention
- recurrent UTIs
- recurrent gross hematuria
- bladder stones
- intolerance/failure of medical therapy

Complications
- acute:
  - infra- or extraperitoneal rupture of the bladder
  - rectal perforation
  - incontinence
  - incision of the ureteral orifice (with subsequent reflux or ureteral stricture)
  - hemorrhage
  - epididymitis
  - sepsis
  - transurethral resection syndrome (also called “post-TURP syndrome”)
    - caused by absorption of a large volume of the hypotonic irrigation solution used, usually through perforated venous sinuses, leading to a hypervolemic hyponatremic state
    - characterized by dilutional hyponatremia, confusion, nausea, vomiting, HTN, bradycardia, visual disturbances, CHF, and pulmonary edema
    - treat with diuresis and (if severe) hypertonic saline administration
- chronic:
  - retrograde ejaculation (>75%)
  - ED (5-10% risk increases with increasing use of cautery)
  - incontinence (<1%)
  - urethral stricture
  - bladder neck contracture


Study: A systematic review to compare perioperative outcomes, positive surgical margin (PSM) rates, and functional outcomes in retropubic radical prostatectomy (RRP), laparoscopic RP (LRP) and robot-assisted radical prostatectomy (RARP).

Methods: Medline database was searched. Weighted means (based on number of participants in each study) were calculated for all outcomes.

Results: 58 articles were reviewed. LRP and RARP were associated with better perioperative outcomes compared to RRP. RRP, LRP and RARP had similar post-operative complication rates ranging from 10.3-10.98%. RARP had a lower overall PSM rate than LRP and RRP. RARP had the highest continence rate and mean potency rates.

Conclusion: In high-volume centers, RRP, LRP and RARP are safe options for treating patients with localized prostate cancer. LRP and RARP are associated with better perioperative outcomes and RARP showed lower PSM rates, higher potency and continence compared to RRP and LRP.
Extracorporeal Shock Wave Lithotripsy (ESWL)

Objective
• to treat renal and ureteral calculi (proximal, middle or distal) which cannot pass through the urinary tract naturally
• shockwaves are generated and focused onto stone → fragmentation, allowing stone fragments to pass spontaneously and less painfully

Indications
• potential first-line therapy for renal and ureteral calculi <2.5 cm
• individuals with calculi in solitary kidney
• individuals with HTN, DM or renal insufficiency
*patient preference and wait-times play a large role in stone management

Contraindications
• acute UTI or urosepsis
• bleeding disorder or coagulopathy
• pregnancy
• obstruction distal to stone

Complications
• bacteriuria
• bacteremia
• post-procedure hematuria
• ureteric obstruction (by stone fragments)
• peri-nephric hematoma

Common Medications

Table 26. Erectile Dysfunction Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>sildenafil</td>
<td></td>
<td>Phosphodiesterase 5 inhibitor</td>
<td>Severe hypotension (very rare)</td>
</tr>
<tr>
<td>tadalafil</td>
<td></td>
<td></td>
<td>Contraindicated if hx of priapism, or in conditions predisposing to priapism (leukemia, myelofibrosis, polycythemia, sickle cell disease)</td>
</tr>
<tr>
<td>vardenafil (for use when some erection present)</td>
<td></td>
<td></td>
<td>Contraindicated with nitrates</td>
</tr>
<tr>
<td>alprostadil (MUSE), PGE1 + phentolamine + papaverine mixture</td>
<td>Prostaglandin E1, Activation of cAMP, relaxing sinusoidal smooth muscle</td>
<td>Penile pain</td>
<td></td>
</tr>
<tr>
<td>triple therapy also used: papaverine, phentolamine, PGE1</td>
<td>See above</td>
<td>See above</td>
<td>Presyncope</td>
</tr>
<tr>
<td>alprostadil, papaverine (intracavernosal injection)</td>
<td></td>
<td></td>
<td>Thickening of tunica albuginea at site of repeated injections (Peyronie’s plaque)</td>
</tr>
<tr>
<td>tamsulosin</td>
<td>α1 blockers</td>
<td>α-adrenergic antagonists reduce stromal smooth muscle tone</td>
<td>Presyncope</td>
</tr>
<tr>
<td>dutasteride</td>
<td>5α-reductase inhibitor</td>
<td>Blocks conversion of testosterone to DHT</td>
<td>Sexual dysfunction</td>
</tr>
</tbody>
</table>

Table 27. Benign Prostatic Hyperplasia Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>terazosin</td>
<td>α1 blockers</td>
<td>α-adrenergic antagonists reduce stromal smooth muscle tone</td>
<td>Presyncope</td>
</tr>
<tr>
<td>doxazosin</td>
<td></td>
<td></td>
<td>Leg edema</td>
</tr>
<tr>
<td>tamsulosin</td>
<td>α1A selective</td>
<td>Reduce dynamic component of bladder outlet obstruction</td>
<td>Retrograde ejaculation Headache</td>
</tr>
<tr>
<td>alfuzosin</td>
<td></td>
<td></td>
<td>Asthenia</td>
</tr>
<tr>
<td>finasteride</td>
<td>5α-reductase inhibitor</td>
<td>Blocks conversion of testosterone to DHT</td>
<td>Sexual dysfunction</td>
</tr>
<tr>
<td>dutasteride</td>
<td></td>
<td></td>
<td>PSA decreases</td>
</tr>
</tbody>
</table>
Table 28. Prostatic Carcinoma Medications (N>0, M>0)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>leuprolide, goserelin</td>
<td>GnRH agonist</td>
<td>Initially stimulates LH, increasing testosterone and causing &quot;flare&quot; (initially increases bone pain) Later causes low testosterone</td>
<td>Hot flashes Headache Decreased libido</td>
</tr>
<tr>
<td>*diethylstilbestrol (DES)</td>
<td>Estrogens</td>
<td>Inhibit LH and cytotoxic effect on tumour cells</td>
<td>Increased risk of cardiovascular events (no longer available commercially in North America)</td>
</tr>
<tr>
<td>*cyproterone acetate</td>
<td>Steroidal antiandrogen</td>
<td>Competes with DHT for intracellular receptors:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Prevent flare produced by GnRH agonist</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Use for complete androgen blockade</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. May preserve potency</td>
<td></td>
</tr>
<tr>
<td>flutamide, bicalutamide</td>
<td>Non-steroidal antiandrogen</td>
<td>As above</td>
<td>Hepatotoxic: AST/ALT monitoring</td>
</tr>
<tr>
<td>*ketoconazole, spironolactone</td>
<td>Steroidogenesis inhibitors</td>
<td>Blocks multiple enzymes in steroid pathway, including adrenal androgens</td>
<td>GI symptoms Hyperkalemia Gynecomastia</td>
</tr>
</tbody>
</table>

*Very rarely used

Table 29. Continence Agents and Overactive Bladder Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Indication</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxybutynin</td>
<td>Antispasmodic</td>
<td>Inhibits action of ACh on smooth muscle</td>
<td>Urge incontinence + urgency + frequency</td>
<td>Dry mouth Blurred vision Constipation Supraventricular tachycardia</td>
</tr>
<tr>
<td>oxybutynin, tolterodine, trospium, solifenacin, darifenacin</td>
<td>Anticholinergic</td>
<td>Muscarinic receptor antagonist Selective for bladder</td>
<td>Urge incontinence + urgency + frequency</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increases bladder volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreases detrusor pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>imipramine</td>
<td>Tricyclic antidepressant</td>
<td>Sympathomimetic effects: urinary sphincter contraction Anticholinergic effects: detrusor relaxation</td>
<td>Stress and urge incontinence</td>
<td>As above Weight gain Orthostatic hypotension Prolonged PR interval</td>
</tr>
</tbody>
</table>

Note: All anti-cholinergics are equally effective and long-acting formulations are better tolerated. Newer muscarinic M3 receptor specific agents (solfenacin, darifenacin) are equally efficacious as older drugs; however, RCTs based on head-to-head comparison to long acting formulations are lacking.
References

General Information

Common Presenting Problems
Teichman JMV. Acute renal colic from ureteral calculi. NEJM 2006;350:684-693.

Benign Renal Neoplasm

Urological Emergencies

Medications

EBM
<table>
<thead>
<tr>
<th>Page Reference</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,6,9 Rule; MI13</td>
<td>Abdominal</td>
</tr>
<tr>
<td>4:2:1 Rule; A13</td>
<td>Anatomy; MI11</td>
</tr>
<tr>
<td>α-1-Antitrypsin Deficiency; R9</td>
<td>Distention; G4</td>
</tr>
<tr>
<td>α-Thalassemia; H19</td>
<td>Imaging; MI27</td>
</tr>
<tr>
<td>β-hCG; GY8, OB3</td>
<td>Incisions; GS2</td>
</tr>
<tr>
<td>β-Thalassemia; H18</td>
<td>Mass; G55, P40</td>
</tr>
<tr>
<td>Pain; ER18, FM13, G4, GS4</td>
<td>Pain, Pediatric; ER58, P38</td>
</tr>
<tr>
<td>Adenocarcinoma; GS14</td>
<td>X-Ray; MI10</td>
</tr>
<tr>
<td>Adenoidectomy; OT41</td>
<td>Adenomyosis; GY17</td>
</tr>
<tr>
<td>Adenoid Hypertrophy; OT40</td>
<td>Adherence; PH10</td>
</tr>
<tr>
<td>Adenoma, Toxic; E25</td>
<td>Adie’s Tonic Pupil; OP31, OP32</td>
</tr>
<tr>
<td>Adenomyosis; GY17</td>
<td>Adjustment Disorder; PS18</td>
</tr>
<tr>
<td>ADHD; PS37</td>
<td>Adolescent Medicine; P15</td>
</tr>
<tr>
<td>Adherent; PH10</td>
<td>Adrenal Mass; MI18</td>
</tr>
<tr>
<td>Adrenal Insufficiency; E29</td>
<td>Adrenaline; PS18</td>
</tr>
<tr>
<td>Adrenal Insufficiency; E35</td>
<td>Adrenal Physician; E29</td>
</tr>
<tr>
<td>Adrenocorticotropin Hormone; E29</td>
<td>Adult Onset Still’s Disease; RH28</td>
</tr>
<tr>
<td>Adverse Drug Reactions; E30</td>
<td>Adult Polycystic Kidney Disease; NP31</td>
</tr>
<tr>
<td>Advanced Cardiac Life Support (ACLS) Guidelines; A28</td>
<td>Advanced Reproductive Technologies; ELOAM14</td>
</tr>
<tr>
<td>Anterior Ischemic Optic Neuropathy; N11</td>
<td>Advanced Drug Reactions; CP10</td>
</tr>
<tr>
<td>Anterior Chamber Depth Test; OP6</td>
<td>Adhesions; G55, P40</td>
</tr>
<tr>
<td>Antibiotics; E30</td>
<td>Adhesions, Gastrointestinal; GS41</td>
</tr>
<tr>
<td>Antibiotics, local; A22</td>
<td>Adhesions, Intra-abdominal; GS42</td>
</tr>
<tr>
<td>Antiarrhythmics; C55</td>
<td>Adhesions, Obstetrical; A22</td>
</tr>
<tr>
<td>Analgesics; A18</td>
<td>Analgesics, Pediatric; A23</td>
</tr>
<tr>
<td>Analgesics, Spinal; A20</td>
<td>Analgesics, Topical; A22</td>
</tr>
<tr>
<td>Anal Fissures; GS38</td>
<td>Analgesics, Vaginal; A23</td>
</tr>
<tr>
<td>Analgesics, Vaginal; A20</td>
<td>Analgesics, Venous; A22</td>
</tr>
<tr>
<td>Analgesics, Venous; A21</td>
<td>Analgesics, Vomiting; A20</td>
</tr>
<tr>
<td>Anal Fissures; G55, P40</td>
<td>Anaphylactic; P57</td>
</tr>
<tr>
<td>Anal Fissures; G55, P40</td>
<td>Anaphylaxis; ER30</td>
</tr>
<tr>
<td>Analgesics, Vaginal; A20</td>
<td>Anaphylactic; P57</td>
</tr>
<tr>
<td>Analgesics, Vomiting; A20</td>
<td>Anaphylactic; P57</td>
</tr>
<tr>
<td>Analgesics, Venous; A21</td>
<td>Anaphylactic; P57</td>
</tr>
<tr>
<td>Anal Fissures; G55, P40</td>
<td>Anaphylactic; P57</td>
</tr>
<tr>
<td>Anal Fissures; G55, P40</td>
<td>Anaphylactic; P57</td>
</tr>
<tr>
<td>Analgesics, Vomiting; A20</td>
<td>Anaphylactic; P57</td>
</tr>
<tr>
<td>Analgesics, Venous; A21</td>
<td>Anaphylactic; P57</td>
</tr>
<tr>
<td>Anal Fissures; G55, P40</td>
<td>Anaphylactic; P57</td>
</tr>
</tbody>
</table>
Dementia; FM21, GM3, N17, PS20
Dementia, Frontotemporal; N20
Dementia with Lewy Bodied; N20
Dengue; ID38
Denis Classification; NS33
Dentition; P9
Denys-Drash Syndrome; PS25
Dependent Personality Disorder; PS32
Depressed Newborn; P68
Depression; FM21, GM3, PS9
Postpartum; OB51
Depressive Disorders; PS10
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatitid; D13, FM45
Atopic; D14
Contact; D15
Herpetiformis; D21
Pediatric; P12
Perioral; D12
Dermatofibroma; D6
Dermatomyositis; RH8, RH15
Dermatophytoses; D26
Dermatoses, Life Threatening; ER42
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Dermatofibroma; D6
Dermatitis; D13, FM45
Dermal Melanocytosis; D8
De Quervain’s Tenosynovitis; PL24
Dermal Melanocytosis; D8
Dermatomyositis; RH8, RH15
Pulmonary Embolism; ER33, GS11, MI8, R17
Pulmonary Function Tests; R4
Pulmonary Hypertension; R16
Pulmonary Nodule; MI7
Pulmonary Regurgitation; C40
Pulmonary Shunt; R6
Pulmonary Stenosis; C40, P19
Pulmonary Vasculitis; R20
Pulmonary Stent; U14
Pulmonary Hypertension; R16
Pulmonary Function Tests; R4
Pulmonary Embolism; ER33, GS11, MI8, R17
Relocation Test; OR11
Renal
Adenoma; U20
Artery Occlusion; NP17
Artery Stenosis; NP17
Cell Carcinoma; U20
Colic; ER40, U16
Diseases, Pediatric; P81
Failure; G37, NP35
Function; NP2
Measurement; NP4
Hamartoma; U20
Hemodynamics; NP4
Parameters; NP3
Infarction; NP17
Mass; MI16, U19
Neoplasms; U19
Nuclear Scan; MI17
Oncocytoma; U20
Osteodystrophy; E46
Parenchymal Hypertension; NP31
Pelvis Carcinoma; U21
Stone; U16
Structure; NP2
Transplantation; NP37
Trauma; U32
Tubules; NP3
Vein Thrombosis; NP18
Renin Release; NP4
Reportable Diseases; PH25
Reporting Requirements; ELOAM8
Research Ethics; ELOAM12
Resource Allocation; ELOAM18
Respiratory Acidosis; R5
Respiratory Alkalosis; R5
Respiratory Distress; OT44, R3
Neonatal; P76
Pediatric; ER57
Respiratory Distress Syndrome; P77
Respiratory Failure; GS11, R24
Respiratory Imaging; MI26
Respiratory Tract Diseases; P92
Restless Leg Syndrome; N42
Restrictive Cardiomyopathy; C37
Resuscitation; A13, ER4
Retained Placenta; DB49
Reticulocytes; h5
Retina; OP23
Retinal Artery Occlusion; OP23
Retinal Detachment; ER42, OP23
Retinal Vein Occlusion; OP24
Retinal Zones; OP41
Retinitis Pigmentosa; OP25
Retinoblastoma; OP41
Retinopathy, Diabetic; E12
Retinopathy of Prematurity; OP41
Regrowth Videlography; MI17
Regrowth Urethrogram; MI17
Retropitoneum; MI11
Rett’s Disorder; PS37
Revascularization; Corona; C28
Reversing Induction Agents; A7
Rheumatoid Fever; C38, P61
Rheumatoid Arthritis; RH8
Rhinorrhea; FM46
Rhinorrhea, Non-Articular; RH26
Rhinorrhea; OT22
Acute; FM19
Allergic; FM13, OT23
Vasomotor; OT24
Rokhsar's Syndome; U16
Relative Afferent Pupillary Defect; OP33
Relative Risk; PH9
Relative Risk Reduction; PH10
Reliability; PH15
Relocation Test; OR11
Richter’s Hernia; GS22
Richter’s Transformation; H47
Rickets; E45, MI25
Rigler’s triad; GS48
Ringworm; D26
Rinne Test; OT9
Risk Reduction Strategies; PH6
Rochester Criteria; P54
Rochester Method; OR26
Rockwood Classification; OR14
Rocky Mountain Spotted Fever; ID27
Rohypnol; PS25
Roldando’s Fracture; PL26
Romberg Test; N4
Rome Ill Criteria; G24
Rooftes; PS25
Root Compression; NS24
Rosacea; D13, FM45
Rosella; P59
Rotational Syndrome; H29
Rosenau; D41
Rotator Cuff Disease; OR12
Rotator Cuff Tests; OR13
Roth’s Spots; ID17
Roundworms; ID34
Routine Induction; A9
Rouviere’s Sulcus; GS46
Rubella; D41, P59
Rule of 9s; PL17
Ruptured Diaphragm; ER12
Sacral; RH21
Sag Sign; OR29
Salivary Gland Neoplasms; OT30
Salmon Patch; D11, P78
Salter-Harris Classification; OR39
Sample; PH8
SAMPLE; ER5
Sarcoidosis; OP38, R13
Scabies; D27
Scalp Injury; NS31
Scaphoid Fracture; OR20
Scar; PL9
Scars; ER41, PS5
Schatzker Classification; OR39
Schiff Test; H23
Schistosoma spp.; ID35, ID36
Schistosomiasis; ID26
Schizoaffective Disorder; PS8
Schizophrenia; PS6
Scierosis; OP36
Schizophreniform Disorder; PS8
Schizotypal Personality Disorder; PS31
Sciaticz; OR24
Scintiscan; MI26
Sclerosis; OP16
Scleroderma; G9, NP30, RH8, RH13
Sclerosing Cholangitis; G41
Scoliosis; OR41
Scrotal Mass; U28
Scrotal Anatomy; U2
Seads; ER15
Seborheic Dermatitis; FM45
Seborheic Keratosis; D6
Secondary Angle-Closure Glaucoma; OP29
Secondary Bilary Cirrhosis; G43
Secondary Hemorrhage, Disorders of; H29
Secondary Open Angle Glaucoma; OP29
Secondary Open Angle Glaucoma; OP29
Secondary Open Angle Glaucoma; OP29
Secondary Open Angle Glaucoma; OP29
Secondary Open Angle Glaucoma; OP29
Secondary Open Angle Glaucoma; OP29
Secondary Open Angle Glaucoma; OP29
Secondary Open Angle Glaucoma; OP29
<table>
<thead>
<tr>
<th>Index</th>
<th>U</th>
<th>V</th>
<th>W</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine Bleeding; GY14</td>
<td>Visual Field, Abnormalities of; N12</td>
<td>Wound; PL8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine Inversion; OB50</td>
<td>Visual Fields Tests; OP6</td>
<td>Abnormal Healing; PL9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine Prolapse; GY35</td>
<td>Vitamin B12 Deficiency; H22, N18</td>
<td>Closure; PL8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine Rupture; OB45</td>
<td>Vitamin D; FM6, FM44</td>
<td>Contaminated/Infected; PL9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine Sarcoma; GY37</td>
<td>Vitamin D Deficiency; E45</td>
<td>Dressings; PL11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterus; GY2</td>
<td>Vitamin K Deficiency; H30</td>
<td>Management; ER17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uveitis; OP20, OP29</td>
<td>Vitamins; G17</td>
<td>Wound Care; G57</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination; P3</td>
<td>Vitamins and Minerals; FM6</td>
<td>Wound Dehiscence; G59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vacuum Aspiration; GY9</td>
<td>Vitamin D Deficiency; E45</td>
<td>Wound Hemorrhage/Hematoma; G59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vacuum Extraction; OB47</td>
<td>Vitiligo; D24</td>
<td>Wright Stain; OB27</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal Nerve Stimulation; FS50</td>
<td>Vitreous Hemorrhage; OP22</td>
<td>Wrist Fracture; OR19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vagina; GY2</td>
<td>Vitreous Hemorrhage; OP22</td>
<td>Wuchereria bancrofti; ID35</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal Birth After Cesarean; OB41</td>
<td>Vocal Cord Nodules/Polyps; OT28</td>
<td>Xanthelasma; OP14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal Bleed; ER39</td>
<td>Vocal Cord Paralysis; OT27</td>
<td>X-Ray Imaging; M12, M14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal Breech Delivery; OB40</td>
<td>Vocal Cystourethrogram; MI17</td>
<td>Abdominal; M10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal Cancer; GY47</td>
<td>Vocal Dysfunction; U6</td>
<td>Bone; M12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal Delivery, Operative; OB46</td>
<td>Voiding Dysfunction, Neurologic; U10</td>
<td>X-Ray Imaging, Orthopedic; OR7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal Discharge; GY6, GY24</td>
<td>Volatile Inhalational Induction Agents; A9, A26</td>
<td>Yeast Infections; D31</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vagus Nerve; N10</td>
<td>Volvulus; GS6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>