THE RESIDENT’S GUIDE
To Ambulatory Care
Frequently Encountered and Commonly Confused Clinical Conditions

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THE RESIDENT’S GUIDE TO AMBULATORY CARE
Frequently Encountered and Commonly Confused Clinical Conditions

SEVENTH EDITION

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FOREWORD TO FIRST EDITION

Each year the scope of clinical problems encountered in Family Practice expands, especially as health care shifts to the ambulatory setting. Recognizing this, the authors have written The Resident’s Guide to Ambulatory Care. An impressive list of outstanding physicians has also contributed to this book. It is a notable achievement, being written by residents for residents. The Guide is a collection of strategies, tips and practical information drawn from the authors’ and contributors’ observations and experience in the day-to-day management of outpatient problems. The authors are two highly committed, conscientious and hard working residents who have justifiably earned my support in their efforts. They have written this book in an easy to read and quick to reference style.

A manual of this type would be extremely valuable not only for any resident practicing ambulatory medicine, but for medical students and physicians alike. The Resident’s Guide to Ambulatory Care belongs in the library of every person learning to provide ambulatory care.

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Michael comes from a long line of physicians; his father is an ophthalmologist, both his grandfathers were general surgeons, and his great grandfather was a barber-surgeon in Russia (this guy you didn’t want to be referred to!). Michael obtained his bachelor’s degree with a major in economics from Northwestern University and his medical degree from The Ohio State University College of Medicine. In 1995, he completed his residency in Family Medicine at Riverside Hospital in Columbus, Ohio, concurrent with the release of the first edition of The Resident’s Guide to Ambulatory Care. In addition to currently working as a full time emergency medicine physician, he spent 12 years as a Clinical Assistant Professor in the Infectious Diseases Clinic at Ohio State University caring for patients and as an HIV/AIDS clinical trials sub investigator. He is now an Adjunct Professor in the Division of Emergency Medicine at The Ohio State University College of Medicine, Chairman and Director of Medical Education in the Emergency Department at Mt. Carmel St. Ann’s, and Medical director of The Ohio Dominican University PA studies program. In addition to the ambulatory care books, he has authored Bouncebacks! Emergency Department Cases: ED Returns, Bouncebacks: Medical and Legal, and the soon to be released Bouncebacks: Pediatrics, a series of books with an engaging and unique format and reviews in Annals of Emergency Medicine and JAMA. Michael was recently appointed risk management section editor of Mel Herbert’s Emergency Medicine Reviews and Perspectives (EM RAP), a CME program with international circulation to over 15,000 physicians. Michael has lectured nationally on issues such as risk management and patient safety and has published papers in peer-reviewed journals. In 1997, he married Beth, a fellow family physician and they have a growing family including four energetic children; Olivia (15), Eli (13), Theo (9), and Annie (7). He has practiced medicine on both a local and global scale, including volunteer medical work in Papua New Guinea, Nepal, and the West Indies. In addition to medicine, other passions include skiing, backpacking, traveling and writing. He is a singer/song writer, guitar and harmonica player and leader of a blues band, Mike Weinstock’s Big Rockin’ Blues Band.
Miriam Chan, PharmD

Miriam Chan, PharmD, is a licensed pharmacist with extensive experience in patient care, medical education, faculty development, and clinical research. She received her Bachelor of Science in Pharmacy and Doctor of Pharmacy from the Ohio State University. Dr. Chan joined Riverside Family Medicine Residency as a full-time faculty member in 1996. In this position, she teaches pharmacotherapeutics, evidence-based medicine, and research to geriatric medicine fellows, family medicine residents, medical students, and PharmD students. She provides monthly pharmacy lectures and is well known for her concise and practical drug handouts. She has contributed to peer reviewed journals and best-selling books such as Conn’s Current Therapy, Handbook of Emergency Drugs, and previous editions of The Resident’s Guide. Dr. Chan has given lectures at national conferences in her areas of expertise including diabetes, geriatrics, medication adherence, polypharmacy, psychopharmacology, opioid therapy, and quality improvement. As a teacher, she also oversees Journal Club, supervises family medicine residents on their scholarly projects, and facilitates faculty research. Dr. Chan holds the appointment as Clinical Assistant Professor of Family Medicine and Pharmacy at the Ohio State University. She received Family Practice Teacher of the Year Award in 1998 and 2003. Dr. Chan was recognized for her dedication to family medicine education and was presented with the Family Medicine Educator of the Decade Award in 2011. In addition to her teaching responsibilities, she provides patient care as a certified diabetes educator and pharmacy consultant at Riverside Family Practice Center.

Daniel M. Neides, MD

Daniel Neides, M.D., MBA, is the Medical Director and Chief Operating Officer of the Cleveland Clinic Wellness Institute. Dr. Neides is board-certified in Family Medicine and has practiced at The Cleveland Clinic since 1996. He earned both his undergraduate and medical degrees from Ohio State University, followed by a residency in Family Medicine at Riverside Methodist Hospital in Columbus. He earned his master’s in business administration from Washington State University. He was awarded the 1999–2000 Educator of the Year award by The Cleveland Clinic Foundation and The Ohio State University College of Medicine and was inducted into the Alpha Omega Alpha Honor Society in 2002 for his dedication to medical student education. In 2004, The Cleveland Clinic Regional Medical Practices awarded him the Outstanding Educator of the Year. In 2006, Dr. Neides was named a Harvard-Macy Scholar and spent 1 month in Boston. He received multiple Scholarship in Teaching awards from Case Western Reserve University for his role in curriculum development. In 2007, Case Western Reserve University School of Medicine honored him during commencement ceremonies with the Kaiser Permanente Award for Excellence in Teaching. When he is not practicing medicine, Dr. Neides enjoys spending time with his wife, Karen, and their three children, Melissa, David, and Adam and taking long walks in the Metroparks with his dog, Sonny. Dr. Neides would like to thank the medical students, residents, and allied health professionals for their support of this book over the years. He would also like to thank his parents, Sharyn and Gary, for their continued encouragement.
PREFACE TO SEVENTH EDITION

It’s hard to believe that a book which was started during our 2nd year of family medicine residency, almost 20 years ago, is now in its 7th edition, with sales over 34,000 copies. Our original mission had been to provide a reference used specifically by residents in the ambulatory care setting; this mission has expanded to include multi-specialty attendings who need an easy to use reference for situations infrequently encountered; a gynecologist treating depression, a pediatrician treating PID, an orthopedist treating sinusitis or an ophthalmologist treating just about anything!

We have come a long way, but some things stay the same: this is a book written by residents, for residents. Each chapter is also reviewed by multiple primary care attendings, specialists for each discipline, and Miriam Chan, PharmD, faculty in the Riverside Methodist Hospital Family Medicine residency, in Columbus, Ohio. She has performed an extensive review of the entire text to ensure medication indications and doses are accurate and consistent with recent published guidelines. In addition to contributions from virtually every subspecialty, contributors also included physician assistants, nurses, medical students and medical educators. Chapters were reviewed not only for medical accuracy but the ability to quickly access important information.

This edition includes new charts and tables, algorithms, and current national guidelines for evaluation and management of many ambulatory conditions. We have added new chapters on child maltreatment, autism spectrum disorders, pneumonia in infants, occupational medicine, chronic pain management, and end of life care. The references have been updated and many chapters have web links for continually updated information.

As in past editions, each chapter reflects the insight of its resident author and the specific material presented. We have provided a guide to evaluation and management of commonly encountered clinical situations, and left the “zebras” for other sources. We continue to provide “clinical pearls” at the end of each chapter, algorithms in selected chapters, and many charts and tables. Medications listed have the dosages and are in bold print for rapid reference. Blank pages are provided for notes and important phone numbers.

The growth of this manual is a testament not only to its comprehensive nature and ease of use, but also to each of its devoted authors, reviewers, and readers. We thank you for your continued support!

Michael B. Weinstock  
Daniel M. Neides  
Miriam Chan  
December 2014
PREFACE TO FIRST EDITION

Our goal in writing The Resident’s Guide to Ambulatory Care is to provide a framework for the rapid diagnosis and management of ambulatory conditions commonly encountered by residents treating patients in the ambulatory setting. Whereas other ambulatory books attempt to incorporate everything that could possibly be encountered in the ambulatory setting, our goal is to provide more detailed chapters on some of the most frequently seen diagnoses. For example, this manual provides well organized, easily accessed, and detailed information on contraception, ambulatory management of HIV/AIDS, and hypertension, and leaves the management of less frequently encountered conditions (Waldenstrom’s macroglobulinemia) to other references. It will neither provide a comprehensive didactic summary nor behave as a textbook for in-depth study.

This pocket manual incorporates essential topics covered by handbooks of internal medicine, family practice, pediatrics, and obstetrics into one easy to access source. It is a “pocket companion / ancillary brain” for the resident who must be familiar with an extraordinary amount of medical knowledge, including:

1) Office based care (Diagnosis and management of frequently encountered clinical conditions)
2) Preventive medicine (Immunization schedules, cancer screening, cholesterol management)
3) Surgery (Pre-op evaluation, pain management, evaluation of abdominal pain, suturing)
4) Geriatric medicine (Drug-drug interactions, side effects more prevalent in the elderly, addressing code status, “pronouncing” a patient, incontinence, falls)
5) Care of the pregnant woman (Prenatal care, sample admission and delivery notes, answers to questions expecting parents commonly ask)
6) Ambulatory management of HIV/AIDS (Schedule of visits, prophylactic medications, algorithms for work-up of cough, diarrhea, headache, FUO, etc.)

The manual emphasizes the diagnostic importance of the history and physical exam, and the importance of preventive medicine in ambulatory care. We feel that these issues are important in an era of health care reform where cost effective ambulatory care is essential.

We have tried to enhance the readability of this reference by including “clinical pearls” at the end of each chapter, including algorithms in selected chapters, and providing charts and tables for quick comparisons. Blank pages are provided for important pager and phone numbers. Most chapters follow a consistent format, but some deviate due to the creative insight of the authors and in the interests of space.

Contributors include a broad spectrum of physicians from the specialties of family medicine, internal medicine, pediatrics, cardiology, dermatology, psychiatry, pulmonology, ophthalmology, urology, neurology, physical medicine and rehabilitation, and obstetrics and gynecology. Other contributors include medical students and medical educators. We hope The Resident’s Guide to Ambulatory Care will serve as a helpful resource for residents, medical students, and clinicians in practice and that it will serve to improve ambulatory patient care and medical education. We welcome feedback for future editions.

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June 1995
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The Resident's Guide to Ambulatory Care

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Related subjects:

Community Acquired Pneumonia ................................................................. see Chapter 52
Ocular Disorders & Screening ........................................................................ see Chapter 70
Seizure Disorders ............................................................................................... see Chapter 61
1. THE NEWBORN EXAM

I. HISTORY

Review perinatal, pregnancy, and family histories, feeding, stooling, voiding, and Apgar scores at birth.

II. THE PHYSICAL EXAM

A. General: Neonate should be completely undressed prior to the exam. Observe for normal muscle tone (flexion of upper and lower extremities), movement of all extremities, and respiratory pattern. Evaluate size:

1. Small for gestational age (SGA): weight < 10th percentile
2. Large for gestational age (LGA) (weight > 90th percentile)

B. Respiratory

1. Color: Central and peripheral (Peripheral cyanosis is normal for several hours after birth)
2. Breathing: Normal respiratory rate is 40–60/minute; grunting and nasal flaring are not normal—if detected, further work-up is necessary. Expiratory grunting and decreased air entry are observed in hyaline membrane disease
3. Auscultation: Perform prior to any manipulation of the infant (holding the infant or providing a gloved finger to suck on may quiet a crying infant). Listen for equal and bilateral breath sounds

C. Cardiovascular

1. Normal rate is 120–160 BPM
2. An irregularly irregular heart rate, caused by premature atrial contractions, is common and benign in the first few days of life
3. Murmurs
   a. Not necessarily an important finding on the newborn exam; infants with major cardiac anomalies may not have a murmur while an infant with a closing ductus arteriosus may; it is important to take into account other factors: color, perfusion, blood pressure, ability to feed
   b. If further work-up is warranted, start with a chest x-ray, ECG, and blood pressure in all 4 extremities
4. Pulses: Palpate femoral pulses (if absent, may indicate coarctation of the aorta)
5. Prior to discharge from the nursery screen all infants for congenital heart disease. This is accomplished by an oxygen saturation by a pulse oximeter in the right upper and lower extremity. Any infant with a positive screen (<90% in either, <95% in both the hand and foot or >3% difference between the hand and foot) should have a diagnostic echo-cardiogram. See algorithm for details

(Algorithm on next page)
1. The Newborn Exam

Care of Children

Child in well-baby nursery ≥ 24 hours of age or shortly before discharge if < 24 hours of age

Screen

< 90% in right hand or foot

90%< 95% in right hand and foot or > 3% difference between right hand and foot

≥ 95% in right hand or foot and ≤ 3% difference between right hand and foot

Repeat screen in 1 hour

< 90% in right hand or foot

90%< 95% in right hand and foot or > 3% difference between right hand and foot

≥ 95% in right hand or foot and ≤ 3% difference between right hand and foot

Repeat screen in 1 hour

< 90% in right hand or foot

90%< 95% in right hand and foot or > 3% difference between right hand and foot

≥ 95% in right hand or foot and ≤ 3% difference between right hand and foot

Positive Screen

Negative Screen


D. Gastrointestinal: Because of relatively weak abdominal musculature, palpation of internal organs is possible
1. The liver should be palpable and often extends below the costal margin
2. The spleen usually is not palpable
3. Palpate for renal/abdominal masses (Wilms’ tumor, neuroblastoma)

E. Genitourinary
1. Males
   a. Palpate testicles (testicles may need to be guided down from above scrotum into scrotum). Hydroceles are common and will usually resolve within the first 6 months. Transilluminate to confirm a hydrocele
   b. Check the penis for hypospadias or epispadias—if present, consult a urologist and do not circumcise the infant
2. Females
   a. The labia majora may appear large because of maternal hormones
   b. Spread the labia, and observe for vaginal wall cysts or imperforate hymen
   c. A white discharge may be seen as well as pseudomenses (due to maternal hormones)
3. Rectal inspection: Check for position and patency (monitor for bowel movement). A fistula can be mistaken for a normal anus; however, position of a fistula is usually anterior or posterior to the location of a normal anus

F. Extremities
1. Hip clicks: 2 maneuvers are performed
   a. Barlow test: Adduction and posterior pressure may produce a “clunk” of subluxation or dislocation of femur
   b. Ortolani test: Abduct and lift femur back into place
2. Assess for club feet (plantar flexion of foot, inversion deformity of heel, and forefoot
varus), polydactyly or syndactyly, and forefoot adduction
3. Examine for crepitus or discoloration over the clavicles and decreased movement of
affected arm (most commonly fractured bones in infants)
4. Examine the back for pilonidal sinus tracts or sacral dimple. If a pilonidal sinus tract
is detected and the base cannot be seen, spine films may be indicated (meningocele)

G. Head, eyes, and mouth
1. Head:
   a. Examine the skull for caput succedaneum (tissue swelling that crosses suture
      lines—no therapy needed), or cephalohematomas (well-demarcated swelling
      that does not cross suture lines, which may be associated with skull fracture)
   b. Mobility of the suture lines (craniosynostosis)—one or more suture lines are not
      mobile
   c. Fontanelles: If head circumference is normal (32–36cm) and suture lines are
      mobile, size of fontanelles are not important; anterior fontanelle should be
      palpated, but the posterior fontanelle may not be palpable
2. Eyes: Examine for bilateral red reflex with ophthalmoscope at a distance of 1–2 feet. If
   there is difficulty opening neonate's eyes, try sitting infant up or holding upside down
   and rapidly bringing to an upright position (infant gets disoriented and instinctively
   opens eyes). Subconjunctival hemorrhages are common after vaginal delivery
3. Mouth: Palpate and visualize for cleft palate. Small white cysts (Epstein's pearls) may
   be noted on the hard palate and are a normal finding. Natal teeth usually require
   removal and may be associated with congenital anomalies

H. Neurologic: Most of the neurologic exam is done while performing the rest of the neonatal
physical exam. Important aspects of the neurologic exam include observation of move-
ment, evaluating body tone when handled, and observing appropriate crying during the
exam. Check for facial nerve paralysis due to trauma during delivery
1. Moro (startle) reflex: Grasp the neonate's hands and carefully pull the baby up—as you
   bring the head back down toward the crib, let go and the Moro reflex should occur.
   (Abduction of arms and legs, extension of elbow and knees followed by flexion)
2. Sucking and rooting reflex:
   a. Rooting occurs when the baby's lips are stroked laterally and the head turns
      toward the ipsilateral side
   b. Assess the suck reflex by placing a finger in the infant's mouth
3. Stepping reflex: Hold the infant upright and lean him/her forward. This should cause
   the baby to instinctively produce a stepping action (this reflex does not always occur)
4. Head control: Assess head lag while holding the infant's hands and pulling him/her
   upright. Head should lag, come to the midline briefly, then fall forward

I. Skin: Common normal findings include:
1. Milia: Small white cysts on the baby's nose, cheeks, or forehead
2. Nevi or Mongolian spots: Brown/blue patches on the torso that typically disappear
   within months
3. Macular hemangiomas: "Angel kiss" or "stork bites" on the face or neck
4. Erythema toxicum neonatorum: Fleeting erythematous papules and pustules
5. Sucking blister: On upper or lower lip
6. Dry skin: With cracking and peeling in post-dates infants
7. Miliaria: Blocked sweat glands ducts appear as papules and/or pustules

III. FOLLOW-UP INSTRUCTIONS
A. Hepatitis B vaccine: See Chapter 3, Childhood Immunization Schedule
B. Follow-up at 2–4 weeks of age for routine exam (1–2 weeks if breast-feeding, see
   Chapter 4, Infant Formula & Breast-feeding)
C. Discuss with the parents signs/symptoms of neonatal sepsis (lethargy, poor feeding
   habits, crying and inconsolable, rectal temperature > 100.4º F). Instruct parents to
   contact family physician if these problems arise

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ties involving the skin, head, neck, chest, and respiratory and cardiovascular systems. Am
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I. CHILD DEVELOPMENTAL STAGE

<table>
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<th>AGE of child</th>
<th>LANGUAGE</th>
<th>GROSS MOTOR</th>
<th>FINE MOTOR</th>
<th>SOCIAL</th>
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<tr>
<td>NEWBORN</td>
<td>crying</td>
<td>asks control of muscle groups</td>
<td>no skill</td>
<td>looks on objects; stares easily</td>
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<tr>
<td>1 MONTH</td>
<td>cooing; single vowel sounds</td>
<td>lifts chin briefly</td>
<td>no skill</td>
<td>indefinite stare at surroundings</td>
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<tr>
<td>2 MONTHS</td>
<td>cooing; single vowel sounds</td>
<td>lifts head up 45 degrees</td>
<td>hand to mouth</td>
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<tr>
<td>4 MONTHS</td>
<td>laughs; squeals</td>
<td>rolls over; head up 90 degrees (prone)</td>
<td>two hand reach and grasp</td>
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<td>5 MONTHS</td>
<td>monosyllable babbling</td>
<td>sits alone without support</td>
<td>reaches for dropped toy; palmar grasp</td>
<td></td>
</tr>
<tr>
<td>6 MONTHS</td>
<td>single syllables; responds to ND</td>
<td>crawls-pulls to stand; &quot;cruises&quot;</td>
<td>thumb-finger (pincer) grasp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2–3 years</td>
<td>6–10 words</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 MONTHS</td>
<td>First word, uses &quot;mama&quot;, &quot;dada&quot; correctly</td>
<td>walks alone; pivots to pick up objects</td>
<td>fine pincer grasp; learns to use cup</td>
<td></td>
</tr>
<tr>
<td>15 MONTHS</td>
<td>4–6 words</td>
<td>stands without support</td>
<td>builds tower of two blocks</td>
<td></td>
</tr>
<tr>
<td>18 MONTHS</td>
<td>Two words together; knows 6–10 words</td>
<td>walks up steps; kicks ball</td>
<td>turns pages two at a time; scribbles</td>
<td></td>
</tr>
<tr>
<td>2 YEARS</td>
<td>50 words; 2–3 word sentences</td>
<td>walks down steps, overhand throw</td>
<td>copy vertical line; turns door knobs</td>
<td>MINE: dry at night</td>
</tr>
<tr>
<td>3 YEARS</td>
<td>knows full name; 4 word sentences</td>
<td>jumps from bottom step; rides tricycle</td>
<td>zips and unzips; copy circle</td>
<td>toilet trained; dresses with help</td>
</tr>
<tr>
<td>4 YEARS</td>
<td>9 word sentences; sings songs</td>
<td>hops on one foot; running jump</td>
<td>puts on shoes; buttons clothes</td>
<td></td>
</tr>
<tr>
<td>5 YEARS</td>
<td>counts to 10; asks &quot;why&quot;</td>
<td>skips; balances on one foot</td>
<td>may tie shoe laces</td>
<td>dresses on own; dresses without help</td>
</tr>
</tbody>
</table>

The chart items in **bold** are important milestones and easy ones to remember

NORMAL PEDIATRIC VITAL SIGNS

<table>
<thead>
<tr>
<th>Age</th>
<th>Pulse</th>
<th>Resp</th>
<th>Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>NB</td>
<td>120–160</td>
<td>30–60</td>
<td>systolic = 60–70</td>
</tr>
<tr>
<td>&lt; 1 yr</td>
<td>120–140</td>
<td>30–50</td>
<td></td>
</tr>
<tr>
<td>1–2 yrs</td>
<td>100–140</td>
<td>30–40</td>
<td>systolic = 70 + (2 x age)</td>
</tr>
<tr>
<td>3–5 yrs</td>
<td>100–120</td>
<td>20–30</td>
<td>diastolic = 2/3 systolic</td>
</tr>
<tr>
<td>6–10 yrs</td>
<td>80–100</td>
<td>16–20</td>
<td></td>
</tr>
</tbody>
</table>

CLINICAL PEARLS

- It is reassuring to inform parents what they can expect developmentally before the next well-baby visit
- If a child falls significantly behind developmentally, complete developmental testing (e.g., Denver Development Screening Test) should be performed
I. CHILDHOOD IMMUNIZATION SCHEDULE

These recommendations must be read with the footnotes of this schedule. Footnotes follow the schedule. Catch-up immunization is encouraged if certain high-risk groups are at risk. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the bars in the tables below. To determine minimum intervals between doses, see the catch-up schedule. School entry and adolescent vaccine age groups are 4-6 yrs and 11-12 yrs.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Range of recommended ages for all children</th>
<th>Range of recommended ages for catch-up immunization</th>
<th>Range of recommended ages for certain high-risk groups</th>
<th>Range of recommended ages during which catch-up is encouraged and for certain high-risk groups</th>
<th>Not routinely recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>Birth to 15 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Birth to 15 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria, tetanus, &amp; acellular pertussis</td>
<td>Birth to 15 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus, diphtheria, &amp; acellular pertussis</td>
<td>Birth to 15 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenza type b</td>
<td>Birth to 15 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal conjugate</td>
<td>Birth to 15 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal polysaccharide</td>
<td>Birth to 15 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated poliovirus</td>
<td>Birth to 15 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>Birth to 15 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td>Birth to 15 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>Birth to 15 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Birth to 15 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>Birth to 15 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal13 (Hib-MenCY)</td>
<td>Birth to 15 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chart continued on next page
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>18 mos</th>
<th>18-23 mos</th>
<th>2-3 yrs</th>
<th>4-6 yrs</th>
<th>7-10 yrs</th>
<th>11-12 yrs</th>
<th>13-15 yrs</th>
<th>16-18 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B&lt;sup&gt;1&lt;/sup&gt; (HepB)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus&lt;sup&gt;1&lt;/sup&gt; (RV)</td>
<td>←3&lt;sup&gt;rd&lt;/sup&gt;dose→</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV-1 (2-dose series); RV-5 (3-dose series)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria, tetanus, &amp; acellular pertussis&lt;sup&gt;3&lt;/sup&gt; (DTaP: &lt;7 yrs)</td>
<td>←4&lt;sup&gt;th&lt;/sup&gt;dose→</td>
<td>←5&lt;sup&gt;th&lt;/sup&gt;dose→</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus, diphtheria, &amp; acellular pertussis&lt;sup&gt;4&lt;/sup&gt; (Tdap: ≥7 yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae type b&lt;sup&gt;5&lt;/sup&gt; (Hib)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal conjugate&lt;sup&gt;6a&lt;/sup&gt; (PCV13)</td>
<td>←3&lt;sup&gt;rd&lt;/sup&gt;dose→</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal polysaccharide&lt;sup&gt;6b,c&lt;/sup&gt; (PPSV23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated poliovirus&lt;sup&gt;7&lt;/sup&gt; (IPV&lt;18 years)</td>
<td>←3&lt;sup&gt;rd&lt;/sup&gt;dose→</td>
<td>←4&lt;sup&gt;th&lt;/sup&gt;dose→</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza&lt;sup&gt;8&lt;/sup&gt; (IV; LAIV) 2 doses for some: see footnote 8</td>
<td>Annual vaccination (IV only)</td>
<td>Annual vaccination (IV or LAIV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella&lt;sup&gt;9&lt;/sup&gt; (MMR)</td>
<td>←2&lt;sup&gt;nd&lt;/sup&gt;dose→</td>
<td>←2&lt;sup&gt;nd&lt;/sup&gt;dose→</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella&lt;sup&gt;10&lt;/sup&gt; (VAR)</td>
<td>←2&lt;sup&gt;nd&lt;/sup&gt;dose→</td>
<td>←2&lt;sup&gt;nd&lt;/sup&gt;dose→</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A&lt;sup&gt;11&lt;/sup&gt; (HepA)</td>
<td>←2 dose series, see footnote 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus&lt;sup&gt;12&lt;/sup&gt; (HPV2: females only; HPV4: males and females)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal&lt;sup&gt;13&lt;/sup&gt; (Hib-MeNCY ≥ 6 wks; MCV4-D29 mos; MCV4-CRM ≥ 2 yrs.)</td>
<td>see footnote 13</td>
<td>←1&lt;sup&gt;st&lt;/sup&gt;dose→</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The above recommendations must be read along with the footnotes of this schedule. Footnotes follow the Schedule 2 Catch-up Schedule.
### Chart continued on next page

#### Care of Children

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Minimum Age</th>
<th>Dose 1 to dose 2</th>
<th>Dose 2 to dose 3</th>
<th>Dose 3 to dose 4</th>
<th>Dose 4 to dose 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B1</td>
<td>Birth</td>
<td>4 weeks</td>
<td>8 weeks</td>
<td>at least 16 weeks after first dose</td>
<td>minimum age for the final dose is 24 weeks</td>
</tr>
<tr>
<td>Rotavirus2</td>
<td>6 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>6 months if first dose administered at younger than age 12 months</td>
</tr>
<tr>
<td>Diphtheria, tetanus, &amp; acellular pertussis</td>
<td>6 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>6 months if first dose administered at younger than age 12 months</td>
</tr>
<tr>
<td>Haemophilus influenzae type b5</td>
<td>6 weeks</td>
<td>4 weeks if first dose administered at younger than age 12 months</td>
<td>8 weeks if first dose administered at age 12 through 14 months</td>
<td>8 weeks (as final dose) if first dose administered at age 12 through 14 months</td>
<td>8 weeks (as final dose) if current age is younger than 12 months and first dose administered at &lt; 7 months old. 9 weeks (as final dose) if current age is 12 through 59 months and first dose administered at age 12 months or older; or first 2 doses were PRP-OMP and administered at younger than 12 months.</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>6 weeks</td>
<td>4 weeks if first dose administered at younger than age 12 months</td>
<td>8 weeks (as final dose for healthy children) if first dose administered at age 12 months or older.</td>
<td>4 weeks if current age is younger than 12 months</td>
<td>8 weeks (as final dose for healthy children) if current age is 12 months or older.</td>
</tr>
<tr>
<td>Inactivated Poliovirus7</td>
<td>6 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>6 months minimum age 4 years for final dose</td>
<td></td>
</tr>
<tr>
<td>Meningococcal13</td>
<td>6 weeks</td>
<td>8 weeks</td>
<td>See footnote 13</td>
<td>See footnote 13</td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td>12 months</td>
<td>4 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella10</td>
<td>12 months</td>
<td>3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A11</td>
<td>12 months</td>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The above recommendations must be read along with the footnotes of this schedule that follow.

**Schedule 2—Catch-up Immunization Schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind.**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Minimum Age</th>
<th>Dose 1 to dose 2</th>
<th>Dose 2 to dose 3</th>
<th>Dose 3 to dose 4</th>
<th>Dose 4 to dose 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A11</td>
<td>12 months</td>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus2</td>
<td>6 weeks</td>
<td>4 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria, tetanus, &amp; acellular pertussis</td>
<td>6 weeks</td>
<td>4 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae type b5</td>
<td>6 weeks</td>
<td></td>
<td>8 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>6 weeks</td>
<td>4 weeks if first dose administered at younger than age 12 months</td>
<td>8 weeks (as final dose for healthy children) if first dose administered at age 12 months or older.</td>
<td>4 weeks if current age is younger than 12 months</td>
<td>8 weeks (as final dose for healthy children) if current age is 12 months or older.</td>
</tr>
<tr>
<td>Inactivated Poliovirus7</td>
<td>6 weeks</td>
<td>4 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal13</td>
<td>6 weeks</td>
<td></td>
<td>8 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td>12 months</td>
<td>4 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella10</td>
<td>12 months</td>
<td>3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A11</td>
<td>12 months</td>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The above recommendations must be read along with the footnotes of this schedule that follow.
**Schedule 2—Catch-up Immunization Schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind • 2014**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Minimum Age for Dose 1</th>
<th>Minimum Interval Between Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dose 1 to dose 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 2 to dose 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 3 to dose 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 4 to dose 5</td>
</tr>
<tr>
<td>Tetanus, diphtheria; tetanus, diphtheria, &amp; acellular pertussis 4</td>
<td>7 years 4</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Human papillomavirus 12</td>
<td>9 years</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A 11</td>
<td>12 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Hepatitis B 1</td>
<td>Birth</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Inactivated Poliovirus 7</td>
<td>6 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Meningococcal 13</td>
<td>6 weeks</td>
<td>8 weeks 13</td>
</tr>
<tr>
<td>Measles, mumps, rubella 9</td>
<td>12 months</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Varicella 10</td>
<td>12 months</td>
<td>3 months if person is younger than age 13 years</td>
</tr>
</tbody>
</table>

**Note:** The above recommendations must be read along with the footnotes of this schedule that follow.
Footnotes — Recommended immunization schedule for persons aged 0 through 18 years
United States, 2014

This schedule includes recommendations in effect as of January 1, 2014. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations. Clinically significant adverse events that follow vaccination should be reported to Vaccine Adverse Event Reporting System (VAERS) online or by telephone (800-822-7967). Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC’s Vaccines and Immunization online site or by telephone (800-CDC-INFO [800-232-4636]).

This schedule is approved by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the American College of Obstetricians and Gynecologists (ACOG).

Additional information
- For contraindications and precautions to use of a vaccine and for additional information regarding that vaccine, vaccination providers should consult the relevant ACIP statement available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For purposes of calculating intervals between doses, 4 weeks = 28 days. Intervals of 4 months or greater are determined by calendar months.
- Vaccine doses administered 4 days or less before the minimum interval are considered valid. Doses of any vaccine administered 5 days earlier than the minimum interval or minimum age should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see MMWR, General Recommendations on Immunization and Reports / Vol. 60 / No. 2; Table 1, Recommended and minimum ages and intervals between vaccine doses available online at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.
- Information on travel vaccine requirements and recommendations is available at http://wwwnc.cdc.gov/travel/destinations/list.

For further guidance on the use of the vaccines mentioned below, see: http://www.cdc.gov/vaccines/hcp/acip-recs/index.html

1. Hepatitis B (HepB) vaccine. (Minimum age: birth)
   Routine vaccination:
   At birth:
   - Administer monovalent HepB vaccine to all newborns before hospital discharge.
   - For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of the HepB series, at age 9 through 18 months (preferably at the next well-child visit).
   - If mother’s HBsAg status is unknown, within 12 hours of birth administer HepB vaccine regardless of birth weight. For infants weighing less than 2,000 grams, administer HBIG in addition to HepB vaccine within 12 hours of birth. Determine mother’s HBsAg status as soon as possible and, if mother is HBsAg-positive, also administer HBIG for infants weighing 2,000 grams or more as soon as possible, but no later than age 7 days.
   
   Doses following the birth dose:
   - The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
   - Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months starting as soon as feasible. See Catch-up Schedule.
   - Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks), administer the third dose at least 8 weeks after the second dose AND at least 16 weeks after the first dose. The final (third or fourth) dose in the HepB vaccine series should be administered no earlier than age 24 weeks.
   - Administration of a total of 4 doses of HepB vaccine is permitted when a combination vaccine containing HepB is administered after the birth dose.
3.  Childhood Immunization Schedule & Health Care

3. Catch-up vaccination:
   - Unvaccinated persons should complete a 3-dose series.
   - A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
   - For other catch-up guidance, see Catch-up Schedule.

2.  Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV1 [Rotarix] and RV5 [RotaTeq])

   Routine vaccination:
   - Administer a series of RV vaccine to all infants as follows:
     1. If Rotarix is used, administer a 2-dose series at 2 and 4 months of age.
     2. If RotaTeq is used, administer a 3-dose series at ages 2, 4, and 6 months.
     3. If any dose in the series was RotaTeq or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

   Catch-up vaccination:
   - The maximum age for the first dose in the series is 14 weeks, 6 days; vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
   - The maximum age for the final dose in the series is 8 months, 0 days.
   - For other catch-up guidance, see Catch-up Schedule.

3.  Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: 6 weeks.

   Exception: DTaP-IPV [Kinrix]: 4 years)

   Routine vaccination:
   - Administer a 5-dose series of DTaP vaccine at ages 2, 4, 6, 15 through 18 months, and 4 through 6 years. The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.

   Catch-up vaccination:
   - The fifth dose of DTaP vaccine is not necessary if the fourth dose was administered at age 4 years or older.
   - For other catch-up guidance, see Catch-up Schedule.

4.  Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine. (Minimum age: 10 years for Boostrix, 11 years for Adacel)

   Routine vaccination:
   - Administer 1 dose of Tdap vaccine to all adolescents aged 11 through 12 years.
   - Tdap may be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine.
   - Administer 1 dose of Tdap vaccine to pregnant adolescents during each pregnancy (preferred during 27 through 36 weeks gestation) regardless of time since prior Td or Tdap vaccination.

   Catch-up vaccination:
   - Persons aged 7 years and older who are not fully immunized with DTaP vaccine should receive Tdap vaccine as 1 (preferably the first) dose in the catch-up series; if additional doses are needed, use Td vaccine. For children 7 through 10 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap vaccine dose at age 11 through 12 years should NOT be administered. Td should be administered instead 10 years after the Tdap dose.
   - Persons aged 11 through 18 years who have not received Tdap vaccine should receive a dose followed by tetanus and diphtheria toxoids (Td) booster doses every 10 years thereafter.
   - Inadvertent doses of DTaP vaccine:
     - If administered inadvertently to a child aged 7 through 10 years may count as part of the catch-up series. This dose may count as the adolescent Tdap dose, or the child can later receive a Tdap booster dose at age 11 through 12 years.
     - If administered inadvertently to an adolescent aged 11 through 18 years, the dose should be counted as the adolescent Tdap booster.
   - For other catch-up guidance, see Catch-up Schedule.

5.  Haemophilus influenzae type b (Hib) conjugate vaccine. (Minimum age: 6 weeks for PRP-T [ACTHIB, DTaP-IPV/Hib (Pentacel) and Hib-MenCY (MenHibrix)], PRP-OMP [PedvaxHIB or COMVAX], 12 months for PRP-T [Hiberix])

   Routine vaccination:
   - Administer a 2- or 3-dose Hib vaccine primary series and a booster dose (dose 3 or 4 depending on vaccine used in primary series) at age 12 through 15 months to complete a full Hib vaccine series.
   - The primary series with ActHIB, MenHibrix, or Pentacel consists of 3 doses and should be administered at 2, 4, and 6 months of age. The primary series with PedvaxHib or COMVAX consists of 2 doses and should be administered at 2 and 4 months of age; a dose at age 6 months is not indicated.
   - One booster dose (dose 3 or 4 depending on vaccine used in primary series) of any Hib vaccine should be administered at age 12 through 15 months. An exception is Hiberix vaccine. Hiberix should only be used for the booster (final) dose in children aged 12 months through 4 years who have received at least 1 prior dose of Hib-containing vaccine.
   - For recommendations on the use of MenHibrix in patients at increased risk for meningococcal disease, please refer to the meningococcal vaccine footnotes and also to MMWR March 22, 2013;62(RR02):1-22, available at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf
Catch-up vaccination:
- If dose 1 was administered at ages 12 through 14 months, administer a second (final) dose at least 8 weeks after dose 1, regardless of Hib vaccine used in the primary series.
- If the first 2 doses were PRP-OMP (PedvaxHIB or COMVAX), and were administered at age 11 months or younger, the third (and final) dose should be administered at age 12 through 15 months and at least 8 weeks after the second dose.
- If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a third (and final) dose at age 12 through 15 months or 8 weeks after second dose, whichever is later, regardless of Hib vaccine used for first dose.
- If first dose is administered at younger than 12 months of age and second dose is given between 12 through 14 months of age, a third (and final) dose should be given 8 weeks later.
- For unvaccinated children aged 15 months or older, administer only 1 dose.
- For other catch-up guidance, see Catch-up Schedule. For catch-up guidance related to MenHibrix, please see the meningococcal vaccine footnotes and also MMWR March 22, 2013;62(RR02):1-22, available at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.

Vaccination of persons with high-risk conditions:
- Children aged 12 through 59 months who are at increased risk for Hib disease, including chemotherapy recipients and those with anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV) infection, immunoglobulin deficiency, or early component complement deficiency, who have received either no doses or only 1 dose of Hib vaccine before 12 months of age, should receive 2 additional doses of Hib vaccine 8 weeks apart; children who received 2 or more doses of Hib vaccine before 12 months of age should receive 1 additional dose.
- For patients younger than 5 years of age undergoing chemotherapy or radiation treatment who received a Hib vaccine dose(s) within 14 days of starting therapy or during therapy, repeat the dose(s) at least 3 months following therapy completion.
- Recipients of hematopoietic stem cell transplant (HSCT) should be revaccinated with a 3-dose regimen of Hib vaccine starting 6 to 12 months after successful transplant, regardless of vaccination history; doses should be administered at least 4 weeks apart.
- A single dose of any Hib-containing vaccine should be administered to unimmunized* children and adolescents 15 months of age and older undergoing an elective splenectomy; if possible, vaccine should be administered at least 14 days before procedure.
- Hib vaccine is not routinely recommended for patients 5 years or older. However, 1 dose of Hib vaccine should be administered to unimmunized* persons aged 5 years or older who have anatomic or functional asplenia (including sickle cell disease) and unvaccinated persons 5 through 18 years of age with human immunodeficiency virus (HIV) infection.
- * Patients who have not received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months of age are considered unimmunized.

6. Pneumococcal vaccines. (Minimum age: 6 weeks for PCV13, 2 years for PPSV23)

Routine vaccination with PCV13:
- Administer a 4-dose series of PCV13 vaccine at ages 2, 4, and 6 months and at age 12 through 15 months.
- For children ages 14 through 59 months who have received an age-appropriate series of 7-valent PCV (PCV7), administer a single supplemental dose of 13-valent PCV (PCV13).

Catch-up vaccination with PCV13:
- Administer 1 dose of PCV13 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
- For other catch-up guidance, see Catch-up Schedule.

Vaccination of persons with high-risk conditions with PCV13 and PPSV23:
- All recommended PCV13 doses should be administered prior to PPSV23 vaccination if possible.
- For children 2 through 5 years of age with any of the following conditions: chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; solid organ transplantation; or congenital immunodeficiency:
  1. Administer 1 dose of PCV13 if 3 doses of PCV (PCV7 and/or PCV13) were received previously.
  2. Administer 2 doses of PCV13 at least 8 weeks apart if fewer than 3 doses of PCV (PCV7 and/or PCV13) were received previously.
  3. Administer 1 supplemental dose of PCV13 if 4 doses of PCV7 or other age-appropriate complete PCV7 series was received previously.
  4. The minimum interval between doses of PCV (PCV7 or PCV13) is 8 weeks.
  5. For children with no history of PPSV23 vaccination, administer PPSV23 at least 8 weeks after the most recent dose of PCV13.
- For children aged 6 through 18 years who have cerebrospinal fluid leak; cochlear implant; sickle cell
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For children aged 6 months through 8 years:

7. Inactivated poliovirus vaccine (IPV). (Minimum age: 6 weeks)

Routine vaccination:
- Administer a 4-dose series of IPV at ages 2, 4, 6 through 18 months, and 4 through 6 years. The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.

Catch-up vaccination:
- If the child is at risk for imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak), a single revaccination with IPV should be administered 5 years after the first dose to children with sickle cell disease or other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; generalized malignancy; solid organ transplantation; or multiple myeloma.

8. Measles, mumps, and rubella (MMR) vaccine. (Minimum age: 12 months for routine vaccination)

Routine vaccination:
- Administer a 2-dose series of MMR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.

- Administer 1 dose of MMR vaccine to infants aged 6 through 11 months before departure from the United States for international travel. These children should be revaccinated with 2 doses of MMR vaccine, the first at age 12 through 15 months (12 months if the child remains in an area where disease risk is high), and the second dose at least 4 weeks later.
10. Varicella (VAR) vaccine. (Minimum age: 12 months)
Routine vaccination:
- Administer a 2-dose series of VAR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.
Catch-up vaccination:
- Ensure that all persons aged 7 through 18 years without evidence of immunity (see MMWR 2007;56 [No. RR-4], available at http://www.cdc.gov/mmwr/pdf/rr/rr5604.pdf), have 2 doses of varicella vaccine. For children aged 7 through 12 years, the recommended minimum interval between doses is 3 months (if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid); for persons aged 13 years and older, the minimum interval between doses is 4 weeks.

11. Hepatitis A (HepA) vaccine. (Minimum age: 12 months)
Routine vaccination:
- Initiate the 2-dose HepA vaccine series at 12 through 23 months; separate the 2 doses by 6 to 18 months.
- Children who have received 1 dose of HepA vaccine before age 24 months should receive a second dose 6 to 18 months after the first dose.
- For any person aged 2 years and older who has not already received the HepA vaccine series, 2 doses of HepA vaccine separated by 6 to 18 months may be administered if immunity against hepatitis A virus infection is desired.
Catch-up vaccination:
- The minimum interval between the two doses is 6 months.
Special populations:
- Administer 2 doses of HepA vaccine at least 6 months apart to previously unvaccinated persons who live in areas where vaccination programs target older children, or who are at increased risk for infection. This includes persons traveling to or working in countries that have high or intermediate endemicity of infection; men having sex with men; users of injection and non-injection illicit drugs; persons who work with HAV-infected primates or with HAV in a research laboratory; persons with clotting-factor disorders; persons with chronic liver disease; and persons who anticipate close, personal contact (e.g., household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity. The first dose should be administered as soon as the adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.

12. Human papillomavirus (HPV) vaccines. (Minimum age: 9 years for HPV2 [Cervarix] and HPV4 [Gardasil])
Routine vaccination:
- Administer a 3-dose series of HPV vaccine on a schedule of 0, 1-2, and 6 months to all adolescents aged 11 through 12 years. Either HPV4 or HPV2 may be used for females, and only HPV4 may be used for males.
- The vaccine series may be started at age 9 years.
- Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks), administer the third dose 24 weeks after the first dose and 16 weeks after the second dose (minimum interval of 12 weeks).
Catch-up vaccination:
- Administer the vaccine series to females (either HPV2 or HPV4) and males (HPV4) at age 13 through 18 years if not previously vaccinated.
- Use recommended routine dosing intervals (see above) for vaccine series catch-up.

13. Meningococcal conjugate vaccines. (Minimum age: 6 weeks for Hib-MenCY [MenHibrix], 9 months for MenACWY-D [Menactra], 2 months for MenACWY-CRM [Menevo])
Routine vaccination:
- Administer a single dose of Menactra or Menevo vaccine at age 11 through 12 years, with a booster dose at age 16 years.
- Adolescents aged 11 through 18 years with human immunodeficiency virus (HIV) infection should receive a 2-dose primary series of Menactra or Menevo with at least 8 weeks between doses.
- For children aged 2 months through 18 years with high-risk conditions, see below.
Catch-up vaccination:
- Administer Menactra or Menevo vaccine at age 13 through 18 years if not previously vaccinated.
- If the first dose is administered at age 13 through 15 years, a booster dose should be administered at age 16 through 18 years with a minimum interval of at least 8 weeks between doses.
If the first dose is administered at age 16 years or older, a booster dose is not needed. For other catch-up guidance, see Catch-up Schedule.

**Vaccination of persons with high-risk conditions and other persons at increased risk of disease:**

- **Children with anatomic or functional asplenia (including sickle cell disease):**
  1. For children younger than 19 months of age, administer a 4-dose infant series of MenHibrix or Menveo at 2, 4, 6, and 12 through 15 months of age.
  2. For children aged 19 through 23 months who have not completed a series of MenHibrix or Menveo, administer 2 primary doses of Menveo at least 3 months apart.
  3. For children aged 24 months and older who have not received a complete series of MenHibrix or Menveo or Menactra, administer 2 primary doses of either Menactra or Menveo at least 2 months apart. If Menactra is administered to a child with asplenia (including sickle cell disease), do not administer Menactra until 2 years of age and at least 4 weeks after the completion of all PCV13 doses.

- **Children with persistent complement component deficiency:**
  1. For children younger than 19 months of age, administer a 4-dose infant series of either MenHibrix or Menveo at 2, 4, 6, and 12 through 15 months of age.
  2. For children 7 through 23 months who have not initiated vaccination, two options exist depending on age and vaccine brand:
     a. For children who initiate vaccination with Menveo at 7 months through 23 months of age, a 2-dose series should be administered with the second dose after 12 months of age and at least 3 months after the first dose.
     b. For children who initiate vaccination with Menactra at 9 months through 23 months of age, a 2-dose series of Menactra should be administered at least 3 months apart.
     c. For children aged 24 months and older who have not received a complete series of MenHibrix, Menveo, or Menactra, administer 2 primary doses of either Menactra or Menveo at least 2 months apart.

- **For children who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, including countries in the African meningitis belt or the Hajj, administer an age- and formulation-appropriate series of Menactra or Menveo for protection against serogroups A and W meningococcal disease. Prior receipt of MenHibrix is not sufficient for children traveling to the meningitis belt or the Hajj because it does not contain serogroups A or W.

- **For children at risk during a community outbreak attributable to a vaccine serogroup, administer or complete an age- and formulation-appropriate series of MenHibrix, Menactra, or Menveo.

- **For booster doses among persons with high-risk conditions, refer to MMWR 2013;62(RR02):1-22, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm**

**Catch-up recommendations for persons with high-risk conditions:**

1. If MenHibrix is administered to achieve protection against meningococcal disease, a complete age-appropriate series of MenHibrix should be administered.
2. If the first dose of MenHibrix is given at or after 12 months of age, a total of 2 doses should be given at least 8 weeks apart to ensure protection against serogroups C and Y meningococcal disease.
3. For children who initiate vaccination with Menveo at 7 months through 9 months of age, a 2-dose series should be administered with the second dose after 12 months of age and at least 3 months after the first dose.

For complete information on use of meningococcal vaccines, including guidance related to vaccination of persons at increased risk of infection, see MMWR March 22, 2013;62(RR02):1-22, available at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf

### II. PREVENTIVE PEDIATRIC HEALTH CARE RECOMMENDATIONS

#### 3. Childhood Immunization Schedule & Health Care

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Recommendations for Preventive Pediatric Health Care

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* = to be performed; • = risk assessment to be performed, with appropriate action to follow, if positive ← • → ≥ range during which a service may be provided.
1. If a child comes under care for the first time at any point on the schedule, or if any items are not accomplished at the suggested age, the schedule should be brought up to date at the earliest possible time.

2. A prenatal visit is recommended for parents who are at high risk, for first-time parents, and for those who request a conference. The prenatal visit should include anticipatory guidance, pertinent medical history, and a discussion of benefits of breastfeeding and planned method of feeding, per the 2009 AAP statement “The Prenatal Visit” (http://pediatrics.aappublications.org/content/124/4/1227.full).

3. Every infant should have a newborn evaluation after birth, and breastfeeding should be encouraged (and instruction and support should be offered).

4. Every infant should have an evaluation within 3 to 5 days of birth and within 48 to 72 hours after discharge from the hospital to include evaluation for feeding and jaundice. Breastfeeding infants should receive formal breastfeeding evaluation, and their mothers should receive encouragement and instruction, as recommended in the 2012 AAP statement “Breastfeeding and the Use of Human Milk” (http://pediatrics.aappublications.org/content/129/3/e482.full). Newborn infants discharged less than 48 hours after delivery must be examined within 48 hours of discharge, per the 2010 AAP statement “Hospital Stay for Healthy Term Newborns” (http://pediatrics.aappublications.org/content/125/2/405.full).


6. Blood pressure measurement in infants and children with specific risk conditions should be performed at visits before age 3 years.

7. If the patient is uncooperative, rescreen within 6 months, per the 2007 AAP statement “Eye Examination in Infants, Children, and Young Adults by Pediatricians” (http://pediatrics.aappublications.org/content/111/4/902.abstract).

8. All newborns should be screened, per the AAP statement “Year 2007 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs” (http://pediatrics.aappublications.org/content/120/4/898.full).


10. Screening should occur per the 2007 AAP statement “Identification and Evaluation of Children with Autism Spectrum Disorders” (http://pediatrics.aappublications.org/content/120/5/1183.full).


13. At each visit, age-appropriate physical examination is essential, with infant totally unclothed and older children undressed and suitably draped. See 2011 AAP statement “Use of Chaperones During the Physical Examination of the Pediatric Patient” (http://pediatrics.aappublications.org/content/127/5/991.full).

14. These may be modified, depending on entry point into schedule and individual need.

15. The Recommended Uniform Newborn Screening Panel (http://www.hrsa.gov/advisorycommittees/mchadvisory/heritabledisorders/recommendedpanel/uniformscreeningschedules.pdf), as determined by The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, and state newborn screening laws/ regulations (http://genes-r-us.uthscsa.edu/sites/genes-r-us/files/nbsdisorders.pdf), establish the criteria for and coverage of newborn screening procedures and programs. Follow-up must be provided, as appropriate, by the pediatrician.

16. Screening for critical congenital heart disease using pulse oximetry should be performed in newborns, after 24 hours of age, before discharge from the hospital, per the 2011 AAP statement “Endorsement of Health and Human Services Recommendation for Pulse Oximetry Screening for Critical Congenital Heart Disease” (http://pediatrics.aappublications.org/content/129/1/190.full).

17. Schedules, per the AAP Committee on Infectious Diseases, are available at: http://aapredbook.aappublications.org/site/resources/izschedules.xhtml. Every visit should be an opportunity to update and complete a child’s immunizations.

18. See 2010 AAP statement “Diagnosis and Prevention of Iron Deficiency and Iron Deficiency Anemia in Infants and Young Children (0-3 Years of Age)” (http://pediatrics.aappublications.org/content/126/5/1040.full).


20. Perform risk assessments or screenings as appropriate, based on universal screening requirements for patients with Medicaid or in high prevalence areas.


23. Adolescents should be screened for sexually transmitted infections (STIs) per recommendations in the current edition of the AAP Red Book: Report of the Committee on Infectious Diseases.
Additionally, all adolescents should be screened for HIV according to the AAP statement (http://pediatrics.aappublications.org/content/128/5/1023.full) once between the ages of 16 and 18, making every effort to preserve confidentiality of the adolescent. Those at increased risk of HIV infection, including those who are sexually active, participate in injection drug use, or are being tested for other STIs, should be tested for HIV and reassessed annually. 


25. Refer to a dental home, if available. If not available, perform a risk assessment (http://www2.aap.org/oralhealth/docs/RiskAssessmentTool.pdf). If primary water source is deficient in fluoride, consider oral fluoride supplementation. For those at high risk, consider application of fluoride varnish for caries prevention. See 2008 AAP statement “Preventive Oral Health Intervention for Pediatricians” (http://pediatrics.aappublications.org/content/122/6/1387.full) and 2009 AAP statement “Oral Health Risk Assessment Timing and Establishment of the Dental Home” (http://pediatrics.aappublications.org/content/111/5/1113.full).


III. FLUORIDE RECOMMENDATIONS
A. Approximately ⅔ of Americans do not benefit from fluoridated drinking water. These populations are at risk for greater incidences of tooth decay
B. Monitor intake of fluoride in children younger than 6 years of age because overuse can result in enamel fluorosis. Use pea-size amount of fluoride toothpaste in children < 6 years. Brushing with fluoride toothpaste should be limited to twice a day, and should be supervised to limit swallowing. Supplements are appropriate for children at high-risk for tooth decay (limited parental education, abuse or neglect victims, those not receiving regular dental care, consumption of high quantities of sugars, use of orthodontic appliances)

IV. LEAD-SCREENING RECOMMENDATIONS
A. Strong association exists between blood lead levels and intellectual function in children
B. Primary prevention: Anticipatory guidance for parents regarding minimizing exposure to lead-based paint chips, dust, soil. Discuss importance of dietary iron to prevent absorption of environmental lead
C. Secondary prevention: Begin at 9–12 months, consider again at 24 months
   1. Targeted screening for at-risk communities and through risk-assessment questionnaires:
      a. Does your child live in or regularly visit a house or child-care facility built before 1950?
      b. Does your child live in or visit a house or child-care facility built before 1978 that is being or has recently been renovated or remodeled?
      c. Does your child have a sibling or playmate who has or did have lead poisoning?
   2. Other populations in which to consider screening: Immigrants from countries with high levels of lead poisoning, iron-deficiency anemia, developmental delay +/- pica, abuse or neglect victims, parental exposure to lead at work, low-income families receiving government assistance
   3. Screening: Venous samples preferable, but finger stick okay if collected correctly
   4. Elevated Blood Lead Levels (BLL): Always obtain confirmatory sample!
      a. BLL 10–14 mcg/dL: General education on reducing environmental lead exposure, repeat BLL in 3 months
      b. BLL 15–19 mcg/dL: Careful environmental history, optimal nutrition including iron and calcium supplementation, frequent small meals to decrease absorption of lead, repeat BLL within 2 months
      c. BLL > 20 mcg/dL: Obtain confirmatory test within 1 week, thorough environmental/nutritional assessment, probable referral to local health department, referral to specialist in lead toxicity therapy/chelation therapy
      d. BLL > 70 mcg/dL: Hospitalize patient, chelation therapy

References
Advisory Committee on Immunization Practices Recommended Immunization Schedules for Persons Aged 0 Through 18 Years—United States, 2014. MMWR February 7, 2014;
4. INFANT FORMULA & BREAST-FEEDING

I. BREAST MILK: The Gold standard of infant nutrition; mothers can nurse up to 4–6 months without supplementing solids

A. Goals: Healthy People 2010 has a goal of having 75% of all mothers initiate breast-feeding and 50% continue breast-feeding at 6 months and 25% breast-feeding at 1 year

B. Benefits of breast-feeding

1. There is no better nutrition for the baby than breast milk. The calorific and nutritional content of the breast milk changes as the baby ages, providing the optimal nutrition for the infant. The nutrients in breast milk are easier to assimilate than those in formula because breast milk is easier to digest

2. Mothers who breast-feed reduce their risks of getting ovarian and breast cancer

3. Breast-feeding utilizes calories (~200 kcal/day) and may help the mother regain her pre-pregnancy weight. A higher caloric intake is required for lactation

4. Breast-feeding is convenient and saves money

5. Enhanced maternal-infant bonding

6. The early breast milk, colostrum, provides antibodies to the infant, decreasing the infant’s incidence of upper respiratory infections, diarrheal illnesses and otitis media in the first year of the child’s life

7. Exclusively breast-feeding the infant for at least 3 months reduces the risk of Type 1 Diabetes Mellitus

8. Breast-fed infants are less likely to develop food allergies, because the breast-milk antibodies prevent the absorption of allergy-provoking proteins

9. Colostrum has a laxative effect assisting with the early evacuation of meconium

10. Exclusive breast-feeding may be an effective birth control method for several months after delivery, although this should not be relied upon

C. Common breast-feeding problems

1. Breast engorgement
   a. Often occurs for the first time when the milk comes in, usually the second or third postpartum day. Can occur at any time when the mother has not breast-fed or pumped her breasts
   b. To decrease engorgement, the mother should pump or express her breasts to release some of the excess milk build-up. Warm compresses or a hot shower can help the milk let-down. Frequent nursing during this stage is important

2. Mastitis
   a. Initially women may experience flu-like symptoms with myalgias, fevers, and chills. One of the breasts then becomes erythematous, tender, and edematous in a particular area
   b. Management
      i. Frequent breast-feedings (with both breasts being utilized), rest, plenty of fluids, acetaminophen
      ii. Warm compresses to the affected breast for pain relief
      iii. ATBs: For the most common mastitis-causing organisms, staphylococcus and streptococcus, use Cephalexin (Keflex) 500mg PO QID or Amoxicillin/Clavulanate 875mg BID. Clindamycin 300mg QID may be used for Penicillin/Cephalexin-allergic patients. Clindamycin is also effective against methicillin-resistant staphylococcus aureus. Duration of treatment is 10–14 days
4. Infant Formula & Breast-Feeding

Care of Children

**c. Bilateral mastitis:** Rare and may be a sign of a Group B Streptococcal infection which has been transmitted to the mother from the infant. (This is a serious infection and would require immediate treatment of the infant and the mother)

3. Yeast infections: If the infant develops thrush, it may transmit the infection to the mother and she may develop “thrush nipples”

   a. The symptoms of “thrush nipples” are erythematous, edematous, cracked, painful nipples. Both the infant and the mother need to be treated
   
   b. The infant is given **Nystatin Oral Suspension** (100,000 u/mL) 1mL PO QID for 2 weeks given after nursing
   
   c. The mother should apply an anti-fungal ointment (Micatin) after nursing (see Chapter 101, Warts, Scabies, Lice & Superficial Tinea Infection Management)

4. Breast abscess

   a. Rare complication of mastitis
   
   b. Treatment: Incision and drainage

5. Cracked or bleeding nipples

   a. Can occur at any time during the nursing process. Prevention is important
   
   b. Infant needs to be properly positioned on the breast
   
   c. Daily shower or bath with warm water is sufficient to keep the breasts clean. Soaps and detergents should not be used on the breasts since they are drying to the skin. Breast creams are unnecessary and may actually cause sore nipples
   
   d. Breast milk that is left on the breast after nursing may be gently rubbed on the nipples
   
   e. Plastic-lined breast pads and wet breast shields should be avoided
   
   f. The mother should invest in several good cotton nursing bras that provide support but are not constricting. Bras that are too tight may lead to blocked ducts

6. Galactocele: Blocked lactiferous duct

   a. Round, well circumscribed, easily mobile cystic mass
   
   b. Treatment: Initially warm compresses and frequent feedings or pumping to open and drain blocked duct. Often needs needle aspiration. Thick milky secretion confirms diagnosis

**D. Nursing frequency**

1. Initially the infant should breast-feed frequently, usually 8–15 feedings in a 24 hr period

2. The infant can be kept on the first breast until interest lost in feeding (usually 10–20 minutes). Then remove from that breast, burp, and place on the second breast. May not feed as long on the second breast. Because of this, should alternate breasts with subsequent feedings

3. Breast-feeding works on a supply-and-demand basis. The more an infant feeds, the more milk the breasts will produce. It is important the infant nurse frequently and for as long as desired so that an adequate milk supply will be produced

4. Supplementation is not necessary and may hinder the establishment of a good breast-feeding relationship

**E. Vitamin supplementation**

1. Vitamin D

   a. According to the 2008 AAP guidelines, all infants and children, including adolescents, should have a minimum daily intake of 400 IU of Vitamin D. Deficiency/insufficiency and rickets have increased due to decreased sunlight exposure (sunscreen, lifestyle changes, dress habits)

   b. Breastfed and partially breastfed infants should be supplemented with 400 IU/day of Vitamin D beginning in the first few days unless the infant is waned to at least 1L/day or 1 qt/day of Vitamin D-fortified formula

   c. Most multivitamin liquid preparations contain Vitamin D 400 IU/1 mL dose

2. Iron

   a. There is debate about when iron supplementation should be done

   b. The term newborn has about a 4 month store of iron accumulated during gestation. At 4 months of age the physician needs to decide if the infant needs iron supplementation or if the infant is eating enough iron-fortified cereal to meet iron needs

   c. The preterm infant should receive supplementation starting at birth

3. Fluoride (F): If a child’s home receives commercially fluoridated water or the family’s well water has > 0.6 ppm F, no systemic supplementation should be given. Systemic supplementation is also not recommended if the child is breastfeeding. If a child
receives water from a nonfluoridated source or a well with < 0.6 ppm F, supplementation should begin with the following dosage guidelines:

a. < 0.3 ppm in water: 0.25 mg F/day for 6 months–3 years of age; 0.50 mg F/day for 3–6 years of age; 1.0 mg F/day for 6–16 years of age

b. 0.3–0.6 ppm in water: none for 6 months–3 years of age; 0.25 mg F/day for 3–6 years of age; 0.50 mg F/day for 6–16 years of age

F. Medications and lactation: See Chapter 22, Medications During Pregnancy & Lactation

II. STANDARD MILK-BASED FORMULA: First line formula

Nutrient profile resembles human milk, heat-treated for easier digesting and to lower allergic potential. Begin with formula containing iron

A. Carbohydrate: Lactose
B. Protein: Whey, casein
C. Fat: Soy, corn, coconut, safflower, or palm olein oils

Formula Available: Advance, Carnation, Gerber, Good Start, Enfamil, Similac, SMA

III. SOY FORMULAS: Second line formula

For infants with cow milk protein allergies or lactose intolerant. Begin with formula containing iron

A. Carbohydrate: Sucrose or corn syrup
B. Protein: Soy, L-methionine, L-carnitine, taurine
C. Fat: Soy, corn, coconut, oleo, or safflower oils

Formula available: Isomil, Isomil SF (sucrose-free), Nursoy, ProSobee (sucrose-free)

IV. SPECIAL NUTRITIONAL NEEDS

A. Alimentum: For infants with problems with digestion or absorption; hypoallergenic
B. Nutramigen: Lactose and sucrose free; hypoallergenic
C. Portagen: For infants who have difficulty digesting fats
D. Pregestimil: For infants with malabsorption problems, allergies, intractable diarrhea, short-gut syndrome, or cystic fibrosis

V. FEEDING SCHEDULES

Formula-fed infants should eat 5–6 ounces of formula/kg/day (see chart). Solid foods (cereals) can safely be started at 4–6 months

<table>
<thead>
<tr>
<th>AGE</th>
<th>Number</th>
<th>Volume per feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth – 1 week</td>
<td>6 – 10</td>
<td>1 – 3 oz</td>
</tr>
<tr>
<td>1 week – 1 month</td>
<td>7 – 8</td>
<td>2 – 4 oz</td>
</tr>
<tr>
<td>1 month – 3 months</td>
<td>5 – 7</td>
<td>4 – 6 oz</td>
</tr>
<tr>
<td>3 months – 6 months</td>
<td>4 – 5</td>
<td>6 – 7 oz</td>
</tr>
<tr>
<td>6 months – 9 months</td>
<td>3 – 4</td>
<td>7 – 8 oz</td>
</tr>
<tr>
<td>10 months – 12 months</td>
<td>3</td>
<td>7 – 8 oz</td>
</tr>
</tbody>
</table>

CLINICAL PEARLS

* Infants should not receive cow’s milk prior to 1 year of age secondary to increase risk of occult GI bleeding and subsequent anemia
* Roughly 50% of all mothers initiate breast-feeding. 25% quit within first month and only 25% continue until 5 months or more

References


Duijts L, Jaddoe VW, Hofman A, Moll HA. Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy. Pediatrics. 2010;126(1). Available at: www.pediatrics.org/cgi/content/full/126/1/e1

5. Hyperbilirubinemia in the Newborn

I. INTRODUCTION
A. Jaundice occurs in most newborns and is usually benign
B. The risk of severe hyperbilirubinemia is acute bilirubin encephalopathy (preferred term). Previously called kernicterus
C. This chapter will focus on newborn infants 35 or more weeks of gestation and is a summary of the most recent guidelines from the American Academy of Pediatrics (AAP)
D. 4 main principles:
   1. Promote breastfeeding
   2. Assess newborns before hospital discharge for risk of severe hyperbilirubinemia
   3. Provide early follow-up based on risk assessment
   4. Treat newborns with phototherapy or exchange transfusion when indicated

II. MAJOR RISK FACTORS FOR SEVERE HYPERBILIRUBINEMIA
A. Total serum bilirubin (TSB) level above 8mg/dL at 24 hrs or 13mg/dL at 48 hrs
B. Observed jaundice in first 24 hrs
C. Blood group incompatibility with positive direct antiglobulin test
D. Gestational age less than 36 weeks
E. Sibling who needed phototherapy or exchange transfusion
F. Cephalohematoma or significant bruising
G. Exclusive breastfeeding
H. Minor risk factors:
   1. TSB level above 6mg/dL at 24 hrs or 8.5mg/dL at 48 hrs
   2. Gestational age 37–38 weeks
   3. Jaundice seen before hospital discharge
   4. Sibling with jaundice
   5. Macrosomic infant of diabetic mother
   6. Maternal age over 25 years
   7. Male gender

III. ASSESSMENT FOR JAUNDICE
A. In well lighted room, blanch the skin with digital pressure to see the color of the underlying skin and tissue. Skin should appear jaundiced with bilirubin levels > 4mg/dL
B. Dermal icterus progresses in a cephalocaudal direction. Jaundice which is not evident below the nipple line is very unlikely to be above 12mg/dL. Jaundice which is below the nipple line may be above or below 12mg/dL

IV. ACTION PLAN FOR PHOTOTHERAPY (Note: Risk factors: Isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, albumin < 3g/dL)
A. At 24–48 hours
   1. If infant is high risk (35–37 weeks plus risk factors) and total serum bilirubin (TSB) is over 8–11
   2. If infant is medium risk (over 38 weeks plus risk factors or 35–37 weeks and well) consider phototherapy if TSB over 10–13
   3. If infant is lower risk (gestation age over 38 weeks and well) consider phototherapy if TSB above 12–15
B. At 48–96 hours
   1. If infant is high risk (35–37 weeks plus risk factors) and total serum bilirubin (TSB)
is over 11–14.5
2. If infant is medium risk (over 38 weeks plus risk factors or 35–37 weeks and well) consider phototherapy if TSB over 13–17
3. If infant is lower risk (gestation age over 38 weeks and well) consider phototherapy if TSB above 15–20

C. Over 96 hours to 7 days
1. If infant is high risk (35–37 weeks plus risk factors) and total serum bilirubin (TSB) is over 11–14.5
2. If infant is medium risk (over 38 weeks plus risk factors or 35–37 weeks and well) consider phototherapy if TSB over 13–17
3. If infant is lower risk (gestation age over 38 weeks and well) consider phototherapy if TSB above 15–20

V. ACTION PLAN FOR EXCHANGE TRANSFUSION
Absolute indications include signs of acute bilirubin encephalopathy including hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry—or—

A. At 24–48 hours
1. If infant is high risk (35–37 weeks plus risk factors) and total serum bilirubin (TSB) is over 15–17
2. If infant is medium risk (over 38 weeks plus risk factors or 35–37 weeks and well) consider phototherapy if TSB over 16–19
3. If infant is lower risk (gestation age over 38 weeks and well) consider phototherapy if TSB above 19–22

B. At 48–96 hours
1. If infant is high risk (35–37 weeks plus risk factors) and total serum bilirubin (TSB) is over 17–19 consider phototherapy
2. If infant is medium risk (over 38 weeks plus risk factors or 35–37 weeks and well) consider phototherapy if TSB over 19–22
3. If infant is lower risk (gestation age over 38 weeks and well) consider phototherapy if TSB above 22–25

C. Over 96 hours to 7 days
1. If infant is high risk (35–37 weeks plus risk factors) and total serum bilirubin (TSB) is over 19 consider phototherapy
2. If infant is medium risk (over 38 weeks plus risk factors or 35–37 weeks and well) consider phototherapy if TSB over 22
3. If infant is lower risk (gestation age over 38 weeks and well) consider phototherapy if TSB above 25

Note: Risk factors: Isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, albumin < 3g/dL
Note: If infants exceed these levels, this constitutes a medical emergency and patient should be directly admitted to pediatric service and not go to the emergency department (delays initiation of treatment)

VI. PHOTOTHERAPY
A. Irradiance in blue-green spectrum at wavelengths 430–490nm
B. Other labs, including repeat TSB levels, blood type, antibody test (Coombs’), G6PD, CBC, reticulocyte count, serum albumin, others per protocol

CLINICAL PEARLS
• Jaundice is usually a benign, self-limited condition that can be managed with close observation and reassurance
• Levels of bilirubin considered safe in healthy full-term infants may be pathologic in the sick or premature infant
• Sunlight was originally described as a way to lower TSB level, but practical difficulties with exposing a naked newborn to sun while avoiding sunburn preclude its use. Sunlight is not recommended for elevated bilirubin levels
• Excessive fluid administration does not affect TSB levels
• Continue breast feeding if infant requires phototherapy

References
6. FEVER WITHOUT A SOURCE IN INFANTS

0–36 MONTHS OF AGE (FEBRILE INFANT & TODDLER)

DEFINITION: An acute febrile illness in which the etiology of the fever is not apparent after a careful history and physical exam

- Fever is defined as rectal temperature $\geq 100.4^\circ$ F (38.0$^\circ$ C)—axillary, oral, and tympanic temperature are not as reliable
- Concern for the possibility of occult bacteremia or underlying sepsis occurs in infants 0–90 days old with temperature $>100.4^\circ$ F and in infants 3–36 months of age with a temperature $>102.2^\circ$ F (39.0$^\circ$ C)
- A finding of otitis media on exam should not be considered a cause of fever in this age group; the incidence or bacteremia does not differ significantly in febrile infants and young children with or without otitis media
- This chapter assumes children 3–6 months of age do not have an obvious source of infection after careful history and physical exam. This chapter also assumes the children are low risk patients (no history of chronic or immunosuppressive illness, prematurity, unvaccinated) and do not appear toxic or septic. If toxic or septic appearing, then immediately refer child to the emergency department for full evaluation
- Response to antipyretic medication does not lower risk of serious bacterial infection

I. GENERAL INFORMATION—WHY THE CONCERN

A. Children with fever without source may have occult bacteremia which can lead to more significant sequelae

B. Incidence of occult bacteremia among well appearing children 3–36 months of age is about 1–2%
   1. Of those, approximately 17% are found to have focal infection (pneumonia, cellulitis, UTI, osteomyelitis, etc.) and about 1.7% are found to have meningitis or sepsis, the most serious sequelae
   2. Summary: Of children 3–36 months of age with fever without source, 0.3% will develop significant sequelae and 0.03% will develop meningitis or sepsis (the most serious sequelae)

C. Prevalence of UTI in children 2 months to 2 years of age with fever without source is 3–8% (girls > boys). Symptoms of UTI are nonspecific and may include vomiting, diarrhea, irritability, and poor feeding. Risk of untreated UTI is renal scarring and subsequent risk of HTN and renal failure. The best way to check for a UTI is with a specimen obtained by urinary catheter

D. Known chronic illness (leukemia, sickle cell, HIV, congenital heart anomalies) places the infant in high-risk category and requires more aggressive therapy—see III. B.)

E. Recent ATB therapy may alter manifestation of serious bacterial infection, e.g., meningitis

F. Day-care attendance may place infant at increased risk for invasive pneumococcal infection. Ask if the infant has received the pneumococcal vaccine

II. FEVER WITHOUT A SOURCE < 28 DAYS

Temperature $>100.4^\circ$ F (Approximately 10% will harbor a serious bacterial infection)

A. Risk factors: Prematurity, premature rupture of membranes (>18hrs), chorioamnionitis, maternal fever, maternal UTI, twin pregnancy, meconium aspiration

B. Signs and symptoms of bacteremia or focal serious infection: Temperature instability, respiratory distress, lethargy, poor feeding, jaundice, diarrhea, tachycardia, seizures, skin rash, parental concern
C. Management: Requires hospital admission including CBC with differential, blood culture, UA and urine culture, lumbar puncture and chest x-ray. If diarrhea present, obtain stool culture and fecal WBC count. Begin empiric parenteral antibiotics after cultures have been obtained: Ampicillin plus Gentamicin (preferred regimen) or Ampicillin plus Cefotaxime (alternate regimen)

III. FEVER WITHOUT A SOURCE 3–36 MONTHS
A. Low Risk Infants
1. If child appears well, no diagnostic tests or ATBs are necessary; Tylenol (15mg/kg) and/or Ibuprofen (10mg/kg) may be given PRN fever; parents should be instructed to return if fever persists > 48hrs or patient’s condition worsens
2. Consider:
   a. Urine testing—cath specimen is best. See above (item I) for prevalence and symptoms of UTI in children. Obtain urinalysis and culture (see Chapter 15, Urinary Tract Infections in Children for indications for further testing after diagnosis of UTI). Culture should be done as up to 15% have UTI but no pyuria or nitrites
   b. Stool culture if blood or mucus in stool or ≥ 5 WBCs/hpf in stool
   c. Chest x-ray if dyspnea, tachypnea, rales, or decreased breath sounds are present
3. Antibiotics—In the past, it was recommended to obtain a WBC count and then give Ceftriaxone (Rocephin) if > 15,000/mm³, but since introduction of Hib and pneumococcal vaccines, incidence of occult bacteremia has plummeted
   a. If child has an obvious viral infection, incidence of bacteremia is 0.2% and no further evaluation is necessary
   b. If child has been immunized against pneumococcus (vaccine was introduced in the US in 2000), many would not pursue further evaluation in a well, interactive, active child
   c. If child has not been immunized against pneumococcus, extra caution and close follow-up are necessary
B. High risk infants—Evaluate in emergency department

CLINICAL PEARLS
- Risk of bacteremia rises as temperature rises, T > 105.6º F (40.9º C) is about 3 times more likely to harbor bacteremia than infant or child with T of 102.2º F (39º C)
- For all febrile neonates < 28 days, a lumbar puncture is recommended. A lumbar puncture is not needed unless neurologic signs are present for febrile children 3 to 36 months
- In febrile children older than 28 days, a chest x-ray is indicated if WBC > 20,000/mm³ or by clinical symptoms
- Urinalysis and urine culture are recommended for all febrile infants 24 months or younger with unexplained fever
- Follow up remains very important; clinical course remains the most sensitive indicator of serious illness

References
I. DEFINITION: Chronic inflammatory disease causing airway hyper-responsiveness, airflow limitation and persistent respiratory symptoms which are usually reversible, either spontaneously or with therapy

II. EPIDEMIOLOGY AND EFFECTS OF ASTHMA ON CHILDREN
A. Approximately 9.5% of children currently have asthma, i.e., 7.1 million of the children in the US (2011 CDC statistics)
B. More severe disability and more frequent hospitalizations in black children than in white children
C. Over the last decade, there has been a 29% increase in prevalence, 43% increase in hospitalization rate, and 46% increase in death rate
D. About 50% of children with asthma miss school because of the disease
E. Uncontrolled childhood asthma can produce permanent damage to the child’s respiratory system

III. HISTORY
A. Symptoms: Episodic or chronic cough, shortness of breath, wheeze or cough with exertion. Symptoms are often worse during the evening or early morning hours
B. Other: Allergies, family history of asthma or allergy, perinatal exposure to tobacco smoke, viral URI history, low birth weight

IV. PHYSICAL EXAM: Enlarged turbinates, rhinitis, nasal polyps, wheezing, increased respiratory effort, use of accessory muscles, eczema/atopic dermatitis. Note: Children with a clear lung exam in the office can still be symptomatic at night or with exertion

V. DIFFERENTIAL DIAGNOSIS
A. Obstruction of large airways—foreign body, congenital
B. Obstruction of large and small airways—infection (bronchiolitis and chlamydia), cystic fibrosis, bronchopulmonary dysplasia

VI. EVALUATION (Individualized)
A. CXR: May show hyperinflation
B. Pulmonary function tests: Pre- and post-bronchodilator spirometry. Post-bronchodilator assessment should be done 15–20 minutes after inhalation of a short-acting bronchodilator. Patients with asthma have a variable airflow obstruction (20% or more) with serial spirometry or peak-flow measurements, and an increase in forced expiratory volume in 1 second (FEV₁) of 12% or more after bronchodilator therapy
C. Peak expiratory flow meter: Increase patient and caregiver awareness of disease status. Highest of 3 peak flow measurements is recorded (patient must exhale as hard and fast as possible). Measurements can be compared to norms for height and weight, and compared to patient’s baseline when asymptomatic
### VII. MANAGEMENT OF CHRONIC ASTHMA

<table>
<thead>
<tr>
<th>TABLE 1: STEPWISE APPROACH</th>
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</thead>
</table>

#### Children 0–4 Years of Age

- **Step 1:** Quick Relief Medication
  - SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms.
  - With viral respiratory symptoms: SABA Q 4–6 hrs up to 24 hrs (longer with physician consult. Consider short course of oral systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations.
  - Caution: Frequent use of SABA may indicate the need to step up treatment. See text for recommendations on initiating daily long-term therapy.

- **Step 2:** Intermittent Asthma
  - Consult with asthma specialist if step 3 care or higher is required. Consider consultation at step 2.
  - Preferred: SABA PRN Low-dose ICS
  - Alternative: Cromolyn or Montelukast

- **Step 3:** Persistent Asthma: Daily Medication
  - Consult with asthma specialist if step 4 care or higher is required.
  - Preferred: SABA PRN Medium-dose ICS + LABA or Montelukast
  - Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

- **Step 4:** High-dose ICS + LABA or Montelukast

- **Step 5:** Oral corticosteroids

- **Step 6:** Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.

#### Children 5–11 Years of Age

- **Step 1:** Quick Relief Medication
  - SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed.
  - Short course of oral systemic corticosteroids may be needed.
  - Caution: Increasing use of SABA or use > 2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

- **Step 2:** Intermittent Asthma
  - Consult with asthma specialist if step 3 care or higher is required.
  - Preferred: SABA PRN Low-dose ICS Low-dose ICS + LABA, LTRA or Theophylline OR Medium-dose ICS
  - Alternative: Cromolyn, LTRA, or Theophylline

- **Step 3:** Persistent Asthma: Daily Medication
  - Consult with asthma specialist if step 4 care or higher is required.
  - Preferred: Medium-dose ICS + LABA
  - Alternative: Medium-dose ICS + LTRA or Theophylline

- **Step 4:** High-dose ICS + LTRA or Theophylline

- **Step 5:** Oral corticosteroids

**Key:** Alphabetical listing is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, inhaled corticosteroid; LABA, inhaled long-acting beta2 agonist; LTRA, leukotriene receptor antagonist; oral corticosteroids, oral systemic corticosteroids; SABA, inhaled short-acting beta2 agonist.

**Notes to Children 0–4 Years of Age**
- The stepwise approach is meant to assist, not replace, clinical decision making required to meet individual patient needs.
- If an alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4–6 weeks, and patient’s/family’s medication technique and adherence are satisfactory, consider adjusting therapy or an alternative diagnosis.
- Studies on children 0–4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.
- Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

**Notes to Children 5–11 Years of Age**
- The stepwise approach is meant to assist, not replace, clinical decision making required to meet individual patient needs.
- If an alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
7. Asthma in Children

- Steps 1 and 2 medications are based on Evidence A. Step 3 ICS and ICS plus adjunctive therapy are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; steps 4-6 are based on expert opinion and extrapolation from studies in older children and adults.
- Immunotherapy for steps 2-4 is based on Evidence B for housedust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than adults.
- Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

Key: Alphabetical listing is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, inhaled corticosteroid; LABA, inhaled long-acting beta2 agonist; LTRA, leukotriene receptor antagonist; oral corticosteroids, oral systemic corticosteroids; SABA, inhaled short-acting beta, agonist.


TABLE 2: MEDICATION FOR LONG-TERM TREATMENT

<table>
<thead>
<tr>
<th>Usual Dosages for Long-Term Control Medications*</th>
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<tbody>
<tr>
<td><strong>Medication</strong></td>
</tr>
<tr>
<td>Inhaled Corticosteroids (See Table 3, Estimated Comparative Daily Dosages for ICSs.)</td>
</tr>
<tr>
<td><strong>Oral Systemic Corticosteroids</strong> (Apply to all three corticosteroids.)</td>
</tr>
<tr>
<td>Methylprednisolone</td>
</tr>
<tr>
<td>2, 4, 8, 16, 32 mg tablets</td>
</tr>
<tr>
<td>5 mg tablets, 5 mg/5 cc, 15 mg/5 cc</td>
</tr>
<tr>
<td>Prednisolone</td>
</tr>
<tr>
<td>5 mg tablets</td>
</tr>
<tr>
<td>1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/5 cc, 5 mg/5 cc</td>
</tr>
<tr>
<td>Prednisone</td>
</tr>
<tr>
<td>1 capsule</td>
</tr>
<tr>
<td>1 blister</td>
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<tr>
<td>12 hours</td>
</tr>
<tr>
<td>Inhaled Long-Acting Beta2-Agonists (LABAs) (Apply to both LABAs.)</td>
</tr>
<tr>
<td>Salmeterol</td>
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<tr>
<td>DPI 50 mcg/ blister</td>
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<tr>
<td>Formoterol</td>
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<tr>
<td>DPI 12 mcg/single-use capsule</td>
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<td></td>
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<tr>
<td>Key: DPI, dry powder inhaler; EIB, exercise-induced bronchospasm; HFA, hydrofluoroalkane; ICS, inhaled corticosteroids; IgE, immunoglobulin E; MDI, metered-dose inhaler; NA, not available (either not approved, no data available, or safety and efficacy not established for this age group); SABA, short-acting beta2 agonist</td>
</tr>
<tr>
<td>*Note: Dosages are provided for those products that have been approved by the U.S. Food and Drug Administration or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.</td>
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(Chart continued on next page)
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<tr>
<th>Medication</th>
<th>0–4 Years of Age</th>
<th>5–11 Years of Age</th>
<th>Potential Adverse Effects</th>
<th>Comments (not all inclusive)</th>
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<tr>
<td>Combined Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone/Salmeterol</td>
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<tr>
<td>DPI 100 mcg/50 mcg, 250 mcg/50 mcg, or 500 mcg/50 mcg</td>
<td>NA</td>
<td>1 inhalation bid, dose depends on level of severity or control</td>
<td>● See notes for ICS and LABA.</td>
<td>● There have been no clinical trials in children &lt;4 years of age. ● Most children &lt;4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery. ● Do not blow into inhaler after dose is activated. ● 100/50 DPI or 45/21 HFA for patients who have asthma not controlled on low- to medium-dose ICS. ● 250/50 DPI or 115/21 HFA for patients who have asthma not controlled on medium to high dose ICS.</td>
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<tr>
<td>DPI 115 mcg/21 mcg, 230 mcg/21 mcg</td>
<td>NA</td>
<td>2 puffs bid, dose depends on level of severity or control</td>
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<tr>
<td>HFA 45 mcg/21 mcg</td>
<td>NA</td>
<td>1 ampule bid, dose depends on level of severity or control</td>
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<tr>
<td>HFA 115 mcg/21 mcg</td>
<td>NA</td>
<td>1 ampule bid, dose depends on level of severity or control</td>
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<tr>
<td>HFA 230 mcg/21 mcg</td>
<td>NA</td>
<td>1 ampule bid, dose depends on level of severity or control</td>
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<tr>
<td>Budesonide/Formoterol</td>
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<tr>
<td>HFA MDI 80 mcg/4.5 mcg</td>
<td>NA</td>
<td>2 puffs qid, dose depends on level of severity or control</td>
<td>See notes for ICS and LABA.</td>
<td>● There have been no clinical trials in children &lt;4 years of age. ● Currently approved for use in youths ≥12 years of age. Dose for children 5–12 years of age based on clinical trials using DPI with slightly different delivery characteristics. ● 80/4.5 for patients who have asthma not controlled on low- to medium-dose ICS. ● 160/4.5 for patients who have asthma not controlled on medium- to high-dose ICS.</td>
</tr>
<tr>
<td>HFA MDI 160 mcg/4.5 mcg</td>
<td>NA</td>
<td>2 puffs qid, dose depends on level of severity or control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cromoly/Nedocromil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cromolyn</td>
<td>MDI 0.8 mg/puff</td>
<td>NA</td>
<td>2 puffs qid</td>
<td>Cough and irritation; 15–20% of patients complain of an unpleasant taste from nedocromil. Safety is the primary advantage of these.</td>
</tr>
<tr>
<td>Nebulizer 20 mg/ampule</td>
<td>1 ampule qid NA &lt;2 years of age</td>
<td>1 ampule qid NA &lt;2 years of age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nedocromil</td>
<td>MDI 1.75 mg/puff</td>
<td>NA &lt;6 years of age</td>
<td>2 puffs qid</td>
<td></td>
</tr>
<tr>
<td>Immunomodulators</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omalizumab (Anti IgE)</td>
<td>Subcutaneous injection, 150 mg/1.2 mL following reconstitution with 1.4 mL sterile water for injection</td>
<td>NA</td>
<td>NA</td>
<td>Pain and bruising of injection sites in 5–20% of patients. Anaphylaxis has been reported in 0.2% of treated patients. Malignant neoplasms were reported in 0.5% of patients compared to 0.2% receiving placebo; relationship to drug is unclear.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Do not administer more than 150 mg per injection site. Monitor patients following injections; be prepared and equipped to identify and treat anaphylaxis that may occur. Whether patients will develop significant antibody titers to the drug with long-term administration is unknown.</td>
</tr>
</tbody>
</table>

Key: DPI, dry powder inhaler; EIB, exercise-induced bronchoconstriction; HFA, hydrofluoroalkane; ICS, inhaled corticosteroids; IgE, immunoglobulin E; MDI, metered-dose inhaler; NA, not available (either not approved, no data available, or safety and efficacy not established for this age group); SABA, short-acting beta, agonist

*Note: Dosages are provided for those products that have been approved by the U.S. Food and Drug Administration or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.

(Chart continued on next page)
### Usual Dosages for Long-Term Control Medications* (continued)

<table>
<thead>
<tr>
<th>Medication</th>
<th>0–4 Years of Age</th>
<th>5–11 Years of Age</th>
<th>Potential Adverse Effects</th>
<th>Comments (not all inclusive)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leukotriene Modifiers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukotriene Receptor Antagonists (LTRAs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montelukast</td>
<td></td>
<td></td>
<td>No specific adverse effects have been identified.</td>
<td>Montelukast exhibits a flat dose-response curve. Doses &gt;10 mg will not produce a greater response in adults.</td>
</tr>
<tr>
<td>- 4 mg or 5 mg</td>
<td>4 mg qhs (1–5 years of age)</td>
<td>5 mg qhs (6–14 years of age)</td>
<td>Rare cases of Churg-Strauss have occurred, but the association is unclear.</td>
<td>No more efficacious than placebo in infants ages 6–24 months. As long-term therapy may attenuate exercise-induced bronchospasm in some patients, but less effective than ICS therapy.</td>
</tr>
<tr>
<td>chewable tablet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 4 mg granule packets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 10 mg tablet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>NA</td>
<td>10 mg bid (7–11 years of age)</td>
<td>Postmarketing surveillance has reported cases of reversible hepatitis and, rarely, irreversible hepatic failure resulting in death and liver transplantation.</td>
<td>For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. Zafirlukast is a microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin. Doses of these drugs should be monitored accordingly. Monitor hepatic enzymes (ALT). Warn patients to discontinue use if they experience signs and symptoms of liver dysfunction. For zileuton, monitor hepatic enzymes (ALT).</td>
</tr>
<tr>
<td>- 10 mg tablet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 20 mg tablet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Lipoxygenase Inhibitor</td>
<td>NA</td>
<td>NA</td>
<td>Elevation of liver enzymes has been reported. Limited case reports of reversible hepatitis and hyperbilirubinemia.</td>
<td>For zileuton, monitor hepatic enzymes (ALT). Zileuton is a microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin and theophylline. Doses of these drugs should be monitored accordingly.</td>
</tr>
<tr>
<td>Zileuton</td>
<td>600 mg tablet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Methylxanthines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
<td></td>
<td>Dose-related acute toxicities include tachycardia, nausea and vomiting, tachyarrhythmias (SVT), central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia, and hypokalemia.</td>
<td>Adjust dosage to achieve serum concentration of 5–15 mcg/mL at steady state (at least 48 hours on same dosage). Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is essential. Patients should be told to discontinue if they experience toxicity. Various factors (diet, food, febrile illness, age, smoking, and other medications) can affect serum concentrations. See EPR—3 Full Report 2007 and package inserts for details.</td>
</tr>
<tr>
<td>Liquids, sustained-release tablets, and capsules</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Starting dose 10 mg/kg/day; usual maximum:</td>
<td></td>
<td></td>
<td>Dose-related acute toxicities include insomnia, gastric upset, aggravation of ulcer or reflux, increase in hyperactivity in some children, difficulty in urination in elderly males who have prostatism.</td>
<td></td>
</tr>
<tr>
<td>1&lt; year of age; 0.2 (age in weeks) + 5 = mg/kg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>— 1 year of age; 16 mg/kg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: DPI, dry powder inhaler; EIB, exercise-induced bronchospasm; HFA, hydrofluoroalkane; ICS, inhaled corticosteroids; IgE, immunoglobulin E; MDI, metered-dose inhaler; NA, not available (either not approved, no data available, or safety and efficacy not established for this age group); SABA, short-acting beta-agonist

*Note: Dosages are provided for those products that have been approved by the U.S. Food and Drug Administration or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.

TABLE 3: ESTIMATED COMPARATIVE DAILY DOSAGES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose Child*</th>
<th>Medium Daily Dose Child*</th>
<th>High Daily Dose Child*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone HFA 40 or 80 mcg/puff</td>
<td>80–160 mcg</td>
<td>&gt; 160–320 mcg</td>
<td>&gt; 320 mcg</td>
</tr>
<tr>
<td>Budesonide DPI 90, 180 or 200 mcg/inhalation</td>
<td>180–400 mcg</td>
<td>&gt; 400–800 mcg</td>
<td>&gt; 800 mcg</td>
</tr>
<tr>
<td>Budesonide Inhaled inhalation suspension for nebulization</td>
<td>0.25–0.5 mg</td>
<td>&gt; 0.5–1.0 mg</td>
<td>&gt; 1.0 mg–2.0 mg</td>
</tr>
<tr>
<td>Flunisolide 250 mcg/puff</td>
<td>500–750 mcg</td>
<td>1,000–1,250 mcg</td>
<td>&gt; 1,250 mcg</td>
</tr>
<tr>
<td>Flunisolide HFA 80 mcg/puff</td>
<td>160 mcg</td>
<td>320 mcg</td>
<td>≥ 640 mcg</td>
</tr>
<tr>
<td>Fluticasone HFA/MDI: 44, 110, or 220 mcg/puff</td>
<td>88–176 mcg</td>
<td>&gt; 176–352 mcg</td>
<td>&gt; 352 mcg</td>
</tr>
<tr>
<td>DPI: 50, 100, or 250 mcg/inhalation</td>
<td>100–200 mcg</td>
<td>&gt; 200–400 mcg</td>
<td>&gt; 400 mcg</td>
</tr>
<tr>
<td>Triamcinolone acetonide 75 mcg/puff</td>
<td>300–600 mcg</td>
<td>&gt; 600–900 mcg</td>
<td>&gt; 900 mcg</td>
</tr>
</tbody>
</table>

*Children ≤ 11 years of age


VIII. ADJUVANT THERAPY

A. Education of family is essential—recognition of change in disease status allows early intervention. Daily self-management plans and emergency action plans can be obtained from the National Asthma Education and Prevention Program of the National Heart, Lung, and Blood Institute (www.nhlbisupport.com)

B. Avoidance of allergens and triggers: Aspirin and NSAIDs, tobacco smoke, remove pets from house (or at least from bedroom), limit outdoor activities when pollen counts are high or if air is cold, dust mite precautions (encasing mattresses, removing carpet and stuffed animals, washing all bedding every 1 to 2 weeks in hot water). Some irritants include fireplace smoke, perfumes, cleaning agents. Stress and GERD can also contribute

C. Ask about nocturnal symptoms and number of inhalers used per year. Children should not use more than 2 or 3 Albuterol inhalers per year—if so, the patient needs better chronic control of the disease. Spacers make MDIs easier to use and are essential in children < 5 years; dry powder inhalers are okay for children if they can master the technique

IX. MANAGEMENT OF ACUTE EPISODES

A. Assessment of signs and symptoms, home PEFR, office PEFR, office pulse oximetry

B. To determine need for hospitalization: Respiratory rate, accessory muscle use, color, lung exam (inaudible breath sounds are sign of severe exacerbation), speech pattern, alertness

C. Medication: Usual dosages for long-term control

(Chart on next page)
### 7. Asthma in Children

#### Care of Children

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose applies to Albuterol</th>
<th>Dose applies to Albuterol/Levalbuterol</th>
<th>Potential Adverse Effects</th>
<th>Apply to all three (SABAs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhaled Short-Acting Beta₂-Agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol CFC</td>
<td>1–2 puffs 5 minutes before exercise</td>
<td>2 puffs 5 minutes before exercise</td>
<td>Tachycardia, skeletal muscle tremor, hypokalemia, increased lactic acid, headache, hyperglycemia. Inhaled route, in general, causes few systemic adverse effects. Patients with preexisting cardiovascular disease, especially the elderly, may have adverse cardiovascular reactions with inhaled therapy.</td>
<td>Drugs of choice for acute bronchoospasm. Differences in potencies exist, but all products are essentially comparable on a puff per puff basis. An increasing use or lack of expected effect indicates diminished control of asthma. Not recommended for long-term daily treatment. Regular use exceeding 2 days/week for symptom control (not prevention of EIB) indicates the need for additional long-term control therapy. May double usual dose for mild exacerbations. For levalbuterol, prime the inhaler by releasing 4 actuations prior to use. For HFA: periodically clean HFA actuator, as drug may plug orifice. For autohaler: children &lt;4 years of age may not generate sufficient inspiratory flow to activate an auto-inhaler. Nonselective agents (i.e., epinephrine, isoproterenol, metaproterenol) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses. May mix with cromoglycin solution, budesonide inhalant suspension, or ipratropium solution for nebulization. May double dose for severe exacerbations. Does not have FDA-approved labeling for children &gt;6 years of age. Compatible with budesonide inhalant suspension. The product is a sterile-filled preservative-free unit dose vial.</td>
</tr>
<tr>
<td>Albuterol HFA</td>
<td>2 puffs every 4–6 hours, as needed for symptoms</td>
<td>2 puffs every 4–6 hours, as needed for symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levalbuterol HFA</td>
<td>NA &lt;4 years of age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nebulizer solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol</td>
<td>0.63 mg/3 mL, 1.25 mg/3 mL, 2.5 mg/5 mL, 5 mg/mL (0.5%)</td>
<td>0.63–2.5 mg in 3 cc of saline q 4–6 hours, as needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levalbuterol (R-albuterol)</td>
<td>0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/5 mL, 2.5 mg/5 mL</td>
<td>0.31–1.25 mg in 3 cc q 4–6 hours, as needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic Corticosteroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doses apply to first three corticosteroids</td>
<td>(Applies to the first three corticosteroids.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Methylprednisolone</strong></td>
<td>Short course &quot;burst&quot;: 1–2 mg/kg/day, maximum 60 mg/day, for 3–10 days</td>
<td>Short course &quot;burst&quot;: 40–60 mg/day as single or 2 divided doses for 3–10 days</td>
<td>Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, facial flushing, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis. Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, diabetes mellitus, osteoporosis, and Strongyloides.</td>
<td>Short courses or &quot;bursts&quot; are effective for establishing control when initiating therapy or during a period of gradual deterioration. Action may begin within an hour. The burst should be continued until patient achieves 80 % PEP personal best or symptoms resolve. This usually requires 3–10 days but may require longer. There is no evidence that tapering the dose following improvement prevents relapse in asthma exacerbations. Other systemic corticosteroids such as hydrocortisone and dexamethasone given in equivalent daily doses are likely to be as effective as prednisolone.</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5 mg tablets, 5 mg/5 cc, 15 mg/5 cc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>1, 2.5, 5, 10, 20, 50 mg tablets, 5 mg/cc, 5 mg/5 cc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repository injection</td>
<td>(Methylprednisolone acetate)</td>
<td>7.5 mg/kg IM once</td>
<td></td>
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<tr>
<td></td>
<td>240 mg IM once</td>
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</tr>
</tbody>
</table>

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34
**8. Community Acquired Pneumonia (CAP) In Infants & Children**

**I. SIGNIFICANCE**
- A. Each year over 2 million children worldwide die of pneumonia
- B. There are a total of 155 million cases of pneumonia per year worldwide
- C. In the developed world, there are 3–4 cases of pneumonia per 100 children < 5 years old

**II. DEFINITION OF CAP**
- A. An acute infection of the pulmonary parenchyma associated with:
  1. Symptoms of acute infection—and—
  2. The presence of an acute infiltrate on chest x-ray or auscultatory findings consistent with pneumonia
- B. Pneumonia is considered nosocomial (not community-acquired) if the patient has been hospitalized 14 days prior to presentation

**III. ETIOLOGY**—Note: A definitive pathogen is found only in about 1⁄3 of patients
- A. Neonate
  1. Group B Streptococcus
  2. Listeria monocytogenes
  3. Gram negatives—E.Coli, Klebsiella
  4. Chlamydia Trachomatis (neonate to 3 mos.)
  5. CMV, HSV, Rubella
- B. < 1 year
  1. Streptococcus pneumoniae
  2. Haemophilus influenza
  3. Staphylococcus aureus

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Care of Children

8. Community Acquired Pneumonia

Key: CFC, chlorofluorocarbon; ED, emergency department; EIB, exercise-induced broncho-spasm; HFA, hydrofluoroalkane; IM, intramuscular; MDI, metered-dose inhaler; NA, not available (either not approved, no data available, or safety and efficacy not established for this age group); PEF, peak expiratory flow; SABA, short-acting beta,-agonist

*Dosages are provided for those products that have been approved by the U.S. Food and Drug Administration (FDA) or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.


**CLINICAL PEARLS**
- Long-term data show that children who use inhaled steroids over a period of years grow to their expected height, comparable with peers and family
- Goals of treatment: Child should sleep through the night, should have no restrictions on activity or attendance at school, normal PFTs, few to no side effects from meds

**References**

Laurie Homema, MD
Michael B. Weinstock, MD
8. Community Acquired Pneumonia

C. > 1 year
1. Streptococcus pneumoniae
2. Haemophilus influenzae
3. Staphylococcus aureus
4. Influenza virus
5. Rhinovirus, Parainfluenza, Adenovirus
6. Chlamydia Pneumoniae, Mycoplasma (school-age)

D. Immunocompromised patient—all of the above plus:
1. Fungal organisms: Histoplasmosis, coccidioidomycosis, cryptoccocus
2. Pneumocystis carinii, mycobacterium spp., CMV

IV. Diagnosis

A. History
1. Symptoms
   a. General: Rigors, chills, fever, lethargy, poor feeding
   b. Lungs: Cough, sputum production, dyspnea
   c. Chest: Pleuritic chest pain
   d. Musculoskeletal: Myalgias and arthralgias
2. Timing and preceding symptoms: Sudden onset (indicative of “classic” pneumococcal pneumoniae), recent influenza infection
3. Risk Factors: Extremes of age, smoking, alcohol or IV drug use, immunocompromised state, nursing or group home resident, child in daycare, hx of influenza-like illness, risk factors for aspiration (syncope, loss of consciousness, cerebral palsy, sedative drugs)

B. Physical exam
1. Vitals—Fever, tachypnea, tachycardia, hypoxia
2. State of hydration—Skin turgor, mucous membranes, urine output
3. Lung exam
   a. Inspection—Retractions, use of accessory muscles
   b. Auscultation—Crackles, rhonchi

C. X-ray
1. Not necessary in all patients treated as outpatient, unless there is a suspicion of hypoxemia or for treatment failure
2. Complications of pneumonia seen on CXR include
   a. Parapneumonic effusions
   b. Necrotizing pneumonia
   c. Pneumothorax

D. Laboratory
1. Oxygenation
   a. Pulse oximetry should be used in ALL patients with pneumonia or suspected hypoxemia
   b. Arterial blood gas - not generally helpful in outpatient setting
2. Labs
   a. Sputum gram stain and culture—Not necessary in outpatient CAP
   b. Blood cultures—Per 2011 ISDA “should not be routinely performed in nontoxic, fully immunized children with CAP managed in the outpatient setting.” They may be helpful in treatment failure
   c. CBC—Generally unhelpful; leukocyte count should not be used in decision-making unless for severe pneumonia
   d. Urine antigens—Not recommended. High number of false positives
   e. Viral testing—A positive influenza test or RSV test decreases possibility of bacterial etiology

V. ADMISSION INDICATIONS:
A. Respiratory distress (note: the findings below may be seen with respiratory distress, tachypnea is the most sensitive finding)
1. Tachypnea
2. Age 0–2 months > 60 breaths/minute
3. Age 2–12 months >50 breaths/minute
4. Age 1–5 years > 40 breaths/minute
5. Age < 5 years > 20 breaths/minute
6. Dyspnea
7. Retractions
8. Grunting
9. Nasal flaring
10. Altered level of consciousness

B. Oxygen saturation ≤90%
C. Infants < 6 months of age
D. Pathogen with increased virulence—e.g., MRSA
E. Concern about compliance or inability to ensure good care at home
F. Toxic appearing or with underlying medical conditions that predispose to complications such as BPD or congenital heart defects

VI. MANAGEMENT
A. Antibiotic therapy should be based on the patient's age and severity of illness, and local resistance patterns of pathogens
B. Antibiotic therapy is not routinely required for preschool-aged children with CAP because viral pathogens are responsible for the great majority of clinical disease (2011 IDSA Guidelines)
   1. Amoxicillin
      a. First-line for mild to moderate CAP
      b. Provides appropriate coverage for Streptococcus pneumonia
      c. Dose: 90mg/kg/day divided BID (if PCN allergic use Cephalosporin or Macrolide)
   2. Alternatives: 2nd or 3rd generation Cephalosporins
      a. Cefpodoxime (Vantin): 10mg/kg/day divided BID (max 400mg/day)
      b. Cefuroxime (Ceftin): 30mg/kg/day divided BID (max 1g/day)
      c. Cefprozil (Cefzil): 30mg/kg/day divided BID (max 1g/day)
      d. Cefdinir (Omnicef): 14mg/kg/day divided BID (max 600mg/day)
      e. Ceftriaxone (Rocephin): IM—50mg/kg × 1
   3. Macrolide therapy if concern for atypical organisms
      a. Azithromycin (Zithromax): 10mg/kg on day one and then 5mg/kg for 4 additional days. Available: 200mg/5mL and 100mg/5mL
      b. Clarithromycin (Biaxin): 15mg/kg/day divided BID for 7–10 days. Avail. 250mg/5mL
   4. Duration of therapy: 7–10 days
C. Antiviral therapy for influenza
   1. Use as early as possible during outbreaks. Do not need to wait for confirmation. Influenza testing may have false negative results. Should be started within 48 hours of illness but may be helpful after 48 hours with severe pneumonia
   2. Oseltamivir (Tamiflu)
      a. Dosing < 1 year—3mg/kg PO BID × 5 days—Available 6mg/mL, pills 30, 45, 75mg
      b. Dosing > 1 year (<15kg)—30mg PO BID × 5 days or 1½ tsp PO BID
      c. Dosing > 1 year (15–23kg)—45mg PO BID × 5 days or 2 tsp PO BID
      d. Dosing > 1 year (23–40kg)—60mg PO BID × 5 days or 2½ tsp PO BID
      e. Dosing > 1 year (>40kg)—75mg PO BID × 5 days

VII. FOLLOW UP
A. Patients should demonstrate clinical improvement within 2–3 days, re-evaluate in the office by that time
B. Return with continued high fever, worsening SOB, inability to swallow medications or keep down liquids, failure to improve after 2 days of antibiotics, chest pain, or hemothysis
C. Follow up CXR is not necessary since initial X-ray findings may take weeks/months to clear

VIII. PREVENTION
A. Pneumococcal 13-valent vaccine in pediatric population is effective in decreasing
9. Otitis Media

9. Otitis Media  

pediatric pneumococcal pneumonia in ages 6 weeks–71 months
B. Influenza vaccine—Indicated yearly for all patients, particularly those at risk for pneumonia, under 2 years of age and older than 65
C. Due to the development of secondary bacterial pneumonia following pertussis infection, and the waning of pertussis immunity over time, it is recommended to replace tetanus boosters with Tdap boosters in all populations
D. All infants should complete Hib vaccination series
E. High risk infants should be provided RSV-specific monoclonal antibodies

CLINICAL PEARLS

• To minimize resistance to antibiotics use the proper dose of an antibiotic focused to the probable organism for the shortest duration possible
• Pneumococcus remains the number–one agent of bacterial pneumonia in children and adults
• Think HIV, esp. with recurrent pneumonia; check the mouth for thrush, OHL—see chapter 120, Ambulatory HIV/AIDS Management
• Viral disease accounts for approx 80% of CAP in children < 2 years of age

References

Michael B. Weinstock, MD
Miriam Chan, Pharm D
Jason Winterhalter, MD
Melissa Winterhalter, MD

9. Otitis Media

I. INTRODUCTION—Note: Much of this chapter is based on the 2013 AAP guideline: Diagnosis and management of acute otitis media
A. Acute Otitis Media (AOM) is the most common medical diagnosis made in children under age 15
B. 85% of children have 1 episode of AOM by age 3
C. Environmental risk factors: Exposure to second-hand smoke, bottle feeding, and enrollment in day care
D. General management considerations
  1. Approximately 80% of cases of AOM achieve clinical resolution without ATB therapy within 7 days
  2. Number needed to treat (NNT) with Amoxicillin to avoid 1 clinical failure at 2–7 days is 8
  3. Rate of mastoiditis in untreated patients is approximately 1/1,000
  4. Studies addressing the use of specific ATBs and duration of ATB therapy fail to demonstrate superiority of any 1 regimen over another
E. Observation without use of ATBs in a child with uncomplicated AOM is an option in selected patients
F. ATB recommended for initial treatment is high-dose Amoxicillin (80–90mg/kg/day×10 days)

II. ETIOLOGY
A. Bacterial: S. pneumoniae, H. influenzae (nontypeable), M. catarrhalis, S. aureus, Group A Strep (a rare cause of otitis media, but is associated with a higher rate of acute perforation and more rapid destruction of the tympanic membrane). In chronic serous otitis media, the most common bacterial agents include P. aeruginosa, S. aureus, S. epidermidis, S. viridans, and S. pneumonia
B. Viral: Parainfluenza, RSV, Influenza, Adenovirus, Enterovirus

III. DIAGNOSIS: AOM must be differentiated from Otitis Media with Effusion (OME) which is defined as the presence of fluid in the middle ear without signs or symptoms of acute ear infection (and does not require ATB treatment)

A. Clinicians should diagnose AOM in children who present with moderate to severe bulging of the tympanic membrane (TM) or new onset of otorrhea not due to acute otitis externa

B. Clinicians may diagnose AOM in children who present with mild bulging of the TM and recent (less than 48 hours) onset of ear pain (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the TM

C. Clinicians should not diagnose AOM in children who do not have middle ear effusion (MEE) (based on pneumatic otoscopy and/or tympanometry)

D. Signs/Symptoms (percentage of children affected in parentheses):
   1. Ear pain (47–83%)
   2. Fever (22–69%)
   3. Associated respiratory symptoms including cough and/or rhinitis (94%)
   4. Irritability (56%)
   5. Pulling at ear (12%)
   6. Drainage from ear (if tympanic membrane is ruptured)

E. Physical exam
   1. MEE (bulging tympanic membrane, cloudy tympanic membrane, impaired mobility of tympanic membrane, air fluid level, otorrhea)
   2. Inflammation (erythema of the tympanic membrane, otalgia)

<table>
<thead>
<tr>
<th>Otoscopic Findings in Children With Acute Symptoms and MEEa</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>TM Finding in Acute Visits With MEE</td>
<td>(Tampere, Finland), %</td>
<td>(Oulo, Finland), %, %</td>
</tr>
<tr>
<td>Color</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distinctly red</td>
<td>69.8</td>
<td>65.6</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>81.3</td>
<td>62.9</td>
</tr>
<tr>
<td>Strongly red</td>
<td>87.7</td>
<td>68.1</td>
</tr>
<tr>
<td>Moderately red</td>
<td>59.8</td>
<td>66.0</td>
</tr>
<tr>
<td>Slightly red</td>
<td>39.4</td>
<td>16.7</td>
</tr>
<tr>
<td>Cloudy</td>
<td>95.7</td>
<td>80.0</td>
</tr>
<tr>
<td>Normal</td>
<td>1.7</td>
<td>4.9</td>
</tr>
<tr>
<td>Position</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulging</td>
<td>96.0</td>
<td>89</td>
</tr>
<tr>
<td>Retracted</td>
<td>46.6</td>
<td>48.6</td>
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<tr>
<td>Normal</td>
<td>32.1</td>
<td>22.2</td>
</tr>
<tr>
<td>Mobility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distinctly impaired</td>
<td>94.0</td>
<td>78.5</td>
</tr>
<tr>
<td>Slightly impaired</td>
<td>59.7</td>
<td>32.8</td>
</tr>
<tr>
<td>Normal</td>
<td>2.7</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*Totals are greater than 100%, because each ear may have had different findings.


F. Diagnosis of AOM requires:
   1. Acute onset of signs and symptoms
   2. Middle ear effusion (MEE)
   3. Middle ear inflammation

IV. TREATMENT

A. Symptom control
   1. Antipyretics/Analgesics (oral)
      a. Acetaminophen 15mg/kg Q 4–6hrs, max 5 doses/day (susp. 160mg/5cc)
      b. Ibuprofen 10mg/kg Q 8hrs, max 40mg/kg/day (drops 1.25mL/50mg, susp. 100mg/5cc)
   2. Analgesic (topical): Auralgan otic suspension 2–4 drops in affected ear QID (do not use with perforated TM)
B. Severe AOM: The clinician should prescribe ATB therapy for AOM (bilateral or unilateral) in children 6 months and older with severe signs or symptoms (i.e., moderate or severe otalgia or otalgia for at least 48 hours or temperature 39°C [102.2°F]).

C. Nonsevere bilateral AOM in young children: The clinician should prescribe ATB therapy for bilateral AOM in children 6 months through 23 months of age without severe signs or symptoms (i.e., mild otalgia for less than 48 hours and temperature less than 39°C [102.2°F]). When observation is used, a mechanism must be in place to ensure follow-up and begin ATB therapy if the child worsens or fails to improve within 48 to 72 hours of onset of symptoms.

D. Nonsevere unilateral AOM in young children: The clinician should either prescribe ATB or offer observation with close follow-up based on joint decision-making with the parent(s)/caregiver for unilateral AOM in children 6 months to 23 months of age without severe signs or symptoms (i.e., mild otalgia for less than 48 hours and temperature less than 39°C [102.2°F]). When observation is used, a mechanism must be in place to ensure follow-up and begin ATB therapy if the child worsens or fails to improve within 48 to 72 hours of onset of symptoms.

E. Nonsevere AOM in older children: The clinician should either prescribe ATB therapy or offer observation with close follow-up based on joint decision-making with the parent(s)/caregiver for AOM (bilateral or unilateral) in children 24 months or older without severe signs or symptoms (i.e., mild otalgia for less than 48 hours and temperature less than 39°C [102.2°F]). When observation is used, a mechanism must be in place to ensure follow-up and begin ATB therapy if the child worsens or fails to improve within 48 to 72 hours of onset of symptoms.

F. Clinicians should prescribe Amoxicillin for AOM when a decision to treat with ATBs has been made and the child has not received Amoxicillin in the past 30 days or the child does not have concurrent purulent conjunctivitis or the child is not allergic to Penicillin.

G. Clinicians should prescribe an ATB with additional β-lactamase coverage for AOM when a decision to treat with ATBs has been made, and the child has received Amoxicillin in the last 30 days or has concurrent purulent conjunctivitis, or has a history of recurrent AOM unresponsive to Amoxicillin.

H. Recommendations for initial management for uncomplicated AOM (applies only to children with well-documented AOM with high certainty of diagnosis)*

1. 6 mo to 2 yr: Otorrhea with AOM, unilateral or bilateral AOM with severe symptoms,† and bilateral AOM without otorrhea—Antibiotic therapy

2. ≥ 2 yr: Otorrhea with AOM and unilateral or bilateral AOM with severe symptoms†—Antibiotic therapy; bilateral AOM without otorrhea and unilateral AOM without otorrhea—Antibiotic therapy or additional observation‡


I. Recommended antibiotic dosages

1. First line
   a. **Amoxicillin**: 80–90mg/kg/day divided BID
   b. For additional β-lactamase coverage: Amoxicillin/Clavulanate (90mg/kg/day Amoxicillin/6.4mg/kg/day Clavulanate [14:1] divided BID)

2. Alternatives (if Penicillin allergy)
   a. **Cefdinir (Omnicef)**: 4mg/kg/d in 1–2 doses
   b. **Cefuroxime (Ceftin)**: 30mg/kd/d in 2 doses
   c. **Cefpodoxime (Vantin)**: 10mg/kg/d in 2 doses
   d. **Ceftriaxone**: 50mg IM/IV/d × 1 or 3 d

J. Duration of therapy

1. 10 days for <2 yr and children with severe symptoms
2. 7 days for children 2–5 yr with mild or moderate AOM
3. 5–7 days for children ≥6 yr with mild or moderate AOM

K. General
1. Patients should be re-evaluated in 2 weeks to see if the treatment was successful. If there is presence of a middle ear effusion, consider:
   a. Re-evaluate in 6 weeks
   b. Re-treat with different ATB

V. TREATMENT FAILURE: No response to initial management (observation or ATBs) after 48–72 hours
A. Reassess the patient and confirm the presence of AOM
B. Consider other diagnoses
   1. Mastoiditis
   2. Meningitis
   3. Other infections
C. Management
   1. Observation failure: High-dose Amoxicillin (or Amoxicillin-Clavulanate with fever >39°C)
   2. Amoxicillin failure: High dose Amoxicillin-Clavulanate (or Ceftriaxone with fever >39°C)
   3. Penicillin allergy: (Ceftriaxone, Clindamycin (30–40mg/kg/day divided TID ± 3rd generation Cephalosporin, or Tympanocentesis with fever >39°C)

VI. OTHER
A. Persistent Middle Ear Effusion (OME)
   1. Effusion may persist for 2–3 months after treatment of AOM; this is expected and does not require retreatment
   2. Check hearing at 3 months in patients with cognitive or developmental delay
B. Recurrent OM
   1. Definition: 3 episodes of OM in 6 months or 4 episodes in 12 months
   2. Consider other diagnosis
      a. Sinusitis
      b. Allergies
      c. Immune deficiencies (C3 and C5 deficiency)
      d. Submucous cleft palate
      e. Tumor of the nasopharynx
   3. Prevention
      a. Clinicians should not prescribe prophylactic ATBs to reduce the frequency of episodes of AOM in children with recurrent AOM
      b. Clinicians may offer tympanostomy tubes for recurrent AOM (3 episodes in 6 months or 4 episodes in 1 year with 1 episode in the preceding 6 months)
C. Ruptured TM
   1. Treat with Cortisporin Otic Suspension 2 drops QID for 3–5 days in addition to oral ATBs per above recommendations
   2. Fluoroquinolone otic solutions (Ofloxacin otic) have been recently approved for use in children and are not known to be ototoxic
   3. Continued otorrhea despite oral ATBs may necessitate a culture of the drainage from the perforation site
   4. Careful otologic examination is required for otorrhea lasting longer than 2 weeks despite ATB use
   5. Chronic otorrhea (lasting 6 or more weeks) is most commonly caused by chronic serous otitis media but may be caused by a myriad of different processes including cholesteatoma, foreign body, granuloma, immunodeficiency and neoplasm
D. Serous OM
   1. Persistent middle ear effusion without infection
   2. Check hearing at 3 months. If decreased, refer to ENT
   3. No role for steroids or decongestants. Oral ATB usually not necessary
VII. PREVENTION

A. Clinicians should encourage exclusive breastfeeding for at least 6 months
B. Clinicians should encourage avoidance of tobacco smoke exposure
C. Clinicians should recommend annual influenza vaccine to all children according to the schedule of the Advisory Committee on Immunization Practices, AAP, and AAFP. 30% efficiency during respiratory illness season
D. Clinicians should recommend pneumococcal conjugate vaccine to all children according to the schedule of the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention, American Academy of Pediatrics (AAP), and American Academy of Family Physicians (AAFP). Pneumococcal conjugate vaccine shows a 6% reduction in AOM

CLINICAL PEARLS

- Decongestants, antihistamines, and glucocorticoids have not been shown to be helpful with AOM
- An erythematous TM may be caused by crying or fever
- Recurrent OM may result in hearing loss. Be alert for behavioral changes or learning difficulties
- Breast feeding for at least 4–6 months decreases risk of AOM and recurrent AOM

References

10. Pharyngitis

I. DEFINITION: An inflammatory process involving the mucous membranes and underlying structures of the oropharynx

II. PRESENTATION

A. History
   1. Chief complaint and associated symptoms (see below)
   2. Immunization history
   3. Sexual history (when indicated)

B. Signs and symptoms
   1. Sore throat
   2. Enlarged tonsils
   3. Fever, chills, headache, malaise, and anorexia
   4. Oropharyngeal erythema and/or exudate
   5. Rash
   6. Cervical adenopathy
   7. Rhinitis

C. Symptomatic tetrad of streptococcal pharyngitis (Centor criteria)
   1. Fever > 102.2°F
   2. Anterior cervical lymphadenopathy
   3. Exudative tonsillitis
   4. Absence of cough

   Note: If all 4 are present, there is a 50% likelihood of group A beta-hemolytic strep (GABHS). If none are present, likelihood of strep is <5%

III. ETIOLOGY

A. Bacterial: Group A beta-hemolytic streptococcus (causal agent in 10% of cases of adult pharyngitis), Mycoplasma pneumoniae, Hemophilus influenzae, Corynebacterium diphtheria, Neisseria gonorrhoeae

B. Viral: Adenovirus, Influenza viruses (A&B), Parainfluenza viruses, Epstein-Barr virus, Herpes simplex virus

IV. EVALUATION

A. Laboratory
   1. Rapid strep test (RSS)—up to 96% sensitive
   2. Many clinicians recommend stopping the evaluation with a negative RSS. Primary reason for treating strep throat is to prevent rheumatic fever. There is an exceedingly low chance that there would be a false negative RSS and that the undetected strep would cause the patient to develop clinically significant rheumatic fever. However, negative RSS in children and adolescents should be backed up by a throat culture (2012 IDSA Guideline)
   3. Strep culture—No longer recommended for adults
   4. Decision to screen adults may be based on the presence or absence of the four Centor criteria (see II. C.)
      a. If none or 1 of the criteria are present—consider not screening
         i. There is a negative predictive value of 80% with the absence of 3 or 4 of the Centor criteria. If none of the criteria are present, < 5% chance of strep
         ii. If recently exposed to strep, use clinical judgment
      b. If 2 or more criteria are present
         i. The patient should be screened, but only treated with ATB if the screen is positive—or—
ii. Diagnostic tests may be deferred in patients with four criteria, and they may be empirically treated with ATBs. If 3–4 of the Centor criteria are present, the positive predictive value of a positive test is 40–60%.

5. Use appropriate culture medium if other bacteria (e.g., Neisseria or Corynebacterium) suspected.

V. TREATMENT
A. The goal of initiating therapy is to decrease the chance of secondary complications (including rheumatic fever). Therapy can safely be initiated up to 9 days after onset of symptoms and still be effective. Note: Rheumatic fever today is rare except in isolated outbreaks.
B. The classic triad of fever, pharyngeal exudate, and anterior cervical lymphadenopathy are present in only 15% of cases of strep pharyngitis.
C. Medical personnel are correct in only 50–75% of cases where diagnosis is made based on clinical criteria alone.
D. 71% of children discontinue ATBs by day 6.
E. Acute GAS pharyngitis
1. Antibiotic of choice: Penicillin or Amoxicillin
   a. Penicillin VK
      i. Children—Penicillin VK: 250mg BID or TID × 10 days
      ii. Adolescents and adults—Penicillin VK: 250mg QID or 500mg BID × 10 days
   b. Amoxicillin oral suspension is more palatable than Penicillin
      i. Amoxicillin: 50mg/kg once daily (max 1g) × 10 days or 25mg/kg (max 500mg) BID × 10 days
      ii. ≥12 yr—Amoxicillin extended-release tablet (Moxatag): 775mg once daily taken within 1 hr of finishing a meal × 10 days
   c. Benzathine Penicillin G (Bicillin LA), long-acting Penicillin to ensure patient adherence
      i. <27kg: 600,000 units IM × 1
      ii. ≥27kg: 1.2 million units IM × 1
2. Alternatives for patients with Penicillin allergy who are not anaphylactically sensitive
   a. Cephalexin: 20mg/kg (max 500mg) BID × 10 days
   b. Cefadroxil (Duricef): 30mg/kg once daily (max 1g) × 10 days
3. Alternatives for patients with Penicillin allergy
   a. Azithromycin: 12mg/kg once a day (max 500 mg) × 5 days
   b. Clarithromycin: 7.5mg/kg (max 250mg) BID × 10 days
   c. Clindamycin: 7mg/kg (max 300mg) TID × 10 days
F. Follow up
1. Patients should have improvement in clinical symptoms within 3–4 days of initiating antibiotic therapy.
2. Clinical failure may be due to nonadherence or presence of β-lactamase producing bacteria.
3. If incomplete adherence to initial regimen is a concern, repeat treatment with IM Benzathine Penicillin.
4. Otherwise, retreat with an antibiotic that has greater β-lactamase stability than the previous agent such as Amoxicillin-Clavulanate
   a. Children: 40mg/kg/day divided TID (max 2g Amoxicillin/day) × 10 days
   b. Adults: 500–875mg BID × 10 days
Note: Persistently positive strep testing may be due to colonization and not persistent infection.

G. Viral
1. Symptomatic relief
   a. Gargle with warm salt water TID
   b. Chloraseptic spray or lozenges PRN sore throat
   c. Acetaminophen or Ibuprofen for pain, fever

VI. COMPLICATIONS
A. Rheumatic fever (secondary to Group A Strep)—Rare
   1. Carditis is the most serious complication associated with acute rheumatic fever (seen in 50 to 91% of cases of pediatric rheumatic fever and 33% of adult rheumatic fever)
2. Can lead to permanent valvular dysfunction
3. Rheumatic fever is rare in adults

B. Post-strep glomerulonephritis
   1. Rare
   2. No evidence that ATB treatment of pharyngitis decreases the incidence of this complication

C. Peritonsillar abscess/Retropharyngeal abscess

D. Scarlet fever

E. Cervical lymphadenitis

F. Sinusitis/mastoiditis

G. Otitis Media

H. Meningitis

I. Bacteremia

J. Pneumonia

CLINICAL PEARLS

- The natural course of untreated, streptococcal pharyngitis will resolve. Antibiotics shorten symptom duration by about 16 hours; the number needed to treat (NNT) for symptom relief at 72 hours is 4
- School-aged children who develop strep pharyngitis can return to school 24hrs after therapy is initiated
- Patients complaining of an associated rhinitis most likely have a viral etiology of their pharyngitis
- A Mono-spot test is a quick way to determine EBV (mononucleosis) infection; associated findings may include posterior cervical adenopathy, prolonged course of symptoms, or splenomegaly

References

11. Croup (Acute Laryngotracheitis)

DEFINITION: A viral illness characterized by a “barky” cough, inspiratory stridor, and fever

I. PRESENTATION
Affects children ages 3 months–3 years. Most frequently occurs in autumn

A. Signs and symptoms: Gradual onset
   1. Barking, spasmodic cough. Inspiratory stridor, hoarseness, and low-grade fever
   2. Upper respiratory infection (coryza) prodrome for 1–7 days
   3. Tachypnea, intercostal retractions, nasal flaring, dyspnea, and fatigue
   4. Cyanosis

B. Differential diagnosis
   1. Epiglottitis
   2. Foreign body aspiration
   3. Bacterial tracheitis
   4. Subglottic stenosis

II. ETIOLOGY
A. Viral
   1. Parainfluenza viruses (most common), Influenza viruses, RSV and Adenovirus
   2. Enteroviruses (coxsackievirus A & B and echovirus) are common causes of “sum-
      mertime croup”
   3. Measles virus (endemic areas)

B. Bacterial: Mycoplasma pneumonie

III. EVALUATION:
The diagnosis is usually a clinical diagnosis. More severe cases may warrant further work-up
A. PA and lateral neck x-rays (obtain only if unsure of diagnosis)
   1. “Steeple Sign”: Common x-ray finding secondary to subglottic narrowing
   2. Will help rule out epiglottitis (“thumb” sign on x-ray) as an etiology
B. Other: Usually only entails a pulse oximetry reading

IV. MANAGEMENT:
Mild cases can be effectively managed at home
A. Dexamethasone: 0.6mg/kg IM or PO as a 1 time dose—Benefit to children with mild,
   moderate, and severe croup. Results in decreased rates of hospitalization and endotra-
   cheal intubation. Also results in improved clinical course—children begin to feel better
   sooner
B. For moderate to severe cases: Nebulized Epinephrine—0.05mL/kg (max 0.5mL) of
   racemic Epinephrine 2.25% or 0.5mg/mL (max 5mL) of L-Epinephrine 1-1000. May
   be rebound so the patient does need to be observed for 2–4hrs after treatment. Hospital-
   ize if more than 1 nebulization is required
C. Inhalation of humidified air (vaporizer): Commonly used in clinical practice but has
   not been demonstrated effective in clinical trials
D. Indications for admission:
   1. Stridor at rest
   2. Low oxygen saturation
   3. Tachypnea/retractions
   4. Ill appearance, poor color, decreased level of consciousness
   5. Questionable diagnosis (possible epiglottis, foreign body, etc.)

CLINICAL PEARLS
   • Croup is usually preceded by a viral prodrome or URI symptoms
• Annual incidence of croup in the US is 18/1000 which peaks at 60/1000 in children 1–2 years of age
• Nebulized Racemic Epinephrine has an onset of action of 10–30 mins

References

12. Bronchiolitis

DEFINITION: An inflammatory process involving the bronchi and bronchioles

I. PRESENTATION
Occurs mostly in winter and spring
A. Criteria for diagnosis
   1. First episode of acute wheezing
   2. Age < 24 months
   3. Symptoms associated with viral infection (cough, fever, coryza)
   4. Pneumonia is ruled out as a cause of the wheezing
   5. No family history of atopy or asthma
B. Signs and symptoms
   1. Expiratory wheezing and inspiratory rales
   2. Temperature usually < 101º F
   3. Grunting, intercostal retractions, dyspnea, tachypnea, prolonged expiratory phase
   4. Sore throat, cough, and coryza
   5. May have associated otitis media
C. Differential diagnosis
   1. Asthma
   2. Allergies (IgE-mediated hypersensitivity)
   3. Foreign body aspiration
   4. Pneumonia
   5. Gastroesophageal reflux disease (GERD)
   6. Congestive heart failure (CHF)
   7. Cystic fibrosis

II. ETIOLOGY
A. Viral: Respiratory syncytial virus (RSV), parainfluenza, adenovirus, rhinovirus, influenza virus
B. Bacterial: Mycoplasma pneumoniae, Chlamydia pneumoniae

III. EVALUATION
A. Chest x-ray (CXR)
   1. Obtain on all “first-time wheezers” to rule out foreign body aspiration, pneumonia or CHF
   2. Common radiologic findings associated with bronchiolitis
      a. Increased A-P diameter
      b. Atelectasis
      c. Flattening of the diaphragms
B. Laboratory: Not typically used in clinical practice

IV. MANAGEMENT

A. Home management
   1. Most patients can and should be treated at home
   2. Symptomatic relief
      a. Anti-pyretics (Tylenol, Ibuprofen)
      b. Mucolytics, antitussives and nasal decongestants are not recommended
      c. Try saline nose drops to thin the mucus, followed by bulb suction to temporarily remove nasal secretions
   3. Bronchodilator therapy
      a. In patients with mild and moderately severe symptoms, studies suggest that bronchodilators improve clinical scores in the short term
      b. Studies suggest that bronchodilators do not improve oxygen saturation or reduce admission rates
      c. May cause tachycardia, increased BP, decreased oxygen saturation, flushing, hyperactivity, prolonged cough and tremors
   4. Adequate hydration
   5. Avoid exposure to other children (incubation period of RSV is 4–6 days)
   6. No smoking around child
   7. Return or go to ER with: respiratory distress, lethargic behavior, poor feeding, signs of dehydration
   8. Note: Steroids have not been shown to be beneficial in altering disease course

B. Criteria for inpatient management of bronchiolitis
   1. Tachypnea, marked intercostal retractions, increasing respiratory distress, cyanosis, hypoxemia, or dehydration
   2. Immunocompromised patients
   3. Patients with a history of cardiopulmonary disease

C. Prevention
   1. Palivizumab (Synagis) prophylaxis
      a. May be given to selected infants and children < 24 months of age with chronic lung disease or a history of prematurity (<35 weeks’ gestation) or with congenital heart disease
      b. 15mg/kg/dose × 5 monthly doses beginning in November or December
   2. Influenza vaccination for children >6 months of age

CLINICAL PEARLS
   • 1 child in 50 will require hospitalization secondary to RSV bronchiolitis. Of these, 3–7% develop respiratory failure and 1% will die
   • The mortality rate from nosocomial RSV in ill infants is as high as 20%
   • ATBs should be withheld unless a bacterial etiology is suspected

References
Available: http://pediatrics.aappublications.org/cgi/content/full/118/4/1774
13. DIARRHEA IN CHILDREN

I. GENERAL
A. Definition: An increase in the frequency, fluidity or volume of bowel movements as compared to the normal habit of the individual. Diarrhea may be acute (< 2 weeks) or chronic
B. Diarrhea worldwide is responsible for 4–5 million deaths/year in children < age 5. In US, acute gastroenteritis (AGE) historically accounts for 10% of hospital admissions of children < age 5

II. ETIOLOGY: Viruses are responsible for 60% of cases; bacteria, 20%; parasites, 5%; parenteral illnesses, 10%; and 5% are in an unknown category
A. Viral: Rotavirus (35% of hospitalizations for acute diarrhea), Adenovirus, Norwalk virus, Enterovirus
B. Bacterial: Aeromonas species, Vibrio cholerae, E. coli, Yersinia enterocolitica, Salmonella, Shigella, Clostridium difficile, Campylobacter jejuni
C. Parasitic: Cryptosporidium, Entamoeba histolytica, Giardia lamblia
D. Other: Formula intolerance, protein intolerance, carbohydrate intolerance, lactose intolerance, post-infectious diarrhea secondary to lactose intolerance, overfeeding, inflammatory bowel disease (IBD), chronic nonspecific diarrhea of infancy, excessive fluid intake, celiac disease, pancreatic disease, constipation with overflow diarrhea, functional tumors, intestinal obstruction, irritable bowel syndrome (IBS), laxative abuse
E. Non-GI causes: Otitis media, sepsis, toxic ingestion, immunodeficiency, hyperthyroidism
F. Etiologies of acute diarrhea by age
  1. Infant: Gastroenteritis (viral), systemic infection, ATB use, primary disaccharidase deficiency and Hirschsprung toxic colitis
  2. Child: Gastroenteritis, food poisoning, systemic infection, ATB use, toxic ingestion, hyperthyroidism
G. Etiologies of chronic diarrhea by age
  1. Infant: Postinfectious secondary lactase deficiency, cow's milk intolerance, soy milk intolerance, celiac disease, cystic fibrosis, secretory tumors, familial villous atrophy, and primary immune defects
  2. Child: IBS, IBD, celiac disease, lactase intolerance, giardiasis, laxative abuse (adolescents), AIDS enteropathy, immune defects, secretory tumors, pseudo-obstruction, and factitious diarrhea

III. HISTORY
A. Chief complaint and associated symptoms (vomiting, tenesmus, malaise/lethargy, fever, weight loss, abdominal pain)
B. Frequency and character of stool (blood, pus, watery, foamy)
C. Onset and duration of illness
D. Dietary history (e.g., poorly cooked meat), well water vs. city water
E. Hydration status: Urine output, tears with cry, ability to take PO fluids/food
F. Travel history and exposures (day care center, sibling with diarrhea, etc.)
G. Developmental history
H. Medications, past medical history, family history (IBD, IBS, etc.)

IV. PHYSICAL EXAM
A. General: Fever, irritability, height, weight, growth charts, mental status
B. Hydration status: Tears with cry, capillary refill, dry mucous membranes
C. GU/GU: Blood or pus in stool, vomiting, urine output
D. Skin: Rash, skin turgor
### 13. Diarrhea in Children

#### Care of Children

<table>
<thead>
<tr>
<th>Degree of dehydration</th>
<th>Rehydration therapy</th>
<th>Replacement of losses</th>
<th>Nutrition</th>
</tr>
</thead>
</table>
| Minimal or no dehydration      | Not applicable                                           | <10 kg body weight: 60–120 mL oral rehydration solution (ORS) for each diarrheal stool or vomiting episode  
>10 kg body weight: 120–240 mL ORS for each diarrheal stool or vomiting episode | Continue breastfeeding, or resume age-appropriate normal diet after initial hydration, including adequate caloric intake for maintenance* |
| Mild to moderate dehydration   | Oral Rehydration solution (ORS), 50–100 mL/kg body weight over 3–4 hours | Same Same                                                                            | Same Same                                                                 |
| Severe dehydration             | Lactated Ringer’s solution or normal saline in 20 mL/kg body weight intravenous amounts  
if status improves; then administer 100 mL/kg body weight ORS over 4 hours or 5% dextrose ½ normal saline intravenously at twice maintenance fluid rates | Same Same; if unable to drink, administer through nasogastric tube or administer 5% dextrose ¼ normal saline with 20 mEq/L potassium chloride intravenously | Same |
C. Dietary management
   1. Continue breast-feeding
   2. Early re-feeding (within 4hrs of rehydration) with milk or food. This may reduce the
duration of diarrhea by about half a day and is recommended by the AAP to restore
nutritional balance. It does not prolong diarrhea

D. Adjunctive therapy: Probiotics (e.g., Lactobacillus GG) have been shown to reduce
the duration of diarrhea. However, recommendations for general use are inconsistent

E. Symptomatic medications: Oral Ondansetron (Zofran ODT) may be tried

F. Prevention
   1. Good hygiene is the most effective intervention
   2. Rotavirus vaccine is a live, oral vaccine indicated for the prevention of rotavirus
gastroenteritis in infants
      a. There are two products available: Rotarix and RotaTeq
         i. Rotarix (serotypes G1, G3, G4, and G9): Given orally as a 2-dose series at 2
            and 4 months of age
         ii. RotaTeq (serotypes G1, G2, G3, and G4): Given orally as a 3-dose series at
            2, 4, and 6 months of age

Seven principles of appropriate treatment for children with diarrhea and dehydration

1. Oral rehydration solutions (ORS) should be used for rehydration.
2. Oral rehydration should be performed rapidly (i.e., within 3–4 hours).
3. For rapid realimentation, an age-appropriate, unrestricted diet is recommended as soon
   as dehydration is corrected.
4. For breastfed infants, nursing should be continued.
5. If formula-fed, diluted formula is not recommended, and special formula usually is not
   necessary.
6. Additional ORS should be administered for ongoing losses through diarrhea.
7. No unnecessary laboratory tests or medications should be administered.

Source: Centers for Disease Control and Prevention. Managing acute gastroenteritis among children:
oral rehydration, maintenance, and nutritional therapy. MMWR 2003;52(No. RR-16):1-16, Box 2
at 6. Available at: http://www.cdc.gov/mmwr/PDF/RR/RR5216.pdf. Adapted from Sandhu BK.

(Chart on next page)
### Symptoms associated with dehydration

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Minimal or no dehydration (&lt;3% loss of body weight)</th>
<th>Mild to moderate dehydration (3%–9% loss of body weight)</th>
<th>Severe dehydration (&gt;9% loss of body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental status</td>
<td>Well; alert</td>
<td>Normal, fatigued or restless, irritable</td>
<td>Apathetic, lethargic, unconscious</td>
</tr>
<tr>
<td>Thirst</td>
<td>Drinks normally; might refuse liquids</td>
<td>Thirsty; eager to drink</td>
<td>Drinks poorly; unable to drink</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Normal</td>
<td>Normal to increased</td>
<td>Tachycardia, with bradycardia in most severe cases</td>
</tr>
<tr>
<td>Quality of pulses</td>
<td>Normal</td>
<td>Normal to decreased</td>
<td>Weak, thready, or impalpable</td>
</tr>
<tr>
<td>Breathing</td>
<td>Normal</td>
<td>Normal; fast</td>
<td>Deep</td>
</tr>
<tr>
<td>Eyes</td>
<td>Normal</td>
<td>Slightly sunken</td>
<td>Deeply sunken</td>
</tr>
<tr>
<td>Tears</td>
<td>Present</td>
<td>Decreased</td>
<td>Absent</td>
</tr>
<tr>
<td>Mouth and tongue</td>
<td>Moist</td>
<td>Dry</td>
<td>Parched</td>
</tr>
<tr>
<td>Skin fold</td>
<td>Instant recoil</td>
<td>Recoil in &lt;2 seconds</td>
<td>Recoil in &gt;2 seconds</td>
</tr>
<tr>
<td>Capillary refill</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Prolonged; minimal</td>
</tr>
<tr>
<td>Extremities</td>
<td>Warm</td>
<td>Cool</td>
<td>Cold; mottled; cyanotic</td>
</tr>
<tr>
<td>Urine output</td>
<td>Normal to decreased</td>
<td>Decreased</td>
<td>Minimal</td>
</tr>
</tbody>
</table>


### CLINICAL PEARLS

- In the US, children < 5 have 1.3–2.3 episodes of acute diarrhea/year
- Rotavirus has an incubation period of 1–3 days. Vomiting may occur for up to 3 days, and watery diarrhea for up to 8 days. May be accompanied by fever and URI signs
- Adenovirus causes more prolonged diarrhea than rotavirus. Norwalk virus usually occurs in epidemic outbreaks
- Children who are dehydrated rarely refuse ORT, whereas those not dehydrated will often refuse secondary to the salty taste of ORT

### References


Cincinnati Children's Hospital Medical Center. Evidence-based clinical care guideline for acute gastroenteritis (AGE) in children aged 2 months through 5 years. 2006. http://www.cincinnatichildrens.org/assets/0/78/1067/2709/2777/2793/9199/32e1493-09fc-4138-85be-7d8fed145537.pdf


14. CONSTIPATION IN CHILDREN

I. INTRODUCTION
A. Definition: Delay or difficulty in defecation present for > 2 weeks which causes distress to patient
B. Normal number of stools in infants is 5/week to 40/week (3/day in breast fed and 2/day in bottle fed) and in children > 3yrs is 3–14/week
C. Approximately 3% of pediatric visits are related to defecation disorder complaints
D. In children the most common cause is functional (idiopathic/functional fecal retention/withholding) constipation

II. HISTORY
A. What family means by constipation (frequency, consistency, size, painful BM), duration of symptoms, toilet training, encopresis, fecal soiling
B. Time after birth of first BM
C. Blood on toilet paper or in stool
D. Abdominal pain
E. Fever, nausea, vomiting, anorexia, weight loss (or poor weight gain)
F. Medications (current meds plus any meds used for constipation in the past)
G. Psychosocial (family dynamics, use of school bathrooms)
H. Other: Coarse hair, dry skin, or other symptoms of thyroid disease, cystic fibrosis, celiac disease
I. Family history of Hirschsprung disease, constipation

III. PHYSICAL EXAM
A. General appearance of infant/child, growth parameters
B. Abdomen: Distention, mass, hepatosplenomegaly
C. GU
1. External exam of perineum and perianal area for perianal wink, sensation, fissures, dermatitis, abscess, fistula
2. If indicated, perform digital rectal exam for anal tone, blood in stool, rectal size, fecal impaction
D. Back/spine: Dimple, tuft of hair
E. Neuro: Tone, strength, cremasteric reflex, DTRs

IV. EVALUATION AND MANAGEMENT OF INFANTS < 1 YEAR
A. Those with a normal history and physical exam and no red flags (fever, vomiting, bloody diarrhea, failure to thrive, anal stenosis, tight empty rectum, impaction or distention, delayed passage of meconium) may be managed for functional constipation with dietary modification or meds (lactulose or sorbitol, malt extract, corn syrup or occasional glycerine suppositories). If any red flags are present, then obtain consultation with pediatric gastroenterologist
1. Malt Soup Extract (Maltsupex)
   a. Breast-fed infant: 1–2 tsp in 2–4 oz of water or juice BID
   b. Bottle-fed infant: 1–2 tsp with every other feeding x 3–4 days, then 1–2 tsp QD
2. Lactose and sorbitol: 1–3mL/kg/day divided BID

V. EVALUATION AND MANAGEMENT OF INFANTS > 1 YEAR
A. General
1. Treat impaction if present with oral meds (mineral oil, polyethylene glycol electrolyte solutions), or rectal disimpaction (phosphate soda, saline, or mineral oil enemas).
May also try glycerine suppositories in infants and bisacodyl suppositories in children
2. Dietary modification (increase fluids, fruit juices, balanced diet)
3. Oral maintenance med including mineral oil, magnesium hydroxide, lactulose or sorbitol or combination of 2. Wean after having regular BMs for several months
4. Parental education and behavioral modification including regular toileting. May keep stool diary with reward system

Management of children >1yr. with constipation

1. Constipation: Delayed or difficult defecation for > 2 weeks
2. History
   - Physical exam
   - Occult blood (if indicated)
3. Are there any red flags?
   - e.g., fever, vomiting, bloody diarrhea, failure to thrive, anal stenosis, tight empty rectum?
4. Evaluate further
5. Functional constipation
6. Is there fecal impaction?
7. Disimpact with oral or rectal medication
8. Effective?
9. Functional constipation without impaction
10. Treatment effective?
11. Treatment effective?
12. Maintenance therapy
13. Treatment effective?
14. Re-assessment
15. Adherence?
16. Re-education
17. Different medication?
18. Blood tests:
   - T4
   - TSH
   - Calcium
   - Lead
19. Abnormal T4, TSH, Ca, Pb?
20. Consultation with Pediatric Gastroenterologist

### B. Medications

| Medications for Use in Treatment of Constipation |
|-----------------------------------------------|---------------------------------|-----------------|
| **Laxatives**                                 | **Dosage**                      | **Side Effects** |
| Osmotic                                       |                                 |                 |
| Lactulose or Sorbitol                         | 1-3 mL/kg/day in divided doses  | Abdominal cramps, flatulence |
| Barley malt extract*                         | 2-10 mL/240 mL of milk or juice| Bloating, flatulence |
| Magnesium hydroxide*                         | > 1 year of age: 1-3 mL/kg/day of 400 mg/5 mL 2-5 years – 5-15 mL/d 6-14 years – 15-30 mL/d 6/14 years – 15-30 mL/d Available as liquid, 400 mg/5 mL, 800 mg/5 mL, and tablets | Magnesium toxicity, dehydration, abdominal cramps |
| Magnesium citrate*                           | 1-6 years – 1-3 mL/kg/day as QD 6-12 years – 100-150 mL/day > 12 years – 150-300 mL/day Single or divided doses | Magnesium toxicity, dehydration, abdominal cramps |
| PEG 3350                                      | Disimpaction: 1-1.5 g/kg/day for 3 days Maintenance: 1 g/kg/day |                 |
| Osmotic Enema                                 | ≥ 2 years old: 6 mL/kg up to 135 mL | Abdominal distention, vomiting |
| Phosphate enemas                              |                                 |                 |
| Lubricant                                     | < 1 year old: not recommended Disimpaction: 15-30 mL/year of age, up to 240 mL daily Maintenance: 1-3 mL/kg/day | Foreign body reaction in intestinal mucosa |
| PEG 3350                                      |                                 |                 |
| Stimulants                                    | ≥ 2 years old: 2.5-7.5 mL/day 6-12 years old: 5-15 mL/day | NV, abdominal cramps |
| Senna                                         |                                 |                 |
| Bisacodyl                                     | ≥ 2 years old: 0.5-1 suppository, 1/2 tablets per dose Available in 5 mg tablets and 10 mg suppositories | Rectal irritation, abdominal pain, bloating |
| Glycerin suppositories                        | < 6 years – 1 infant supp > 6 years – 1 adult supp |                 |

*Adjust dose to induce a daily bowel movement for 1-2 months


### VI. HIRSCHSPRUNG DISEASE

A. Lack of ganglion cells in distal colon which results in sustained contraction and dilation of bowel in segment proximal to aganglionic segment (due to distal obstruction)

B. Occurs in 1/5,000 births, often associated with trisomy 21

C. Mean age of diagnosis is 2½ months, but 8–20% are diagnosed after age 3

D. Symptoms may include bilious vomiting, abdominal distension, and refusal to feed

E. Approximately 90% of normal infants pass meconium in the first 24 hours of life compared to less than 10% of patients with Hirschsprung disease

F. May present later in childhood with “short segment” Hirschsprung disease

G. Enterocolitis is most serious complication with a mortality of 20% and symptoms including sudden onset of fever, abdominal distension, and bloody diarrhea (which may be explosive)

H. Diagnosis through rectal manometry and rectal biopsy

### CLINICAL PEARLS

- Soapsuds, tap water, and magnesium enemas are not recommended for rectal disimpaction
- In children with constipation refractory to treatment, consider Hirschsprung disease
- Risk factors for developing chronic constipation: acute constipation, painful defecation, or harsh or too early toilet training

### References


15. Urinary Tract Infections in Children

I. TWO MONTHS TO TWO YEARS OF AGE (For evaluation of infants younger than 2 months with fever, see Chapter 6, Fever without a Source in Infants. For children older than 2 yrs, see II. below)

A. Prevalence of UTI
   1. Approximately 5%
   2. Prevalence in girls is more than twice that in boys
   3. Rate in uncircumcised boys may be between 5–20 times higher than in circumcised boys

B. Risk of Undiagnosed UTI
   1. Initial UTI may bring to attention obstructive congenital anomalies
   2. Incidence of vesicoureteral reflux (VUR) is much higher in age group < 2 yrs; this group is at much higher risk for incurring renal injury. Severity of VUR is greater in infants. Severe form (intrarenal reflux) is limited to infants
   3. Delay in instituting treatment for UTI, especially acute pyelonephritis, increases the risk of kidney damage
   4. Risk of renal damage increases with the number of UTI recurrences

C. Etiology
   1. E. coli—75–90%
   2. Klebsiella
   3. Proteus
   4. Staph saprophyticus

D. Classification of UTI in children
   1. Pyelonephritis is characterized by the following: abdominal or flank pain, fever, malaise, nausea, vomiting, and occasionally diarrhea. Infants may show nonspecific symptoms such as jaundice, poor feeding, irritability, and weight loss
   2. Cystitis—Dysuria, urgency, frequency, suprapubic pain, incontinence, and malodorous urine. Cystitis does not cause fever nor result in renal injury
   3. Asymptomatic bacteriuria—A positive urine culture without any manifestations of infection; occurs almost exclusively in girls. This condition is benign and does not cause renal injury

E. History and physical exam
   1. History
      a. Clinical symptoms (dysuria, frequency) may be absent, but may include a history of fever, crying on urination, foul-smelling urine, or an altered voiding pattern
      b. Ask about nonspecific findings of increased irritability, vomiting, diarrhea or constipation
   2. Physical exam
      a. Vital signs including temperature
      b. Degree of toxicity and dehydration
      c. Irritability

F. Lab/evaluation—A urine culture is recommended for confirmation and appropriate therapy
   1. In toilet-trained children, a midstream urine sample is usually satisfactory. If the culture shows greater than 100,000 colonies of a single pathogen, or if there are 10,000 colonies and the child is symptomatic, it is considered a UTI
   2. A catheterized specimen should be obtained when assurance to rule in or rule out the diagnosis is necessary. This is the most accurate way to diagnose a UTI
   3. In infants, the application of an adhesive, sealed, sterile collection bag after disinfection of the skin of the genitals can be used, but this approach is problematic as a positive urinalysis and culture may reflect a contaminant, particularly in girls
and uncircumcised boys
   a. If the urinalysis result is positive, the patient is symptomatic, and there is a single
      organism cultured with a colony count greater than 100,000, a diagnosis of a
      UTI can be made
   b. If any of these criteria are not met, confirmation of infection with a catheterized
      sample is recommended

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity % (Range)</th>
<th>Specificity % (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte esterase</td>
<td>83 (67–94)</td>
<td>78 (64–92)</td>
</tr>
<tr>
<td>Nitrite</td>
<td>53 (15–82)</td>
<td>98 (90–100)</td>
</tr>
<tr>
<td>Leukocyte esterase or nitrite positive</td>
<td>93 (90–100)</td>
<td>72 (58–91)</td>
</tr>
<tr>
<td>Microscopy: WBCs</td>
<td>73 (32–100)</td>
<td>81 (45–98)</td>
</tr>
<tr>
<td>Microscopy: bacteria</td>
<td>81 (16–99)</td>
<td>83 (11–100)</td>
</tr>
<tr>
<td>Leukocyte esterase or nitrite or microscopy positive</td>
<td>99.8 (99–100)</td>
<td>70 (60–92)</td>
</tr>
</tbody>
</table>

From: American Academy of Pediatrics. Practice Guidelines. The diagnosis, treatment, and evaluation of the initial urinary tract
infection in febrile infants and young children (AC9830). Pediatrics 1999;103; 843–52.

G. Treatment—UTI
   1. If the patient is assessed as toxic/dehydrated/unable to maintain PO intake, the patient
      should be hospitalized
   2. In the non-toxic child with a positive urinalysis or urine culture:
      a. Amoxicillin-Clavulanate (Augmentin): 25–45mg/kg/day in 2 doses. Available
         in 200mg/5mL or 400mg/5mL suspension
      b. TMP/SMX (Bactrim): 8mg/kg TMP and 40mg SMX per day in 2 doses. Available
         in 40mg TMP/200mg SMX/5mL suspension
      c. Cefixime (Suprax): 8mg/kg Q24h or 4mg/kg Q12h. Available in 100mg/5mL
         or 200mg/5mL suspension
      d. Cefpodoxime (Vantin): 10mg/kg/day in 2 doses. Available in 50mg/5mL or 100
         mg/5mL suspension
      e. Cefprozil (Cefzil): 15mg/kg Q12h. Available in 125mg/5mL or 250mg/5mL
         suspension
      f. Cephalexin (Keflex): 25–50mg/kg/day divided Q6–12 hr. Available in 125mg/
         5mL or 250mg/5mL suspension
   3. Be aware of local bacterial resistance pattern that affect antibiotic choices, particularly
      TMP/SMX and Cephalexin
   4. Do not use Nitrofurantoin in febrile infants with UTIs due to insufficient therapeutic
      serum concentration
   5. If the expected response does not occur in 2 days, the child should be re-evaluated
      and another urine specimen should be cultured
   6. Duration: 7–14 days

H. Treatment—Pyelonephritis
   1. Well-appearing children may be treated with oral therapy
   2. Children who are dehydrated, are unable to drink fluids, or in whom sepsis is a
      possibility should be admitted to the hospital

I. Evaluation
   1. UTIs in infants and young children serve as markers for abnormalities of the urinary
      tract. Imaging of the urinary tract is recommended in every febrile infant and
      young child with a first UTI
   2. Ultrasound of kidneys and bladder
      a. Should be done promptly in patients who do not respond within 2 days of ATB
         therapy. Can be delayed in children responding to treatment
b. A normal ultrasound does not exclude VUR

3. Voiding cystourethrography (VCUG)
   a. Will detect vesicoureteral reflux. Grades of severity are recognized (I–V)
   b. Child should be free of infection at time of this study to avoid bladder irritability

4. If vesicoureteral reflux is present, a DMSA (Dimercaptosuccinic acid) scan should be performed to assess whether renal scarring is present

II. GREATER THAN 2YRS OF AGE
A. Diagnosis may be simpler as the child may be able to localize symptoms to the urinary tract as well as provide a clean-catch specimen
B. Children in this age group are much less likely to have factors predisposing them to renal damage and are at lower risk of developing renal damage
C. In all patients < 5yrs and in boys > 5yrs diagnostic imaging with ultrasound and voiding cystourethrogram should be considered. Further management is dictated by findings on diagnostic imaging and clinical course
D. In girls > 5yrs with no systemic signs, diagnostic imaging is not necessary with the first UTI, but may be indicated in cases of recurrent UTI

CLINICAL PEARLS
   • Between 1–2yrs, the prevalence of UTIs in febrile girls is 8.1% and in boys is 1.9%
   • Treatment of asymptomatic bacteriuria is controversial, but some studies have indicated that the risk of renal scarring is low and that treatment does not decrease the risk of UTI recurrence
   • Recurrent UTI is 2 UTIs over a 6 month period. It is important to determine if a subsequent UTI is a recurrence or an inadequately treated initial UTI

References
16. Enuresis

I. Definitions
   A. Involuntary or intentional loss of urine into bedclothes or undergarments after age 5, without medical or medication causes
   B. Primary enuresis refers to a failure to ever achieve bladder control. Primary nocturnal enuresis accounts for 90% of all causes of enuresis and is 3 times as common in boys
   C. Secondary enuresis refers to a return to incontinence after bladder control was previously achieved and is usually associated with psychological stressors (birth of a sibling, significant loss or family discord), anxiety, or psychiatric disorders

II. Etiology
   A. Delayed maturation of the cortical mechanisms that allow voluntary control of the micturition reflex
   B. Reduced antidiuretic hormone production at night, resulting in an increased urine output
   C. Genetic factors, with chromosomes 12 and 13q the likely sites of the gene for enuresis: if one parent was enuretic, each child has a 44% risk of enuresis; if both parents were enuretic, each child has a 77% likelihood of enuresis
   D. Psychologic factors
   E. Organic factors, such as urinary tract infection (UTI) or obstructive uropathy
   F. Sleep apnea

III. History:
   A. Type and severity: Determine if the episodes of enuresis are nocturnal (nighttime), diurnal (daytime), mixed (day and night) and primary or secondary. Determine number of enuretic nights per week, the number of episodes per night, and the amount voided with each episode
   B. Voiding history: Weak urinary stream, urgency, infrequent voiding, previous UTI, encopresis, constipation
   C. Evaluation for other conditions which may cause enuresis including diabetes, constipation, seizure disorders, neurologic disorders, UTIs
   D. Family history: Enuresis or urinary tract abnormalities

IV. Physical Exam
   A. Neurologic: Complete neurological exam
   B. Spinal cord pathology: Inspect back for evidence of sacral dimpling or cutaneous abnormalities suggesting spinal pathology
   C. Abdominal and genital exam
   D. Rectal exam: Consider performing after voiding to assess for chronically distended bladder

V. Laboratory Evaluation
   A. Urinalysis and urine culture to exclude renal, metabolic, and infectious pathology
   B. If indicated, consider a renal sonogram, a voiding cystourethrogram, and spine films (if spinal pathology is suspected on history and physical)

VI. Treatment:
   A. Fluid restriction: after 7 PM
16. Enuresis

Care of Children

1. Less than 75 lb: 2 oz
2. 75-100 lb: 3 oz
3. 100 lb or more: 4 oz
4. In addition, the parents should be certain that the child voids at bedtime

B. Star Chart for dry nights—positive reinforcement

C. Conditioning therapy: Auditory alarm attached to electrodes in the underwear. The alarm sounds when voiding occurs and is intended to awaken children and alert them to void. Therapy is curative with success rate of 30-60%

D. Desmopressin (DDAVP) tablets: Approved for ≥6 yr of age
   1. Consider first-line pharmacologic therapy
   2. Give the dose 1 hr before bedtime
   3. Start with 0.2mg at bedtime. If complete dryness is not achieved after 1–2 weeks, increase dose to 0.4mg. Most guidelines do not recommend exceeding the dose of 0.4mg
   4. Assess response at 4 weeks
      a. If there are signs of a response, continue treatment × 3 months. May continue treatment up to 6 months if needed
      b. If there is a lack of response, consider stopping DDAVP therapy. The most common reason for unresponsiveness is reduced nocturnal bladder capacity.
      Another cause is persistent nocturnal polyuria
   5. Tapering Desmopressin gradually if using repeated courses
   6. Efficacy: 30% of patients achieve total dryness. 40% have decreased in nighttime wetting. 60%-70% relapse after discontinuation of therapy
   7. Adverse effects: Water intoxication with hyponatremia. Discontinue the drug if headache, nausea, or vomiting develops. Advise the parents not to administer the medication on nights when there is excess fluid intake. Withdraw Desmopressin at times of sickle cell crisis
   8. Desmopressin nasal spray is no longer indicated for enuresis due to a high risk for water intoxication

E. Oxybutynin (Ditropan): Indicated for the treatment of overactive bladder in adults
   1. Consider a second-line therapy for children who do not have a response to other therapies
   2. As an anticholinergic drug, it increases bladder capacity and reduces detrusor overactivity
   3. Efficacy: Not effective as monotherapy; better response if combined with Desmopressin
   4. Dose: Give 5mg before bedtime
   5. Adverse effects: Constipation, dry mouth, blurred vision, dizziness, tachycardia, headache, nausea and GI upset

F. Imipramine (Tofranil): Indicated for enuresis in children ≥6 yr of age
   1. Consider a third-line therapy, when all other therapeutic options have failed
   2. Give 25mg 1 hr before bedtime; if response is not achieved after 1–2 weeks, may increase the dose to 50mg in children 7–12 yr of age and up to 75mg in older children
   3. Assess in 3 months for response
   4. Withdraw Imipramine gradually when stopping treatment
   5. Efficacy: 20% of children became dry when compared to placebo
   6. Adverse effects: mood changes, nausea, sleep disturbance, seizure, and cardiotoxicity with potential for death with overdose

CLINICAL PEARLS

• Incidence of primary nocturnal enuresis at ages 5, 10, and 14 is 15%, 3–5%, and 1% respectively
• Primary nocturnal enuresis accounts for approximately 80% of all cases of enuresis
• Spontaneous remission occurs at about 15% per year
• 23–36% of parents use punishment for enuresis
17. Rashes in Children

Note: See chapter 96, Describing Dermatologic Lesions, for description and diagrams of different rashes

I. MACULOPAPULAR EXANTHEMS

A. Measles (Rubeola) Low incidence due to immunization
   1. Incubation: 10–14 days
   2. Prodrome: Cough, coryza, conjunctivitis, 3 days high fever; child appears toxic
   3. Exanthem: Fever peaks when rash appears: Erythematous macules and papules appear on upper neck and face, then begin to progress down to extremities and become confluent. Petechial eruption may appear on the soft palate 1–2 days before rash followed by Koplik’s spots (blue-white macules with surrounding erythema found on the buccal mucosa adjacent to the second molars). Rash co-exists with fever and leukopenia and lasts 7–10 days
   4. Lab: Measles IgM antibody at least 3 days after onset of rash
   5. Management: Supportive and control pain caused by oral ulcers
      a. Acetaminophen
      b. Topical viscous Lidocaine—Apply with a cotton-tipped swab several times daily
      c. Mixture of Diphenhydramine, Mylanta and Carafate: swish and spit
   6. Management: Supportive

B. Rubella
   1. Incubation: 14–21 days
   2. Prodrome: Nonspecific respiratory symptoms and lymphadenopathy (postauricular, suboccipital)
   3. Exanthem: Pink, begins on face and progresses downward, lasts 2–3 days, and fades in reverse direction
   4. Complications: Arthritis common in women after 2–3 days of illness (knee, wrist, finger), encephalitis, thrombocytopenia
   5. Virus can be isolated from throat or urine up to 2 weeks after onset of rash
   6. Management: Supportive—isolate patient from pregnant women (virus is highly teratogenic if exposure occurs in first trimester)

C. Erythema infectiosum (fifth disease—Parvovirus B19)
   1. Incubation: 7–14 days, occurs in winter-spring epidemics in school-age children
   2. Prodrome: None
   3. Exanthem:
17. Rashes in Children

Stage I. Red-flushed cheeks with circumoral pallor (slapped cheek)
Stage II. Maculopapular eruption on proximal extensor surfaces of extremities spreads distally and often to trunk, neck and buttocks. Palms and soles are spared (lacelike)
4. Complications: Arthritis, aplastic crisis
5. Management: Supportive

D. Roseola (Human herpes virus—Type 6): Occurs in children age 6 months to 3 years
1. Incubation: 10–14 days
2. Prodrome: 3–4 days of high fever which precedes rash; child looks great despite fever
3. Exanthem: Macules with secondary erythema which appear when fever breaks. Initially seen on chest, it spreads to involve face and extremities. Lymphadenopathy may be present (suboccipitally)
4. Complications: Febrile seizures
5. Management: Supportive

E. Scarlet fever (Group A B-hemolytic streptococci)
1. Incubation: 2–4 days. Follows pharyngitis or skin infection
2. Prodrome: Low-grade temperature, sore throat, malaise, lymphadenopathy
3. Exanthem: Erythematous, sandpaper texture; starts on neck, axillae, inguinal areas and then spreads to rest of body. Petechiae in antecubital and axillary skin folds (Pastia’s Lines) are helpful in making diagnosis. Lasts 7 days and then desquamates. Can also see red strawberry tongue
4. Complications: Rheumatic fever, acute glomerulonephritis
5. Management: Penicillin—see Chapter 10, Pharyngitis, for dosage information

F. Hand, foot and mouth disease (enteroviruses: Coxsackie virus a16, a5, and a10)
1. Incubation: 4–6 days (exposure through enteric route; oral-oral or fecal-oral)
2. Prodrome: Low-grade temperature, sore throat, malaise, lymphadenopathy
3. Exanthem: Aphthae-like lesions anywhere in the mouth followed by 3–7mm red macules on palms and soles. These develop into cloudy vesicles with red halos. Can also see mild peri-orbital edema
4. Complications: None
5. Management: Supportive including viscous Lidocaine and Diphenhydramine elixir—both swish and spit

G. Kawasaki’s disease (Mucocutaneous lymph node syndrome)
1. Incubation: Unknown
2. Prodrome: Abrupt, high spiking fever (101–104°F), unresponsive to antipyretics. Occasionally diarrhea, cough or abdominal pain
3. Exanthem: Within 3 days of fever
   a. Bilateral bulbar conjunctival congestion
   b. Erythematous mouth and pharynx with strawberry tongue and red, cracked lips
   c. Edema of the hands and feet with erythema of the palms and soles
   d. Cervical lymphadenopathy
4. Complications: Arthritis, meningitis, coronary, aneurysm (20–25%)
5. Management: Supportive care, detection of coronary disease and anti-inflammatories (IVIG and Aspirin). Hospital admission

H. Lyme disease
1. Etiology: Vector-borne illness caused by spirochete Borrelia burgdorferi, transmitted by bite of Ixodes scapularis tick (deer tick)—size of pin head
2. Prodrome: Erythema migraines develop in about 80% of patients with disease and appear 2–20 days after bite. May be accompanied by fever, chills, myalgia, headaches, arthralgia
3. Exanthem: Appears at site of inoculation as enlarging erythematous macular rash with central clearing
4. Complications: Secondary and tertiary illness may involve facial palsy, chronic
5. Treatment of early infection:
   a. **Doxycycline** (not recommended for children < 8 y) ≥ 8 y: 2 mg/kg BID. Max 100mg/dose
   b. **Amoxicillin**: 50 mg/kg/d in 3 doses. Max 500mg/dose
   c. **Cefuroxime (Ceftin)**: 30 mg/kg/d in 2 doses. Max 500 mg/dose

6. Routine prophylaxis

II. VESICULAR EXANTHEM

A. Chickenpox (varicella zoster virus)
   1. Incubation: 10–20 days
   2. Prodrome: Malaise; low grade fever
   3. Exanthem: Develops over 3–6 day period usually starting along hairline of face; each lesion begins as a macule that progresses to a papule and vesicle and finally a crusted vesicle; rash emerges in crops over the trunk and finally the extremities; lesions in different stages are present throughout the first week
   4. Complications: Bacterial infection of vesicular lesions, pneumonia, hepatitis, arthritis, glomerulonephritis, CNS disease
   5. Prevention: Routine immunization with varicella vaccine (Varivax) in children ≥ 12 months of age: 2 doses SC at ≥ 4 weeks apart
   6. Management
      a. Cut patient's fingernails short to prevent scratching and secondary infection
      b. Wash lesions BID with soap and water
      c. **Benadryl**, cold washcloth or oatmeal baths (Aveeno bath) will help decrease itching
      d. Routine use of antiviral agent in healthy children is not recommended
      e. **Acyclovir (Zovirax)** should be considered in:
         i. Severe infection in infants and immunocompromised children: 10mg/kg Q8h IV × 7 days
         ii. Healthy children with severe infection and children receiving high-dose steroid or long-term salicylate therapy: 20 mg/kg QID PO × 5 days
      f. **Varicella Zoster Immune Globulin (Human), VARIZIG** is indicated for post-exposure prophylaxis in high risk individuals. Dosing of VARIZIG is based on body weight
      g. Post-exposure varicella vaccination: ACIP recommends that after being exposed to varicella, people who do not have evidence of immunity and are eligible for vaccination should get varicella vaccine. The vaccine is effective in preventing chickenpox or reducing the severity of the disease if administered within 3 days, and possibly up to 5 days, after exposure

B. Rhus dermatitis (poison ivy)—See Chapter 97, Contact Dermatitis

III. PETECHIAL RASH

A. Meningococemia
   1. Etiology: Meningococci are gram-negative organisms which contain endotoxins in their cell walls
   2. Prodrome: Cough, headache, sore throat, nausea, vomiting (all may be of very short duration prior to rash appearing). Patient usually appears toxic
   3. Rash: May be maculopapular in early stages. Purpura and petechiae are seen over the extremities and trunk
   4. Complications: Acute purulent meningitis, DIC, septic arthritis, pericarditis
   5. Differential: H. flu, pneumococcus, enterovirus, rickettsial disease, Henoch-Schonlein purpura, and blood dyscrasias can all cause a similar petechial rash
   6. All children who are ill-appearing and febrile with a petechial rash should be hospitalized until meningococemia is ruled-out

B. Rocky Mountain Spotted Fever
   1. Incubation: 3–12 days after tick bite
   2. Etiology: Tick-borne illness caused by Rickettsia rickettsii. Dogs and rodents are
reservoirs. Transmission requires tick attachment for greater than 6hrs; occurs most commonly along eastern seaboard, Oklahoma, Arkansas, Texas
3. Prodrome: High fever, severe headache, myalgia, shaking rigor, photophobia, nausea
4. Exanthem: Typically develops around fourth day of illness. Begins as pink macules on wrists, forearms, ankles, palms, and soles, and then spreads centrally within 6–18hrs to arms, thighs, trunk, and face. Within 2–4 days, lesions become petechial
5. Complications: Splenomegaly, conjunctivitis, edema, irritability, and confusion. Mortality rate is 5–7% due to severe vasculitis
6. Treatment: **Doxycycline** is the first-line treatment for adults and children of all ages. Dosage: <45 kg: 2.2mg/kg given BID × 7–14 days; ≥ 45 kg: 100mg BID

**CLINICAL PEARLS**
- VZV vaccine if used within 3–5 days postexposure of household or hospital contact may abort infection and reduce symptoms
- The management of most rashes in children is supportive—rule out the “life threatening” causes of rashes with a thorough history and physical exam
- Most petechial rashes are caused by viruses
- Risk of Lyme disease transmission is small with ticks attached < 48hrs, and significantly increases with attachment > 72hrs

**References**
18. ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

DEFINITION: a psychological disorder that is characterized by a short attention span, impulsivity, distractibility, and hyperactivity

I. INTRODUCTION
A. Prevalence of 5–10% of school-aged children. The most common neurobehavioral disorder in childhood
B. Male to female ratio 3:1
C. High prevalence in first-degree relatives and twins, i.e., genetic component is likely
D. Increased risk with Fetal Alcohol Syndrome, exposure to drugs of abuse in utero, prior brain injury, and AIDS

II. HISTORY
A. Evaluate for ADHD in any child presenting with complaint of inattention, impulsivity, hyperactivity, academic underachievement, or behavioral problems
B. Assess school performance at each visit for all children
C. Use strict DSM-V criteria to diagnose ADHD and specify subtype (see below)
D. Obtain evidence directly from parents or caregivers regarding DSM-V criteria
E. The use of specialized questionnaires and ratings scales is helpful. Connor’s scales have sensitivity and specificity of over 94% in high-risk populations (the use of Global, nonspecific questionnaires and ratings scales that assess for a variety of behavioral conditions is not recommended in the diagnosis of ADHD)
F. Evidence regarding core symptoms, duration of symptoms, and degree of impairment from classroom teacher or other school professional is required
G. If a child routinely spends a significant amount of time in another setting (daycare, etc.), evidence concerning diagnosis can be obtained from professionals in that setting. Discrepancies between sources is common and should lead the physician to seek information from further sources
H. Evaluate for coexisting conditions (depression, anxiety, learning disabilities, oppositional defiant disorder, conduct disorder) as they are present up to 33% of the time

III. PHYSICAL EXAM
A. Thorough physical exam including complete neurologic exam
B. Any abnormalities should prompt work-up for another diagnosis, as there are no physical findings of ADHD

IV. LABS/OTHER TESTS
A. Generally lab studies are not indicated unless directed by the history or physical exam
B. If indicated, consider CBC, iron studies, lead level, thyroid tests
C. Consider chromosomal studies if mental retardation or fragile X (etc.) are suspected
D. EEG if seizures (absence seizures) are suspected
E. EKG and other cardiac considerations
1. A supplementary statement released in August 2008 by the American Academy of Pediatrics did NOT recommend getting an electrocardiogram (ECG) to screen for heart problems before prescribing stimulants. However, if the patient has suspected cardiac disease including suspected arrhythmia and/or syncope, an ECG should be obtained

V. DSM-V CRITERIA FOR ADHD
A. People with ADHD show a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development:
1. Inattention: 6 or more symptoms of inattention for children up to age 16, or 5 or more for adolescents 17 and older and adults; symptoms of inattention have been present for at least 6 months, and they are inappropriate for developmental level:
   - Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities
   - Often has trouble holding attention on tasks or play activities
   - Often does not seem to listen when spoken to directly
   - Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., loses focus, side-tracked)
   - Often has trouble organizing tasks and activities
   - Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework)
   - Often loses things necessary for tasks and activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones)
   - Is often easily distracted
   - Is often forgetful in daily activities

2. Hyperactivity and Impulsivity: 6 or more symptoms of hyperactivity-impulsivity for children up to age 16, or 5 or more for adolescents 17 and older and adults; symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for the person’s developmental level:
   - Often fidgets with or taps hands or feet, or squirms in seat.
   - Often leaves seat in situations when remaining seated is expected.
   - Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless)
   - Often unable to play or take part in leisure activities quietly
   - Is often “on the go” acting as if “driven by a motor”
   - Often talks excessively
   - Often blurts out an answer before a question has been completed
   - Often has trouble waiting his/her turn.
   - Often interrupts or intrudes on others (e.g., butts into conversations or games)

3. In addition, the following conditions must be met:
   - Several inattentive or hyperactive-impulsive symptoms were present before age 12 years
   - Several symptoms are present in two or more settings (e.g., at home, school or work; with friends or relatives; in other activities)
   - There is clear evidence that the symptoms interfere with, or reduce the quality of, social, school, or work functioning
   - The symptoms do not happen only during the course of schizophrenia or another psychotic disorder. The symptoms are not better explained by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder)

4. Based on the types of symptoms, 3 kinds (presentations) of ADHD can occur:
   - Combined Presentation: if enough symptoms of both criteria inattention and hyperactivity-impulsivity were present for the past 6 months
   - Predominantly Inattentive Presentation: if enough symptoms of inattention, but not hyperactivity-impulsivity, were present for the past 6 months
   - Predominantly Hyperactive-Impulsive Presentation: if enough symptoms of hyperactivity-impulsivity but not inattention were present for the past 6 months

Because symptoms can change over time, the presentation may change over time as well

VI. DIFFERENTIAL DIAGNOSIS OF ADHD

A. Dysfunctional family
   1. Acute family stressors: e.g., divorce, death
   2. Poor parenting: Lack of limit setting, teen parents, parental depression, mental illness in parents

B. Learning disability
C. Mental retardation or lower IQ
D. Hearing or visual disorder
E. Oppositional defiant disorder
F. Conduct disorder
G. Cognitive impairment from other disorders
   1. Lead poisoning
   2. Medication reaction (Theophylline, Phenobarbital, antihistamines)
   3. Hyperthyroidism
H. Childhood depression
I. Inappropriate parental expectations for normal developmental maturity
J. Tourette’s syndrome
K. Absence seizures

VII. TREATMENT
A. Establish a management plan that recognizes ADHD as a chronic condition. Educate parents, coordinate health services, offer support groups
B. Set appropriate target outcomes that are realistic, attainable, and measurable
C. Parental interventions
   1. Rules and limits: Must be consistent and firm in enforcing them; consequences should be predictable
   2. Environmental structure: Routines at home will help the child accept consistency
   3. Reinforce positive behavior: One method involves a “token economy” where the child earns tokens for good behavior, doing homework, finishing tasks, etc., and then trades in the tokens for rewards
   4. Set aside time each day where all of the attention is on the child (reading or playing age appropriate games)
   5. Provide a special place for doing homework that is quiet and free of distractions
D. Teacher interventions
   1. Seat the child in the front of the classroom
   2. Allow the child to move around occasionally by having him/her hand out papers or erase the chalkboard
   3. Keep instructions brief and clear
   4. Give the child positive reinforcement whenever possible
   5. A weekly report will allow parents to monitor behavior
   6. Supervise the child closely in the cafeteria or the playground (fighting or acting out)
E. Medications: Stimulants
   1. General
      a. Stimulants are highly effective
      b. No single stimulant has been proven superior over another, but individual children respond differently to different stimulants, therefore, try at least 3 different stimulants (short- and long-acting) before abandoning the class (80% of children will respond to at least 1)
      c. Monitor height, weight, blood pressure and heart rate for cardiac adverse effects of stimulants
      d. Side effects of stimulants include insomnia, headache, stomachaches, and appetite suppression which can lead to weight loss. Stimulants can also cause or exacerbate vocal and motor tics
      e. “Drug holidays” over weekends or school holidays are not recommended since ADHD is a chronic condition present in all settings. This area is controversial, so therapy should be individualized for the child
      f. If there is history of substance abuse in patient or household member, avoid stimulants (consider Strattera, Intuniv, or Kapvay) or use stimulants with less potential for abuse (e.g., Lisdexamfetamine, osmotic-release preparation, Methylyphenidate patch)
   2. Methylphenidate
      a. Immediate-release (IR): Ritalin, Methylin
         i. Start 0.3 mg/kg PO BID or 2.5–5mg PO BID, increase each week by 0.1mg/kg/
dose or 5–10mg/day
ii. Average dose is 20–30mg/day. Maximum dose is 60mg/day
iii. Available 5, 10, 20mg scored tablets
iv. The first dose is in the morning. If BID, add the second dose at lunch. Take 30–45 minutes before meals
v. Peak effect 2hrs after ingestion, most effect gone after 6hrs
vi. Some children may need a mid-afternoon dose to concentrate on homework or extra-curricular activities. The last dose should not be taken after 6 PM
vii. Available in 2.5mg, 5mg, 10mg tablets and chewable tablets (Methylphenidate), and 5mg/5mL and 10mg/5mL solutions

b. Intermediate-acting (Ritalin SR, Metadate ER)
   i. Duration: 2–8 hr; given once daily or BID
   ii. Initial dose: 20mg QAM for children tolerating 10mg IR in AM and noon; may add another dose or IR tab (5 or 10mg) at 2PM if needed
   iii. Must be swallowed whole
   iv. Ritalin SR is available in 20 mg tabs; Metadate ER is available in 10mg and 20mg tabs

c. Extended Release (Concerta, Metadate CD, Ritalin LA)
   i. Dosing is QD
   ii. Duration of action is 8–12hrs
   iii. Less potential for abuse due to the special formulation that provides IR and ER components
   iv. Concerta: Available in 18, 27, 36, 54 mg OROS tabs (osmotic system has hole for drug release with IR overcoat). Must be swallowed whole
   v. Metadate CD: available in 10, 20, 30, 40, 50, 60mg bead-filled capsules (30% IR and 70% ER). Swallow whole or may be sprinkled over applesauce
   vi. Ritalin LA: Available in 10, 20, 30, 40mg bead-filled capsules (50% IR and 50% ER). Swallow whole or may be sprinkled over applesauce

d. Quillivant XR
   i. First extended-release oral suspension approved for children aged 6–12 years
   ii. Start dose at 20mg once daily in the morning. May increase dose weekly in increments of 10–20mg/day. Max dose 60mg/day
   iii. Duration of action: 8–12 hrs

3. Dexmethylphenidate (Focalin): 2.5–10mg BID
   a. Start at 2.5mg BID and increase by 2.5–5mg/day every week to maximum of 20mg/day
   b. If converting from Methylphenidate, cut dose by 50%
   c. Only indicated for ages 6 and over
   d. Duration: 4–5 hrs
   e. Available in 2.5, 5, 10mg tab
   f. Extended release formulation: Focalin XR
      i. Start at 5mg/day and titrate weekly in 5mg/day increments to a max of 30mg/day
      ii. May convert IR to XR form given QAM at same total daily dose
      iii. Available in 5, 10, 15, 20, 25, 30, 35, 40mg caps. Swallow whole or sprinkle over applesauce

4. Amphetamine mixtures
Adderall

i. In children >6yrs, 5mg QAM or BID, may increase by 5mg every week up to 40mg/day

ii. In children 3–5yrs, the initial dosage is 2.5mg QAM, may increase by 2.5mg every week until optimum response is attained

iii. Can convert to extended release (Adderall XR) given QAM at same total daily dose, maximum 30mg/day

iv. Duration: 6 hrs (IR tab), 10 hrs (XR cap)
v. Available in 5, 7.5, 10, 12.5, 15, 20, 30mg IR tabs. 5, 10, 15, 20, 25, 30mg XR caps

b. Vyvanse (Lisdexamfetamine)

i. Considered to have less potential for abuse compared to Adderall. Vyvanse is a prodrug and is not chemically active until the Lisdexamfetamine is metabolized and the lysine molecule is cleaved from the dextroamphetamine.

ii. Once daily dosing indicated for patients 6 and older

iii. Starting dose is 20–30mg and may increase weekly by 10-20 mg for a maximum daily dose of 70mg

iv. Duration of action: 10–12 hrs

v. Available in 20, 30, 40, 50, 60, 70mg caps

Dextroamphetamine (Dexedrine)

a. 3–5yrs: 2.5mg QD, increase 2.5mgQ wk until response

b. ≥ 6yrs: 5mg QD or BID, increase by 5mg Q wk until response; maximum 40mg/day

c. Available in 5, 10mg tabs and 5mg/5mL solution

d. Alternative drug when Ritalin is not effective or side effects occur

e. Can convert to extended release formulation (Dexedrine spansule—5, 10, 15 mg) when dosing is stable

f. High potential for abuse

g. Side effects: Weight loss, HTN, difficulty with sleep

F. Medications: Non-stimulants

1. Atomoxetine (Strattera):

a. Norepinephrine reuptake inhibitor that increases both norepinephrine and dopamine levels

b. Comparable efficacy with stimulants and is the drug of choice for children with the following:

i. Contraindication to stimulants

ii. Psychiatric comorbidities

iii. Heavy use of behavioral health care

iv. Adolescents with substance abuse problems

v. Tic disorders

c. Children up to 70kg: start at 0.5mg/kg PO QAM × 3 days, increase to a target dose of 1.2mg/kg; maximum dose 1.4mg/kg or 100mg

Children > 70kg: 40mg PO QAM, up to 100mg maximum dose

d. Available 10, 18, 25, 40, 60, 80, 100mg caps

2. Intuniv (Guanfacine)—1mg PO QD and increase to 1–4mg/day (avail. 1, 2, 3, 4mg ER)

a. A selective alpha2a-adrenergic receptor agonist which can be used as monotherapy or as adjunctive therapy to stimulant medications

b. Indicated for children between the ages of 6–17

c. Dosed once daily. Begin with 1mg once daily and adjust in increments of no more than 1mg/week. Maintain the dose within the range of 1mg–4 mg/day depending on clinical response and tolerability

d. Available in 1, 2, 3, 4mg XR tabs. Swallow the whole tablet. Do not chew, crush or break tablet
e. Little abuse potential. May be used adjunctively with stimulants in children to
treat stimulant-induced tics and insomnia
f. Side effects: sedation, somnolence, fatigue, nausea, lethargy, and hypotension
g. Monitor heart rate and blood pressure
h. When discontinued, taper the dose in decrements of ≤1mg Q 3–7 days
3. **Kapvay (Clonidine)**–0.1mg PO HS and increase by 0.1mg in weekly intervals to
reach target of 0.1–0.4mg/day
   a. A selective alpha2a-adrenergic receptor agonist; can be used as monotherapy or
      as adjunctive therapy to stimulant medications
   b. Indicated for children between the ages of 6–17
c. Typically used twice daily. Dosing should be initiated with one 0.1mg tablet at
   bedtime, and the daily dosage should be adjusted in increments of 0.1mg/day at
   weekly intervals. After the first day, doses should be taken twice a day, with
   either an equal or higher split dosage being given at bedtime
d. Available in 0.1, 0.2mg tabs. Swallow the whole tablet. Do not chew, crush or
   break tablet
e. Little abuse potential. May be used adjunctively with stimulants in children to
   treat stimulant-induced tics and insomnia
f. Side effects: sedation, somnolence, hypotension and bradycardia
g. Monitor heart rate and blood pressure
h. Abrupt discontinuation can cause rebound hypertension and irritability. Dis-
   continue slowly in decrements of ≤0.1mg Q 3–7 days
G. Periodically review progress
   1. Use original target outcomes as basis for measurement
   2. Can space out visits to Q3–6 months if child is stable
H. Refer to psychiatrist if patient has true treatment failure or has comorbidities

**CLINICAL PEARLS**

- Stimulants can cause weight loss, but do not affect overall growth potential
- The normal attention span is approximately 3–5 minutes per year of age
- Controlled studies have NOT shown that children with ADHD benefit from dietary
  control of sugar and other additives
- Studies exploring the link between television exposure and ADHD have had inconsis-
  tent results
- Recognizing and treating ADHD is extremely important for the patient’s long-term
  prognosis. Studies have shown that untreated hyperactive boys showed a signifi-
  cantly higher rate of adult psychiatric problems including antisocial and drug abuse
disorders

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I. INTRODUCTION
   A. Autism Spectrum Disorders (ASD) include a broad spectrum of characteristics with deficits in communication and social skills as well as stereotypical behaviors. Age of onset before 3 years old
   B. Prevalence increased 10-fold over the past 50 years due to increased inclusion criteria from DSM-IV and improved support through the Americans for Disabilities Act. Per the CDC about 1 in 88 children have ASD
   C. Etiology is not known, but theories support genetic inheritance. Males are predominantly affected
   D. Specific types
      1. With or without accompanying intellectual impairment
      2. With or without accompanying language impairment
      3. Associated with a known medical or genetic condition or environmental factor
      4. Associated with another neurodevelopmental, mental, or behavioral disorder
      5. With catatonia

II. RED FLAGS
   A. No babbling or pointing by 12 months
   B. No single words by 16 months
   C. No 2-word spontaneous phrases by 24 months
   D. Loss of language or social skills
   E. Other risk factors—Siblings with ASD, parental or caregiver concern, physician concern

III. SYMPTOMS/SIGNS
   A. Joint attention deficits (key factor suggestive of ASD)—Difficulty sharing enjoyment of event/object with another person
   B. Social skill deficits
      1. Difficulty sharing the emotional state of others
      2. Content being alone
      3. Rarely make eye contact
   C. Communication deficits—Lack the desire to communicate; decreased pre-speech with delayed babbling; lack of expressions like “uh-oh,” lack of recognition of parental voice
   D. Regression—Up to one-third of children will begin speaking, but have regression by 15–24 months. May be gradual or sudden
   E. Play skills—Usually lack creativity, usually ritualistic; e.g., lining up crayons rather than coloring with them
   F. Stereotypical behaviors—Unusual attachments to objects, peculiar mannerisms, obsessions, compulsions, self-injury, head banging, rocking, twirling for internal stimulation

IV. SURVEILLANCE
   A. Ask routine developmental questions at each well child visit (see Chapter 2, The Developing Child)
   B. If surveillance is negative, schedule next preventative visit
   C. If surveillance is positive, provide education and refer for comprehensive ASD evaluation, early intervention, or early childhood education services and audiologist evaluation

V. SCREENING
   A. Formal screening should be done with ASD-specific screening tools at each 18- and 24-month well child visit. The AAP recommends the Modified Checklist for Autism in Toddlers (M-CHAT)—see section X. Resources, below
   B. If screening is negative, schedule next preventative visit
   C. If screening is positive, assess for false positives. If the screening test was concerning, provide parental education, refer for a comprehensive ASD evaluation or early intervention
VI. DIAGNOSIS: VIA A COMPREHENSIVE ASD TEAM
A. Thorough history including past medical, developmental, behavior and three generation family history
B. Complete physical exam for dysmorphic features or neurologic abnormalities, suggesting secondary ASD
C. Developmental evaluation for functioning levels of social skills and communication.
D. Assess parental education
E. Routine lab work is not necessary, unless there is concern for secondary causes
F. Consider EEG

VII. MANAGEMENT: Goals of multidisciplinary treatment are to optimize independence and quality of life while reducing core features of ASD and family distress
A. Behavioral therapy: early intervention with >25 hours per week leads to improved cognition, language and adaptive skills
B. Family therapy: support caregivers’ stress, financial responsibilities, and improve patient and family outcomes
C. Identify medical causes for new onset maladaptive behavior
D. Pharmacologic therapy: focus on adverse symptom reduction while managing medication side effects
   1. Probiotics: GI upset
   2. Melatonin: sleep dysfunction
   3. SSRI (e.g., Fluoxetine): anxiety, behavior rigidity or repetition, OCD symptoms
   4. Atypical antipsychotics: consider for self injury, aggression, explosive outbursts
E. Complementary and alternative medicine (CAM)
   1. Lack evidence-based medicine support
   2. A majority of families will try at least one CAM
   3. A strong patient-doctor relationship can help identify proven ineffective or potentially harmful treatments

VIII. PROGNOSIS: Multifactorial and difficult to predict when less than 3 years old
A. Improved outcomes: Early intervention, early onset of joint attention, functional speech by 5 years old, IQ >70
B. Poorer outcomes: Earlier diagnosis, association with medical condition, comorbid mental retardation, seizures
C. Treatment of psychiatric aspects such as anxiety, depression improves overall function

IX. RESOURCES
A. CDC immunization program: www.cdc.gov/nip
B. Autism Society of America: www.autism-society.org
C. Center for the Study of Autism: www.autism.org
D. M-CHAT: http://www2.gsu.edu/~psydlr/DianaLRobins/Official_M-CHAT_Website.html

X. VACCINE SAFETY
There have been many studies demonstrating the lack of association between vaccines and autism. Per the Institute of Medicine (IOM) consensus report, “the evidence favors rejection of a causal relationship between thimerosal–containing vaccines and autism.” CDC supports the IOM conclusion that there is no relationship between vaccines containing thimerosal and autism rates in children. Bottom line: Vaccines do not cause autism

CLINICAL PEARLS
- Autism spectrum disorder is a broad definition of deficits in communication, social skills, and maladaptive behavior
- Evidence has shown that earlier intervention has improved functional independence. Do not wait for a formal diagnosis before starting services. Avoid the “wait and see” approach
- Formal screening should be performed at the 18– and 24–month well child visits with formal ASD tools, such as M-CHAT
- Any red flags, parental concerns or positive screenings should have a comprehensive ASD evaluation
20. Child Abuse

INTRODUCTION: The components necessary for the clinician to adequately address child maltreatment include awareness of the problem, recognition, disclosure, understanding (clinician and victim) and advocacy.

I. DEFINITIONS
A. Child abuse or neglect - Any recent act or failure to act on the part of a parent or caretaker, which results in death, serious physical or emotional harm, sexual abuse or exploitation, or an act or failure to act which presents an imminent risk of serious harm.

B. Sexual abuse
   1. The employment, use, persuasion, inducement, enticement, or coercion of any child to engage in, or assist any other person to engage in, any sexually explicit conduct or simulation of such conduct for the purpose of producing a visual depiction of such conduct; or
   2. The rape, and in cases of caretaker or inter-familial relationships, statutory rape, molestation, prostitution, or other form of sexual exploitation of children, or incest with children.

C. Withholding of medically indicated treatment—the failure to respond to the infant's life-threatening conditions by providing treatment (including appropriate nutrition, hydration, and medication).

II. TYPES OF MALTREATMENT
A. Neglect (most common type of abuse in the US)—Failure of a parent or caregiver to provide for the child
   1. Physical—Failure to provide food, shelter or appropriate supervision.
   2. Medical—Failure to provide necessary medical, dental or mental health treatment.
   3. Emotional—Failure to attend to the child’s emotional needs or to provide psychological care.
      a. Permitting the child to use dangerous substances such as alcohol or drugs.
      b. Prenatal exposure of a fetus to harm.
   4. Educational—Failure to provide educational or special educational needs of the child.
   5. Abandonment—Leaving a child alone in situations where the child suffers serious harm.

B. Physical (second most common type of abuse in the US)—Non-accidental/purposeful physical injury ranging from minor bruising to severe fractures or death. These injuries are considered abuse regardless of caregiver’s intent.

C. Sexual (third most reported type of abuse in the US)—The employment, use, persuasion,
inducement, enticement, or coercion of any child to engage in, or assist any other person to engage in, any sexually explicit conduct or simulation

D. Emotional—A pattern of behavior impairing a child's emotional development or self-esteem; continued criticism, threats, rejection, withholding love or affection, support or guidance

III. BACKGROUND—Epidemiology

A. Incidence (All types of abuse)
   1. 3.3 million referrals involving 6 million children
   2. 24% of investigations confirmed one or more victims of abuse
   3. Highest rate of victimization occurs to children 1 year of age

B. Sexual Abuse Incidence
   1. 34% of victims under the age of 12
   2. 14% of victims under the age of 6
   3. 40% of perpetrators to victims younger than 6 are juveniles
   4. Most victims know the perpetrator

C. Deaths
   1. 1770 deaths (~5/day)
   2. Approximately 81% of all fatalities < 4 years of age

D. Perpetrator
   1. Parent (78.5%)
   2. Other relative (6.5%)
   3. Unmarried partner (4.1%)
   4. Female (58%); Male (42%)

IV. DIFFERENTIAL DIAGNOSIS

A. Infectious
   1. Bullous impetigo
   2. Staphyloccal scalded skin syndrome
   3. Bacterial or viral petechiae

B. Congenital or genetically-acquired
   1. Osteogenesis imperfecta
   2. Ehlers-Danlos syndrome

C. Metabolic
   1. Rickets
   2. Electrolyte disturbances

D. Dermatologic
   1. Dermatitis
   2. Mongolian spots
   3. Vascular malformation
   4. Subcutaneous lipoma or necrosis

E. Hematologic
   1. Idiopathic thrombocytopenic purpura
   2. Henoch-Schonlein purpura
   3. Von Willebrand's disease
   4. Hemophilia

F. Accidental or situational
   1. History is key in these situations. A history that does not match the injury(ies) is highly suspicious for abuse

G. High pain threshold
H. Nursemaid's elbow
I. Stress fractures

V. HISTORY AND PHYSICAL

A. History
   1. General—behavioral indicators
      a. Do the child and caregiver make appropriate eye contact with each other?
      b. Is the interaction between child and caregiver appropriate?
c. Does the caregiver minimize or deny existence of the child’s problems?
d. Does the caregiver blame the child for the child’s problems?
e. Does the caregiver see the child as burdensome, “bad,” worthless or useless?
f. Does the caregiver look to the child for care, attention or emotional needs?

2. Physical maltreatment
   a. Is there a “magical (spontaneously appearing)” injury?
   b. Is the injury consistent with the history?
   c. Is the child disabled or frequently ill with multiple problems?
   d. Is the child alone for increasing periods of time (“home-alone” syndrome)?
   e. Are there behavioral or developmental difficulties?
   f. Is there a history of domestic violence in the home?
   g. Are there frequent visits to medical personnel with or without clearly defined diagnoses?
   h. Are there different forms of injuries (e.g., burns and bruising together)?
   i. Are there injuries in various stages of healing?
   j. Are there pathognomonic or patterned injuries such as belt or cord marks?

3. Neglect
   a. Is the child constantly hungry, fatigued or listless?
   b. Does the child have poor hygiene?
   c. Is the child appropriately dressed?
   d. Are there unattended physical or dental problems?
   e. Is there a failure to thrive?

4. Sexual (the clinician should note that the child’s report is the single most significant indicator of sexual abuse)
   a. Are there changes in behavior such as anorexia, nightmares, insomnia, excessive bathing or hand washing activities, withdrawal from usual activities?
   b. Is there a return to thumb-sucking or nocturnal enuresis?
   c. Is there a difficulty in concentrating at school and/or an unwillingness to attend school?
   d. Irritation or bleeding, swelling, pain, itching, cuts, or bruises in genital, vaginal or anal areas?
   e. Does the patient cry without provocation?
   f. Is there an inappropriate display of sexuality, or sexual knowledge by the child?

B. Physical Examination (note location, size, color, shape of all obvious injuries)
   1. Inspect for obvious injuries, signs of neglect, or other obvious concerns
   2. Examine eye grounds and ear canals for occult injuries (retinal injuries or hemotympanum suggestive of coup-contrecoup injury—shaken baby syndrome)
   3. Examine the oral cavity, groin and scalp
   4. Measure and record each injury—take photographs
   5. Note irritability, vomiting, abnormal respiration or alterations in consciousness
   6. Bruises/abrasions/lacerations
      a. Unexplained injuries to buttocks, back, thighs, torso, ears, and neck
      b. “Normal” childhood bruising typically presents anteriorly on shins, forehead and forearms. Note: Bruises in a non-ambulatory infant are suspicious
      c. Look for shaped or patterned bruising or injury. Encirclement of injury as occurs with flexible objects such as belts or cords, etc. should raise suspicion
   7. Burns
      a. Cigarette or cigar—reddened circumference with central zone of eschar
      b. Immersion injuries to hands or feet secondary to scalding, typically bilateral
      c. Immersion or “doughnut” burns from submersion in hot water, encircling buttocks
      d. Unexplained or excessive splash burn injuries

VI. RADIOLOGIC EVALUATION
   1. Multiple fractures (especially if in various stages of healing)
   2. Epiphyseal separation or metaphyseal lesion—bucket handle fractures
   3. Posterior or multiple rib fractures—especially in infants—may be in conjunction with coup-contrecoup injuries
   4. Skull fractures, especially in infants without a clear history of trauma, especially if
5. Digital fractures, especially without a clear mechanism of injury
6. Vertebral fractures/subluxations or dislocations
7. Scapular fractures
8. Sternal fractures

VII. DISCLOSURE
A. Phases
1. Self—the victim must internally understand the victimization
2. Confidant selection-reaction: the victim typically chooses a time, place and person
3. Consequences—informs victim as to continue or not

B. Reasons for non-disclosure
1. Family
   a. Not believed
   b. Shame
   c. Fear of causing trouble
2. Child Protective Services (CPS) or other services
   a. Ignorance of resources
   b. Service functioning—overwhelming, supportive?
   c. Secrecy—other cultural aspects
   d. Mistrust of adults and/or other professionals

C. Eliciting Disclosure
1. Raise index of suspicion
2. Engage child—ask direct questions
3. Create appropriate situation conducive to disclosure and trust
4. Provide positive emotional suggestions and support

VIII. INTERVENTION
A. Manage life-threatening situations
B. Attend to obvious injuries
C. Activate social services and/or child protective services network—Determine in collaboration with social services safe disposition of the child
D. Document with great care—frequently becomes evidence in criminal prosecutions
E. Maintain resources for parents, caregivers and staff

References
II. Care of the Pregnant Patient & Breast-Feeding

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22. Medications During Pregnancy & Lactation ....................................................... 86
23. Questions Expecting Parents Commonly Ask/Radiation in Pregnancy .... 94
24. OB Admission Note .............................................................................................. 97
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Related subjects:

Infant Formula & Breast-Feeding ............................................................ see Chapter 4

Radiation Exposure in Pregnancy, Table: Estimated fetal exposure of various diagnostic imaging methods.................. see Chapter 23
21. Prenatal Care

(See table “Estimated fetal exposure for various diagnostic imaging methods,” and Questions Expecting Parents Commonly Ask, V, in Chapter 23)

I. SCHEDULE OF PREGNATAL VISITS: Schedules vary by patient population and practitioner

   Note: Pre-conception counseling: Ideally should be first visit. Patient should be given 400mcg Folic Acid supplementation to reduce the risk of neural tube defects. Rubella immunity should be checked and consideration of vaccination if not immune (patients should be counseled to not become pregnant for 3 months after receiving immunization)

   A. Every 4 weeks until 28 weeks
   B. Every 2 weeks from 28–36 weeks
   C. Every week from 36 weeks until delivery
   D. Bi-weekly non stress tests if post-term. Consider modified biophysical profile for amniotic fluid index (AFI) depending on risk factors
   E. Consider induction in uncomplicated patient at 41 weeks

II. INITIAL ASSESSMENT: Forms may vary by practice

   A. History
      1. Pregnancy: Date of first day of last menstrual period (LMP) and timing and flow (normal or light) of LMP
      2. Birth history: History of preterm labor, PIH/preeclampsia, gestational diabetes, incompetent cervix, gestational age of previous births, birth weights, type of anesthesia used, use of vacuum or forceps, episiotomy, history of postpartum hemorrhage, history of shoulder dystocia
      3. Past medical history
         a. History of sexually transmitted diseases (STDs), depression or post-partum depression, history of varicella, and immunization history
         b. History of chronic illness: As more women are delaying pregnancies, more chronic medical conditions, such as diabetes, hypertension and hyperlipidemia, are seen in older pregnant women
      4. Past surgical history: Cesarean section (determine classical vs. low transverse and obtain confirmation if possible), prior gynecological or cervical surgeries, LEEP
      5. Medications
         a. Assess chronic meds for fetal harm and stop medications which are no longer needed
         b. Caution with statins, non-SSRI antidepressants, anti-seizure medications, immunosuppressants. Note: See Chapter 22, Medications during pregnancy and lactation
         c. Continue asthma medications
      6. Drug sensitivities/allergies
      7. Family history including history of genetic abnormalities
      8. Social history: Alcohol, tobacco and drug use, physical and/or emotional abuse
      9. Family support systems, involvement of “father of the baby”
      10. Diet and exercise, weight gain with past pregnancies
      11. Patient preferences: Anesthesia/analgesia, breast vs. bottle feeding, post partum contraception, etc.

   B. Physical: Perform a full physical including thyroid, breast and pelvic exams

   C. Labs and other tests
      1. Routine
         a. Blood group type and Rh factor (this is essential if ectopic or SAB)
         b. Indirect Coombs (antibodies to other blood group antigens)
         c. Hepatitis surface antigen (chronic hepatitis B)

---

Kristen Rundell, MD
Beth Weinstock, MD
Bill Gegas, MD
Curt Gingrich, MD
d. H/H
e. Blood glucose
f. Rubella antibody titer
g. Syphilis serology at intake and repeat in third trimester
h. HIV: If first test is negative and patient has significant risk factors, then repeat in 3–6 months
i. Urinalysis and culture
j. Gonorrhea, Chlamydia cultures (DNA probe)
k. Pap smear if age > 21
l. If history of blood transfusions, check titers for Duffy and Kell antibodies. If increased, then patient is a candidate for amniocentesis

2. Optional
a. Sickle cell (at-risk populations)
b. PPD (pregnancy mimics immunocompromised state): Consider in high-risk patients
c. Ultrasound: Obtain if unsure of LMP or the LMP was abnormal. Not necessary if EDC by dates is reliable
d. Toxo, CMV, varicella: Varicella zoster antibodies if patient has not been exposed

D. Vaccines
1. Influenza vaccine: Should be given to all pregnant women (no longer trimester specific)
2. Varicella (Varivax): Should not be given to pregnant women. Women should avoid pregnancy within 1 month of receiving the vaccine
3. Pertussis booster (Tdap: Adacel or Boostrix): Should be given during each pregnancy irrespective of the patient’s prior history of receiving Tdap (ACIP, October 24, 2012)
   a. Optimal timing for Tdap administration is between 27–36 weeks gestation
   b. Recommend family members and infant care givers to get booster as well

III. INITIAL VISIT TO 28 WEEK VISITS

A. History
1. Contractions: Frequency, intensity
2. Fetal movements (First felt at 18–20 weeks in primip, 16–18 weeks in multip)
3. Vaginal discharge or bleeding
4. Symptoms of preeclampsia (after 20 weeks)
   a. Edema (distinguish ankle edema vs. hand/face edema—latter is more significant for preeclampsia, particularly in third trimester)
   b. Headache
c. Blurred vision
d. Abdominal pain (round ligament pain begins at approx. 20 weeks)
5. Alcohol or drug use
6. Compliance with prenatal vitamins

B. Physical
1. Blood pressure (should be below 140/90)
2. Weight gain: Based on body mass index
   a. Underweight women: 28–40 pounds desired
   b. Normal weight women: 25–35 pounds desired (5 lbs in first 20 weeks, then 1 lb/wk through end of pregnancy)
   c. Overweight women: 15–20 pounds desired (need supervision and diet instruction)
3. Fetal heart tones: Heard by Doppler at 10–12 weeks
4. Fundal height (FH): Measure with bladder empty and legs extended, from the pubic symphysis to top of uterine mass (full bladder can increase FH 3 cm)
5. Urine dip (done in office at every visit): Check for protein, glucose, ketones and leukocytes
   a. Protein: “Trace” or 1+ is WNL. If 2+ or more, then check 24hr urine for protein
   b. Glucose: “Trace” is normal with pregnancy due to increased GFR. If risk factors or more than “trace,” then consider one 1hr glucola screen
   c. Asymptomatic bacteriuria (incidence during pregnancy is 2–7%): Major cause of
maternal and fetal morbidity. If untreated, 25–30% may develop pyelonephritis
i. Diagnosis based upon isolation of > 10^5 organisms per mL of urine in 2
consecutive clean-catch specimens. E Coli is most common offending
organism
ii. Give 3 day course of Nitrofurantoin (Macrobid) or Amoxicillin and screen
with Q month cultures
iii. If greater than 1 UTI or more than 1 incidence of asymptomatic bacteriuria:
Need prophylaxis for duration of pregnancy
iv. Symptomatic bacteriuria. Treat with Cephalexin (Keflex). Fluoroquinolones
are contraindicated in pregnancy. Trimethoprim/sulfamethoxazole
(Bactrim) and Nitrofurantoin (Macrobid) are not recommended after
36 weeks gestation

C. Genetic screening: All women should be offered a blood test for neural tube defects
and trisomy 21 and 28 (see 2. Quad screen, below). Women at increased risk of
aneuploidy should be offered amniocentesis or CVS (see 4. and 5. below). Some offer
fetal nuchal translucency (NT) - can be measured by ultrasonography combined with
maternal serum analyte levels (i.e., free hCG and pregnancy-associated plasma pro-
tein A).
1. Women at increased risk of aneuploidy:
   a. Age > 35 at time of delivery (or age > 32 with twins)
   b. Fetus with major structural anomaly identified by US
   c. US markers of aneuploidy (e.g., increased nuchal thickness)
   d. Previously affected pregnancy
   e. Couples with translocation, chromosome inversion or aneuploidy
   f. Positive maternal serum alpha fetal protein (MSAFP) screen
2. Quad Screen
   a. Indication: To screen pregnancies for neural tube defects (NTD) and Down’s
      syndrome
   b. Perform at 16–20 weeks
   c. Quad analyte screen includes maternal serum alpha fetal protein, HCG
      unconjugated estriol, and inhibin A. Detects 90 % of anencephalic cases, 80 %
      of spina bifida cases, and 70 % of Down’s syndrome
   d. Risks for these anomalies are given as odds. e.g., 1 in 200 chance of having a
      child with Down’s syndrome. The calculation is done by measuring the level
      of each analyte, taking the age of the patient and comparing to other patients
      at same gestational age
   e. If a patient has an abnormal screen, the most likely reason is that the gestational
      age is incorrect. The next step is to obtain an ultrasound to confirm dates and
      repeat the calculation
      i. Statistically 4–5% of all AFPs will be low
      ii. Down’s syndrome occurs in 1.3 of 1000 live births
3. Nuchal translucency (NT)
   a. Indication: Screen for trisomy
   b. Perform at 10–13 weeks
   c. Sensitivity 70% for Down’s
4. Chorionic Villus Sampling
   a. Indication: To determine karyotype and genetic disorders in women with ad-
      vanced maternal age (> 35) or high risk for genetic abnormalities as above.
      Does not screen for spina bifida
   b. Perform at 10–12 weeks
   c. Risk of fetal loss is 1–1.5%. May be associated with transverse limb defects in
      0.1–0.3% undergoing the procedure
5. Amniocentesis: Recommended option of choice for age > 35
   a. To test for chromosomal abnormalities including Down’s, Tay-Sachs, Sickle Cell
disease
   b. Indications
      i. Advanced maternal age (> 35) or women with high risk of genetic
abnormalities as above
ii. Follow-up abnormal analyte screen
c. Perform at 15–20 weeks gestation
d. The chance of fetal trisomies at maternal age 35 is 1/200; age 45 is 1/20
e. There is a 1/200 risk of fetal loss from amniocentesis if performed with ultrasound guidance

IV. WEEKS 28–36
A. History: Same as above. Inquire about > 4 contractions/hr, vaginal bleeding, leaking, fluid or UTI symptoms
B. Physical: Same as above
C. Other
   1. 1 hr post glucola (1 hr PG): Done at 26–30 weeks
      a. Consists of 50g glucose load
      b. 15% of population will be abnormal. 1–2% of pregnant mothers are diabetic
      c. Normal is < 140. If > 140 then obtain 3hr GTT
      d. 3hr GTT is abnormal if 2 or more values are abnormal:
         i. Fasting < 105
         ii. 1hr < 190
         iii. 2hrs < 165
         iv. 3hrs < 145
   2. H/H: 28 weeks (get with 1hr PG)
   3. Syphilis serology is repeated at 28 weeks, regardless of first test result
   4. Repeat GC/Chlamydia in high risk population or if patient was positive in first trimester
   5. If mother is Rh negative: RhoGAM 300mcg IM at 28–32 weeks. If “father of baby” is Rh+, check indirect Coombs prior to giving RhoGAM
   6. If desired, sign consent for tubal ligation/tubal referral
   7. Counsel patient on fetal movements/kick graph. Should count 10 kicks/hr
   8. Counsel patient on fetal movements/give kick graph. (She should feel 10 fetal movements by 6 PM. If not, then she must call and may need to be scheduled for a NST)
   9. Discuss birthing classes (Lamaze or patient’s preference)

V. WEEK 36—DELIVERY
A. History: Same as above
B. Physical: Same as above—plus—
   1. Weekly cervical exams beginning at 37 weeks
   2. Palpate abdomen for fetal lie and position
C. Labs: Group B strep screening per recommendations below
D. Discuss anesthesia during labor (Epidural, Nubain), episiotomy, and labor and delivery procedures. Offer patient opportunity to watch labor and delivery videotape if available
E. Advise patient to call physician or report to Labor and Delivery if:
   1. She suspects ROM
   2. If contractions are Q 5–6 minutes for 1hr for primip, Q 8–10 minutes for 1hr if multip
   3. Vaginal bleeding
   4. Reduced or absent fetal movement (< 10 kicks/hr)
F. HSV prophylaxis, if necessary

VI. RECOMMENDATIONS FOR PROPHYLAXIS OF GROUP B STREPTOCOCCUS
(Centers for Disease Control guidelines)
A. Intrapartum treatment based on risk factors (maternal and infant) vs. universal screening. Vaginal and perirectal culture at 35–37 weeks gestation. All positive cultures should be treated with intrapartum prophylaxis (see chart on next page)
B. Summary of Recommendations for Prevention of Neonatal Group B Streptococcus Disease
Indications and nonindications for intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal (GBS) disease

<table>
<thead>
<tr>
<th>Intrapartum GBS prophylaxis indicated</th>
<th>Intrapartum GBS prophylaxis not indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Previous infant with invasive GBS disease</td>
<td></td>
</tr>
<tr>
<td>• GBS bacteriuria during any trimester of the current pregnancy*</td>
<td></td>
</tr>
<tr>
<td>• Positive GBS vaginal-rectal screening culture in late gestation† during current pregnancy</td>
<td></td>
</tr>
<tr>
<td>• Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following:</td>
<td></td>
</tr>
<tr>
<td>– Delivery at &lt;37 weeks’ gestation§</td>
<td></td>
</tr>
<tr>
<td>– Amniotic membrane rupture ⩾ 18 hours</td>
<td></td>
</tr>
<tr>
<td>– Intrapartum temperature ⩾ 100.4°F (= 38.0°C)¶</td>
<td></td>
</tr>
<tr>
<td>– Intrapartum NAAT** positive for GBS</td>
<td></td>
</tr>
<tr>
<td>• Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)</td>
<td></td>
</tr>
<tr>
<td>• GBS bacteriuria during previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)</td>
<td></td>
</tr>
<tr>
<td>• Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors</td>
<td></td>
</tr>
<tr>
<td>• Cesarean delivery performed before onset of labor on a woman with intact amniotic membranes, regardless of GBS colonization status or gestational age</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NAAT = Nucleic acid amplification tests

* Intrapartum antibiotic prophylaxis is not indicated in this circumstance if a cesarean delivery is performed before onset of labor on a woman with intact amniotic membranes.

† Optimal timing for prenatal GBS screening is at 35–37 weeks’ gestation.

§ Recommendations for the use of intrapartum antibiotics for prevention of early-onset GBS disease in the setting of threatened preterm delivery are presented in Figures 5 and 6.

¶ If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

** NAAT testing for GBS is optional and might not be available in all settings. If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (delivery at <37 weeks’ gestation, amniotic membrane rupture at ⩾ 18 hours, or temperature ⩾ 100.4°F [= 38.0°C]) is present, then intrapartum antibiotic prophylaxis is indicated.


C. Antibiotics

1. **Penicillin G** IV 5 million units initially then 2.5–3 million units Q 4hrs until delivery (preferred agent— or —)
2. **Ampicillin** IV 2g, then 1g Q 4hrs until delivery
3. **PCN allergic**

Recommended regimen for intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal (GBS) disease*

<table>
<thead>
<tr>
<th>Patient allergic to penicillin?</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G, 5 million units IV initial dose, then 2.5–3.0 million units§ every 4 hrs until delivery or Ampicillin, 2 g IV initial dose, then 1 g IV every 4 hrs until delivery</td>
<td>Patient with a history of any of the following after receiving penicillin or a cephalosporin?:</td>
<td></td>
</tr>
<tr>
<td>- Anaphylaxis</td>
<td></td>
<td></td>
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<tr>
<td>- Angioedema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Respiratory distress</td>
<td></td>
<td></td>
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<tr>
<td>- Urticaria</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cefazolin, 2g IV initial dose, then 1 g IV every 8 hrs until delivery</th>
<th>Isolate susceptible to clindamycin§ and erythromycin??</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vancomycin, 1 g IV every 12 hrs until delivery</th>
<th>Clindamycin, 900 mg IV every 8 hrs until delivery</th>
</tr>
</thead>
</table>
| (Notes on following page)
Abbreviation: IV = intravenously

* Broader spectrum agents, including an agent active against GBS, might be necessary for treatment of chorioamnionitis.

† Doses ranging from 2.5 to 3.0 million units are acceptable for the doses administered every 4 hours following the initial dose. The choice of dose within that range should be guided by which formulations of penicillin G are readily available to reduce the need for pharmacies to specially prepare doses.

§ Penicillin-allergic patients with a history of anaphylaxis, angioedema, respiratory distress, or urticaria following administration of penicillin or a cephalosporin are considered to be at high risk for anaphylaxis and should not receive penicillin, ampicillin, or cefazolin for GBS intrapartum prophylaxis. For penicillin-allergic patients who do not have a history of those reactions, cefazolin is the preferred agent because pharmacologic data suggest it achieves effective intraamniotic concentrations. Vancomycin and clindamycin should be reserved for penicillin-allergic women at high risk for anaphylaxis.

¶ If laboratory facilities are adequate, clindamycin and erythromycin susceptibility testing (Box 3) should be performed on prenatal GBS isolates from penicillin-allergic women at high risk for anaphylaxis. If no susceptibility testing is performed, or the results are not available at the time of labor, vancomycin is the preferred agent for GBS intrapartum prophylaxis for penicillin-allergic women at high risk for anaphylaxis.

** Resistance to erythromycin is often but not always associated with clindamycin resistance. If an isolate is resistant to erythromycin, it might have inducible resistance to clindamycin, even if it appears susceptible to clindamycin. If a GBS isolate is susceptible to clindamycin, resistant to erythromycin, and testing for inducible clindamycin resistance has been performed and is negative (no inducible resistance), then clindamycin can be used for GBS intrapartum prophylaxis instead of vancomycin.


D. Newborn management: Newborn guidelines apply to all neonates regardless of maternal GBS status

Algorithm for secondary prevention of early-onset group B streptococcal (GBS) disease among newborns
Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).

Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including Escherichia coli and other gram-negative pathogens) and should take into account local antibiotic resistance patterns.

Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life).

See table 3 for indications for intrapartum GBS prophylaxis.

If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.

If =37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

Some experts recommend a CBC with differential and platelets at age 6–12 hours.


CLINICAL PEARLS

- 5–10% of patients will deliver on their due date
- Women should ideally receive folate at 28 days prior to conception through the first 8 weeks of pregnancy to decrease the risk of neural tube defects. If patient has had a previous pregnancy affected by a neural tube defect, then a daily 4mg dose of folate is recommended.
- A 20 week uterus will be palpated at the umbilicus
- If patient experiences vaginal bleeding associated with a closed cervix, and a fetus with cardiac activity is seen on ultrasound, then miscarriage rate is < 3 %
- Antiretroviral use during pregnancy decreases risk of transmission of HIV by at least ½ and should be strongly recommended (in consultation with an HIV specialist) to every HIV positive woman

References

PART 1: MEDICATION USE DURING PREGNANCY

I. INTRODUCTION
   A. Drugs that can cause birth defects are commonly prescribed to women of reproductive age
   B. 50% of pregnancies in the US are unplanned
   C. Major malformations in the general population: 2%–3%. Among the major malformations, drug exposure accounts for 2%–3%

II. FACTORS INFLUENCING TERATOGENICITY OF DRUGS
   A. Dose reaching the fetus
   B. Gestational age at exposure
      1. Conception to 14 days: spontaneous abortion
      2. 31 to 71 days after last menstruation (weeks 4–10) is the most vulnerable period of risk for major congenital malformations
      3. 2nd and 3rd trimester: growth, physiologic functioning, reproduction, neurological and mental development
   C. Duration of exposure
   D. Environmental factors: e.g., mercury in polluted fish, maternal folate level
   E. Genetic susceptibility
   F. Clinical consistency

III. GENERAL APPROACH TO MEDICATION USE DURING PREGNANCY
   A. Many drugs with systemic effects in the mother will cross the placenta and their effects on the fetus are not known
   B. Data on drug safety in pregnant women is very limited; therefore, it is important to not prescribe medications during pregnancy unless the benefit outweighs the risk
   C. Women with chronic illness such as psychiatric or seizure disorders frequently require drug therapy throughout pregnancy. In such patients, care must be taken to select the safest drug from the necessary class of medication
   D. Effective communication is essential for the clinicians to engage patients in shared decision-making on the risks and benefits of medications that can cause birth defect

IV. FDA CLASSIFICATIONS
   Category A: Controlled studies in humans have demonstrated no fetal risks
   Category B: Animal studies have indicated no fetal risk, but there are no human studies to support the data, OR, fetal risks have been demonstrated in animals, but not in well-controlled human studies
   Category C: No adequate studies in either humans or animals have been done—or—adverse effects have been seen in animal studies, but there is no human data available
   Category D: There is evidence of fetal risk, but the benefits of the medication may outweigh the risks to the fetus
   Category X: There are proven fetal risks which clearly outweigh the benefits of using the medication

V. MEDICATIONS USED DURING PREGNANCY FOR VARIOUS CONDITIONS
## Care of the Pregnant Patient

### 22. Medications During Pregnancy & Lactation

<table>
<thead>
<tr>
<th>Class of Drug/Condition</th>
<th>Drugs Considered Low Risk in Pregnancy</th>
<th>Drugs to Avoid or Use With Caution in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>Topical: azelaic acid (B), clindamycin (B), erythromycin (B except solution which is C), benzoyl peroxide (C), adapalene (C), Systemic antibiotics: erythromycin (B)</td>
<td>Isotretinoin (X), acitretin (2nd generation retinoid) (X) - contraindicated as exposure at any time in pregnancy is associated with embryopathy, Topical tazarotene (X) Oral tretinoin (D)- contraindicated in 1st trimester, Avoid tetracyclines (D) due to teeth and bone abnormalities, Topical allitretinoin (D)- significant absorption can occur to cause fetal harm</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Penicillin (B), ampicillin (B), amoxicillin (B), Augmentin (B) Cephalosporins (B) Macrolides: erythromycin (B), azithromycin (B) Clindamycin (B) Metronidazole (B) - For bacterial vaginosis and trichomoniasis: the CDC STD 2010 guidelines recommend metronidazole for all pregnant women Nitrofurantoin (B) - Avoid use when close to delivery due to risk of hemolytic anemia in newborns, One study shown possible association with birth defects</td>
<td>Fluoroquinolones (C) - Avoid use due to risk of fetal cartilage damage and arthropathies Sulfamethoxazole/trimethoprim (Bactrim) (C) - Avoid use near term due to risk of kernicterus in newborns, Caution: trimethoprim (a dihydrofolate reductase inhibitor) may be associated with CV defects and neural tube defects Tetracyclines (D) - Contraindicated in 2nd and 3rd trimesters due to potential for developmental toxicity, and teeth and bone abnormalities</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Unfractionated heparin (C) Low molecular weight heparins (LMWH): (B)</td>
<td>Avoid warfarin: - Birth defects following 1st trimester exposure - Category D for women with mechanical heart valves - Category X for other indications</td>
</tr>
<tr>
<td>Antiepileptic drugs (AEDs)</td>
<td>All AEDs can cause birth defects, but maternal benefit outweighs these risks. Newer AEDs have limited data - e.g., Felbamate (C), lamotrigine (C), pregabalin (C)</td>
<td>AEDs that cross the placenta in potentially clinically important amounts: - Probably: Phenytoin (D), primidone, phenytoin (D), carbamazepine (D), levetiracetam (C), valproate (D) - Possibly: gabapentin (C), lamotrigine (C), oxcarbazepine (C), topiramate (D) Fetal risks: - Valproate: neural tube defects (NTDs), facial clefts, cognitive impairment - Carbamazepine: NTDs, CV and urinary tract defects, cleft palate - Phenobarbital: cardiac malformations, cognitive impairment - Phenytoin: major abnormalities, bleeding, cognitive impairment - Topiramate: oral clefts, cognitive impairment</td>
</tr>
<tr>
<td>Asthma</td>
<td>Inhaled steroids (ICS) (C) except budesonide (B) which is the preferred controller Inhaled short-acting beta agonists (C): albuterol is preferred because it has been studied extensively Inhaled long-acting beta agonists (LABA) (C): limited data - Preferred add-on therapy to medium- or high-dose ICS Inhaled steroid/LABA (C) Leukotriene-receptor antagonists (B)- alternative for mild asthma or as add-on therapy to ICS Cromolyn (B)- alternative for mild asthma Theophylline (C)- alternative for mild asthma or as add-on therapy to ICS</td>
<td>Systemic steroid: risk of prematurity, low birth weight</td>
</tr>
</tbody>
</table>

Chart continued on next page
<table>
<thead>
<tr>
<th>Class of Drug/Condition</th>
<th>Drugs Considered Low Risk in Pregnancy</th>
<th>Drugs to Avoid or Use With Caution in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Bulk-forming laxatives: e.g., Metamucil Milk of magnesia (A) Stool softeners: docusate</td>
<td>Mineral oil (C): Avoid, may impair vitamin K absorption Strong cathartics: Aloe (reputed abortifacient), senna (C): avoid</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Drug of choice: Insulin  • Category B: Regular insulin, NPH, Regular/NPH, aspart (Novolog), lispro (Humalog), detemir (Levemir), Humalog Mix 75/25  • Category C: Glulisine (Apidra), Glargin (Lantus), Novolog Mix 70/30 Oral hypoglycemic agents: use when insulin therapy is not feasible  • Metformin (B): crosses the placenta and may not provide adequate glycomic control  • Sulfonlyureas (C) except gliburide (B) which has the least placental transfer</td>
<td>Oral hypoglycemic agents not recommended due to limited efficacy and safety data:  • Acarbose (B)  • DDP4 inhibitors (B)  • GLP-1 agonists (C)  • Meglitinide (C)  • Thiazolidinediones (C) Stop statins (X), ACEIs and ARBs (C/D)</td>
</tr>
<tr>
<td>Heartburn</td>
<td>Calcium or magnesium containing antacids H₂ blockers (B):  • Ranitidine is preferred due to documented efficacy Sucralfate (B): poorly absorbed Metoclopramide (B) Proton pump inhibitors:  • Category B for dexlansoprazole, esomeprazole, pantoprazole, rabeprazole  • Category C for omeprazole and omeprazole/NaHCO₃ (Zegerid)</td>
<td>Antacids may interfere with iron absorption Avoid NaHCO₃ due to risk of maternal or fetal metabolic alkalosis and fluid overload. Cimetidine has a weak antiandrogenic effect. Misoprostol (X): contraindicated</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Oral drug of choice: methyldopa (B), labetalol (C), metoprolol (C) IV drug of choice: labetalol, hydralazine (C)</td>
<td>Avoid atenolol (D): risks of IUGR and reduced placental weight Avoid ACE inhibitors and ARBs (C/D):  • Category C in 1st trimester: CV and CNS malformations  • Category D in 2nd and 3rd trimesters: fetal hypocalvaria and renal defects</td>
</tr>
<tr>
<td>Migraine</td>
<td>Treatment:  • Acetaminophen (APAP) (B)  • Opioid/APAP (C)  • Opioids (C) except oxycodone (B): pose risks of neonatal withdrawal and maternal dependence  • Metoclopramide (B) Prophylaxis:  • Beta-blockers (C), except atenolol (D)  • Amitriptyline (C)  • Verapamil (C)</td>
<td>Aspirin (C), NSAIDs (C), COX-2 inhibitors (C):  • Avoid chronic use or intermittent high doses due to increased risk of bleeding  • Avoid use due to risk in 1st and 3rd trimesters: risk of miscarriage and malformation; risk of premature closure of the ductus arteriosus and pulmonary hypertension in newborns Caffeine &gt;100 mg/day: fetal growth restriction Isomethylenepethylene combination: safety in pregnancy unknown Triptans (C): currently not recommended due to limited safety data Ergotamines (X): contraindicated as they are abortifacients Prophylaxis: Avoid  • Atenolol (D)  • ACE inhibitors and ARBs (C/D)  • Nortriptyline (D)  • Topiramate (D): risks of cleft lip and/or cleft palate  • Depakote (X): contraindicated due to fetal risk and neurodevelopmental effects</td>
</tr>
</tbody>
</table>

Chart continued on next page
### Nausea and Vomiting of Pregnancy

<table>
<thead>
<tr>
<th>Class of Drug/Condition</th>
<th>Drugs Considered Low Risk in Pregnancy</th>
<th>Drugs to Avoid or Use With Caution in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbs: Ginger</td>
<td>Pyridoxine (A): 25 mg q6-8h; max 200 mg/day</td>
<td>Doxylamine 10 mg/pyridoxine 10 mg (Diclegis) (A): 2 tabs qhs; max 4 tabs/day (1 in am, 1 mid-afternoon, 2 hs)</td>
</tr>
<tr>
<td></td>
<td>Antihistamines: Diphenhydramine (B), dimenhydrinate (B), doxylamine (C) Refractory cases: Ondansetron (B), metoclopramide (B), promethazine (C) Severe cases, last resort: methylprednisolone (C)</td>
<td>Promethazine: safety information is limited Chlorpromazine: caution with its adverse side effects</td>
</tr>
</tbody>
</table>

### Psychiatric Disorders: Depression

<table>
<thead>
<tr>
<th>Drugs to Avoid or Use With Caution in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal antidepressant exposure: a small increase risk of congenital malformations, preterm delivery, lower birth weight and lower Apgar scores</td>
</tr>
<tr>
<td>TCAs (C) except nor triptyline (D):</td>
</tr>
<tr>
<td>• Neonatal withdrawal symptoms with 3rd trimester exposure</td>
</tr>
<tr>
<td>• Concerns with side effects and safety in overdoses</td>
</tr>
<tr>
<td>SSRIs (C) except paroxetine (D):</td>
</tr>
<tr>
<td>• Have more reassuring data than other classes of drugs</td>
</tr>
<tr>
<td>• Risks in 3rd trimester: neonatal adaptation syndrome, persistent pulmonary hypertension of the newborn, neurodevelopmental difficulties in older children</td>
</tr>
<tr>
<td>SNRIs (C):</td>
</tr>
<tr>
<td>• Risks in 3rd trimester similar to that of the SSRIs</td>
</tr>
<tr>
<td>• Venlafaxine has more data than other SNRIs</td>
</tr>
</tbody>
</table>

### Psychiatric Disorders: Antipsychotics

| First-generation antipsychotics (FGAs) (C): Haloperidol, perphenazine, fluphenazine |
| Second-generation antipsychotics (SGAs) (C) except clozapine (B): limited data |

### Psychiatric Disorders: Anxiolytics

<table>
<thead>
<tr>
<th>Drugs to Avoid or Use With Caution in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buspirone (B)</td>
</tr>
<tr>
<td>Hydroxyzine (C)</td>
</tr>
</tbody>
</table>

### Psychiatric Disorders: Hypnotics

<table>
<thead>
<tr>
<th>Drugs to Avoid or Use With Caution in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-benzodiazepine (C): Eszopiclone, zaleplon, Ramelteon (C)</td>
</tr>
</tbody>
</table>

### Psychiatric Disorders: Mood Stabilizers

<table>
<thead>
<tr>
<th>Drugs to Avoid or Use With Caution in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine (C):</td>
</tr>
<tr>
<td>• Limited data</td>
</tr>
<tr>
<td>• Potential risk of developmental toxicity</td>
</tr>
</tbody>
</table>

Avoid Lithium (D) if possible: |
| • 1st trimester: small risk of cardiac defect (Eisen’s anomaly) fetal echocardiography and ultrasonography recommended |
| • Developmental toxicity, kidney and thyroid defects |
| Avoid carbamazepine (D) |
| Avoid valproate (D) |
### VI. USE OF HERBS DURING PREGNANCY

A. Safety data is lacking

B. AVOID:
   1. Echinacea: Causes fragmentation of hamster sperm at high concentration
   2. Black cohosh: Speeds labor and acts like estrogen
   3. Garlic, gingko, and willow barks: Anticoagulant properties
   4. Licorice: Increases BP and is potassium wasting

### PART II: MEDICATION USE IN BREAST-FEEDING MOTHER

#### I. INTRODUCTION

A. There are many benefits to breast-feeding, see Chapter 4, Infant Formula and Breast-feeding

B. Many mothers need to use medications during breast-feeding

C. All drugs transfer into breast milk to some degree and this may pose a risk to the breast-fed infant

#### II. FACTORS DETERMINING DRUG EXPOSURE TO THE BREASTFED INFANT

A. Maternal drug plasma level

B. Drug properties: protein binding, lipid solubility, ionization

C. Infant’s drug exposure:
   - Drug’s concentration in the breast milk
   - Amount of breast milk consumed by the infant
   - Infants have lower drug clearance than adults
   - Increased drug transfer in pre-term infants and infants with significant illness

#### III. GENERAL APPROACH TO MEDICATION USE IN A NURSING WOMAN

A. Avoid maternal drug therapy if possible

B. Use topical therapy when possible

C. Select medications that are safe for use and are well-studied in infants

D. Select drugs with the shortest half-life, highest protein-binding, and lowest lipid solubility to minimize drug transfer to breast milk

#### IV. WAYS TO MINIMIZE RISK TO THE BREAST-FED INFANT FROM MATERNAL MEDICATIONS

A. Reduce infant’s drug exposure:
   1. Administer once-daily medication just before the longest sleep interval for the infant, usually after the bedtime feeding
   2. Breast-feed the infant immediately prior to a dose as concentrations in milk are likely to be lowest at the end of a dosing interval
   3. Assess plasma concentration of the drug in the infant if needed. The drug is considered “safe” if an infant dose is close to 1% of the weight-adjusted maternal dose

---

### Class of Drug/Condition | Drugs Considered Low Risk in Pregnancy | Drugs to Avoid or Use With Caution in Pregnancy
---

### Upper Respiratory Symptoms

| Cold and cough products
| Dextromethorphan (C): data suggest low risk
| Guaifenesin (C): limited data, appear safe
| 1st generation: diphenhydramine (B), chlorpheniramine (C)
| 2nd generation: cetirizine (B), loratadine (B), desloratadine (C), fexofenadine (C)
| Topical nasal steroids (C), except budesonide (B)

Cold and cough products
- Avoid use in 1st trimester
- Limit to short-term use
- Pseudoephedrine (C): risk of developmental toxicity
- Avoid alcohol containing antitussive products (Fetal Alcohol Syndrome in alcoholism)
4. If the drug is not considered safe in breastfeeding, breast milk may be expressed and discarded for the treatment duration. Breast-feeding may be resumed after the drug has been eliminated from the maternal blood stream (approximately 4–5 half-lives of the drug).

B. Monitor effects of the drug in the infant
- Monitor the infant for adverse effects such as failure to thrive, irritability and sedation
- Hemolysis may occur even at a very low concentration of certain drugs in an infant with glucose-6-phosphate dehydrogenase deficiency

V. FDA LABELING ON LACTATION:
- A. Risk Summary
- B. Clinical Consideration
- C. Data

VI. MEDICATIONS COMMONLY PRESCRIBED FOR VARIOUS CONDITIONS IN BREAST-FEEDING WOMEN

<table>
<thead>
<tr>
<th>Class of Drug/Condition</th>
<th>Drugs Considered Compatible with Breast-feeding</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic rhinitis</td>
<td>Intransal steroids</td>
<td>1st generation antihistamines can cause sedation in infant. Avoid chronic use of pseudoephedrine as it is concentrated in human milk. May cause irritability. May interfere with milk production.</td>
</tr>
<tr>
<td></td>
<td>• Low systemic concentrations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Budesonide, fluticasone, mometasone also have poor oral bioavailability. 2nd generation antihistamines ( cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine) Pseudoephedrine</td>
<td></td>
</tr>
<tr>
<td>Analgesics</td>
<td>Acetaminophen</td>
<td>Avoid high dose aspirin therapy. Chronic use of naproxen can accumulate in breast-fed infants. Avoid NSAIDs in nursing infants with ductal-dependent cardiac lesions. Use of codeine and hydrocodone can result in significant exposure in the nursing infants. Methadone has long half-life and can accumulate in infants. Meperidine has toxic metabolite which can accumulate in infants. Oxycodone is not recommended in lactating women. Buprenorphine +/- naloxone, naltrexone should not be used.</td>
</tr>
<tr>
<td></td>
<td>Low dose aspirin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NSAIDs: ibuprofen, flurbiprofen, naproxen (short term use only)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Celecoxib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydromorphone may be compatible but FDA labeling discourages use. Methadone use in treatment of opioid dependence</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Penicillins, cephalosporins, aminoglycosides, macrolides, clindamycin, ciprofloxacin, ofloxacin, trimethoprim/sulfamethoxazole Fluconazole</td>
<td>Avoid tetracyclines due to risk of teeth and bone toxicities. Trimethoprim/sulfamethoxazole should be avoided in &lt;2 mo old nursing infants due to risk for increased bilirubin level. Metronidazole: Discontinue breastfeeding for 12-24h to allow excretion of the drug when a single, 2-g dose is used by mother. Levofloxacin, moxifloxacin: excreted into breast milk, but effects of exposure on a nursing infant are unknown.</td>
</tr>
<tr>
<td></td>
<td>Unfractionated heparin Low molecular heparin Warfarin</td>
<td></td>
</tr>
</tbody>
</table>

(Chart continued on next page)
## Medications During Pregnancy & Lactation

### Care of the Pregnant Patient

<table>
<thead>
<tr>
<th>Class of Drug/ Condition</th>
<th>Drugs Considered Compatible with Breast-feeding</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiepileptic drugs (AEDs)</strong></td>
<td>Phenobarbital, primidone, phenytoin, carbamazepine, levetiracetam, valproate, gabapentin, lamotrigine, oxcarbazepine and topiramate cross the placenta in significant amounts</td>
<td>Lamotrigine, primidone, levetiracetam, gabapentin, topiramate transfer significantly into breast milk Valproate, phenobarbital, and primidone are not preferred due to their potential side effects in the infants.</td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td>Inhaled steroids:</td>
<td>Theophylline is rated by the AAP as compatible with breast-feeding. However, it may cause irritability or other signs of mild toxicity in breast-feeding infants. Oral steroids are safe for short-term use. Prednisolone is preferred and infant exposure can be minimized by withholding nursing for 4 h after taking the drug.</td>
</tr>
<tr>
<td></td>
<td>• Low systemic concentration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Budesonide, fluticasone, and mometasone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>also have the poorest oral bioavailability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhaled short-acting beta agonists</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhaled long-acting beta agonists: no human data</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukotriene-receptor antagonists: effect of exposure on a nursing infant is unknown</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cromolyn: limited data</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>ACE inhibitors: enalapril, lisinopril, moexipril, quinapril, ramipril ARBs: limited data Beta blockers: labelatro, pranproanol, timolol CCBs: Nifedipine, verapamil Diuretics: chlorothiazide, hydrochlorothiazide Hydralazine</td>
<td>Atenolol, metoprolol, nadolol, and sotalol are concentrated in human milk and may lead to bradycardia and hypotension in breast-fed infants. Diltiazem is excreted in higher amount than other CCBs, select safer alternatives.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>Insulin</td>
<td>1st generation sulphonylureas: chlorpropamide, tolbutamide excreted in milk breast and hypoglycemia has occurred in infants DDP4 inhibitors: may excrete into breast milk, use caution. GLP-1 agonists: may excrete into breast milk, use caution. Pioglitazone may excrete into breast milk, use caution.</td>
</tr>
<tr>
<td></td>
<td>Metformin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd generation sulfonylureas: glipizide and glyburide, glimepiride – limited data, potential for hypoglycemia Acarbose: no data, probably compatible</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking cessation</strong></td>
<td>Nicotine replacement products: short-acting (e.g. gum or lozenges)</td>
<td>Bupropion: excreted into breast milk with exposures &gt;10% maternal dose and report of seizure. Its use is not advised. Varenicline can cause serious neuropsychiatric adverse events and its use is not recommended.</td>
</tr>
<tr>
<td><strong>Vaccines</strong></td>
<td>Inactivated vaccines and most vaccines</td>
<td>Smallpox and yellow fever vaccine are contraindicated in nonemergency situations</td>
</tr>
</tbody>
</table>

This table is provided as an information resource only and does not replace the use of clinical judgment.

### VII. DRUGS TO AVOID IN BREASTFEEDING

A. Anticancer drugs
B. Cyclosporine
C. Radioactive compounds
D. Drugs of abuse
E. Alcohol: avoid or occasional limited ingestion (8 oz wine or 2 cans beer/day)—no more than 1 drink 2–3 hrs prior to breastfeeding
F. Herbal products
   1. Fenugreek and fennel are not recommended due to lack of efficacy data
   2. Other herbs such as chamomile, black cohosh, blue cohosh, chastetree, Echinacea, ginseng, gingko, St John’s wort, and valerian are not recommended for use due to lack of safety data, potentially toxic undeclared ingredients, and reports of adverse events
### VIII. DRUGS THAT MAY BE OF CONCERN DURING BREAST-FEEDING

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Possible Effects in Breast-fed Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiolytic drugs: e.g., diazepam, alprazolam</td>
<td>Lethargy, poor weight gain, withdrawal symptoms</td>
</tr>
<tr>
<td>Antidepressants: SSRIs</td>
<td>Citalopram, fluvoxamine, sertraline: infant serum conc=10% maternal plasma conc; Fluoxetine: long half-life, potential for accumulation in breast milk, may cause colic and irritability</td>
</tr>
<tr>
<td>Antidepressants: others</td>
<td>Bupropion, mirtazapine, venlafaxine: infant serum conc=10% maternal plasma conc; Bupropion, mirtazapine, venlafaxine</td>
</tr>
<tr>
<td>Antidepressants: TCAs</td>
<td>Clomipramine, doxepin, norlaidazine: infant serum conc=10% maternal plasma conc; Clomipramine, doxepin, norlaidazine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Chlorpromazine: galactorrhea in mother; drowsiness and lethargy in infant; decline in developmental scores; Haloperidol: decline in developmental scores; Olanzapine: infant serum conc=40% maternal plasma conc; Other 2nd generation antipsychotics: monitor for side effects of the drugs</td>
</tr>
<tr>
<td>Lithium</td>
<td>Excreted into breast milk with milk levels 40%-50% of the maternal serum concentration. Infant serum and milk levels are approximately equal.</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>High level of drug transfer into breast milk, risk of tardive dyskinesia</td>
</tr>
</tbody>
</table>

### CLINICAL PEARLS

- Consider a non-drug modality first if possible when treating a woman who is pregnant
- Avoid prescribing a medication during the first trimester if possible
- When the benefit of a medication is felt to outweigh potential risks, use the lowest effective dose of the drug with the most data on safety in pregnancy
- Prefer older medications with good safety records to newer drugs with less supporting data
- Provide effective contraception to women taking potentially teratogenic medications who do not desire pregnancy
- Careful consideration is necessary for drugs that are concentrated in human milk or result in significant exposure in the infant

### Online Resources
- Teratology Information Services (TERIS): http://depts.washington.edu/terisweb/teris/
- ReproTox: www.reprotox.org
- Motherisk: www.motherisk.org
- Organization of Teratology Information Specialists: http://www.mothertobaby.org/

### References

23. **QUESTIONS EXPECTING PARENTS COMMONLY ASK/RADIATION IN PREGNANCY**

Many of these issues should be discussed with your patients before they ask.

I. **WHAT ACTIVITIES ARE SAFE TO PARTICIPATE IN?**

   Pregnancy is not an illness and expecting mothers should not be treated as if they were sick. Pregnant women may have sexual intercourse, drive a car, fly in an airplane, go swimming, take tub baths and paint the nursery. Adequate rest, exercise and nutrition are advisable for the best pregnancy outcomes.

II. **WHAT ACTIVITIES SHOULD BE AVOIDED?**

   Douching, cleaning the litter-box, dieting to lose weight, high risk activities (skiing, sky diving), new vigorous exercise programs, high impact aerobics, vibrating machines, tanning booths, saunas and hot tubs.

III. **WHICH DANGER SIGNS SHOULD NOT BE IGNORED?**

   A. Bleeding (more than a few spots) from the vagina
   B. A sudden gush of fluid or a slow leak of fluid
   C. Severe abdominal pain
   D. Chills and fever
   E. Fainting
   F. Pain or burning with urination
   G. Unilateral leg pain and swelling
   H. Chest pain and shortness of breath

IV. **WHAT CAN BE DONE TO HELP WITH MORNING SICKNESS?**

   Eat crackers or toast before getting out of bed. Sit on the edge of the bed for several minutes before getting up in the morning. Eat more frequently, but smaller meals (5–6 times per day). Avoid greasy and spicy foods. Drink water freely between meals. Take the prenatal vitamin after eating. Participate in stress relieving activities like walking outside 20–30 minutes 5 times per week or practicing deep breathing, asking others to help with stressful activities, and participating in organized stress relief groups. **Vitamin B**$_6$ 10–25mg PO TID; **Emetrol** 15–30mL PO Q1–2hrs as tolerated (maximum 5 doses) **Ondansetron (Zofran)**: 4 mg PO every 8 hrs, Ranitidine (Zantac) 150mg–300mg PO daily

V. **ARE X-RAYS SAFE IN PREGNANCY?**

   There is always a risk vs. benefit in medical testing and therapies. The most sensitive time of central nervous system development is 10–17 weeks and routine testing should be delayed until after this time. Generally an x-ray is safe as there is only a very small amount of radiation exposure to the fetus. It is recommended the unborn children not be exposed to more than 5.0 rads during the pregnancy. As reference point, the amount of radiation in a 2 view chest x-ray is 0.00007 rads.
### Estimated Fetal Exposure for Various Diagnostic Imaging Methods

<table>
<thead>
<tr>
<th>Examination type</th>
<th>Estimated fetal dose per examination (rad)*</th>
<th>Number of examinations required for a cumulative 5-rad dose†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain films</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skull</td>
<td>0.004</td>
<td>1,250</td>
</tr>
<tr>
<td>Dental</td>
<td>0.0001</td>
<td>50,000</td>
</tr>
<tr>
<td>Cervical spine</td>
<td>0.002</td>
<td>2,500</td>
</tr>
<tr>
<td>Upper or lower extremity</td>
<td>0.001</td>
<td>5,000</td>
</tr>
<tr>
<td>Chest (two views)</td>
<td>0.00007</td>
<td>71,429</td>
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<tr>
<td>Mammogram</td>
<td>0.020</td>
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<tr>
<td>Abdominal (multiple views)</td>
<td>0.245</td>
<td>20</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>0.009</td>
<td>555</td>
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<tr>
<td>Lumbarosacral spine</td>
<td>0.359</td>
<td>13</td>
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<tr>
<td>Intravenous pyelogram</td>
<td>1.398</td>
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<tr>
<td>Pelvis</td>
<td>0.040</td>
<td>125</td>
</tr>
<tr>
<td>Hip (single view)</td>
<td>0.213</td>
<td>23</td>
</tr>
<tr>
<td>CT scans (slice thickness: 10 mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head (10 slices)</td>
<td>&lt;0.050</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Chest (10 slices)</td>
<td>&lt;0.100</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Abdomen (10 slices)</td>
<td>2.600</td>
<td>1</td>
</tr>
<tr>
<td>Lumbar spine (5 slices)</td>
<td>3.500</td>
<td>1</td>
</tr>
<tr>
<td>Pelvimetry (1 slice with scout film)</td>
<td>0.250</td>
<td>20</td>
</tr>
<tr>
<td>Fluoroscopic studies</td>
<td></td>
<td></td>
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<tr>
<td>Upper GI series</td>
<td>0.056</td>
<td>89</td>
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<tr>
<td>Barium swallow</td>
<td>0.006</td>
<td>833</td>
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<tr>
<td>Barium enema</td>
<td>3.986</td>
<td>1</td>
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<tr>
<td>Nuclear medicine studies</td>
<td></td>
<td></td>
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<tr>
<td>Most studies using technetium (⁹⁹mTc)</td>
<td>&lt;0.500</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Hepatobiliary technetium HIDA scan</td>
<td>0.150</td>
<td>33</td>
</tr>
<tr>
<td>Ventilation-perfusion scan (total)</td>
<td>0.215</td>
<td>23</td>
</tr>
<tr>
<td>• Perfusion portion: technetium</td>
<td>0.175</td>
<td>28</td>
</tr>
<tr>
<td>• Ventilation portion: xenon (¹³³Xe)</td>
<td>0.040</td>
<td>125</td>
</tr>
<tr>
<td>Iodine (¹³¹I), at fetal thyroid tissue</td>
<td>590.000</td>
<td>1‡</td>
</tr>
<tr>
<td>Environmental sources (for comparison)</td>
<td>0.100</td>
<td>N/A</td>
</tr>
</tbody>
</table>

CT=computed tomographic; GI=gastrointestinal; HIDA=hepatobiliary iminodiacetic acid; N/A=not applicable.

*Where the reference provides a range of estimated doses, the highest value of the range is listed here.
†Authors’ calculation from data provided in reference; values rounded to lowest whole number.
‡-Iodine (¹³¹I) is contraindicated during pregnancy.


### VI. WHAT IF I HAVE A HISTORY OF HERPES? WHAT IF I HAVE ACTIVE HERPES?

The American Academy of Pediatrics and the American Congress of Obstetrics and Gynecology recommend prophylactic (preventive) treatment of herpes starting at 36 weeks gestation or treatment for active herpes with antiviral drugs such as Acyclovir, Valacyclovir and Famciclovir.

### VII. WHAT IF I AM EXPOSED TO A VIRUS OR OTHER ILLNESS?

#### A. Chickenpox:
If you are immune, there is no further therapy warranted. If you are not immune, see your doctor immediately to test for immunity and possibly receive a medication to decrease the severity of your infection.

#### B. Fifth disease (slapped cheek):
Fifth disease does not cause birth defects but can cause miscarriage and may cause anemia, so you should see your doctor for further evaluation.

#### C. Influenza:
Influenza can be a life threatening illness during pregnancy. A flu vaccine is recommended for all pregnant women at any gestational age. The only contraindication is an allergy to eggs or to the flu vaccine.
D. Pertussis (Whooping Cough): The RedBook recommends that all close contacts of persons diagnosed with pertussis be given prophylactic treatment. Contact your physician for the correct medication and dosing.

VIII. TENDER BREASTS
Wearing a good support bra may help. If not effective, consider wearing it at night. Leaking breasts may be managed with nursing pads or tissues placed in the bra.

IX. CONSTIPATION
Increase intake of fresh fruits and vegetables, grains and bran. Increase fluid intake and consider a cup of hot water 3 times per day. Continue to exercise including walking 20–30 minutes 5 × per week. Psyllium (Metamucil): 1 tsp in 8 oz water or 1 wafer QD–TID. Perdiem (Senna-fiber): Start with 1 tsp PO QD, may increase to 2 tsp PO QID.

X. LOW BACK PAIN
Reassure that this is to be expected. Rest frequently during the day. Maintain good posture. Use a footstool while sitting. Wear low heeled shoes and avoid overly soft beds and chairs.

XI. PELVIC PAIN (ROUND LIGAMENT PAIN)
As the uterus enlarges the ligaments supporting it will stretch, causing pelvic pain. May use Tylenol as needed. Do not make sudden movements. Get out of bed slowly. Massage may be helpful.

XII. ARE DENTAL PROCEDURES SAFE DURING PREGNANCY?
Use of local anesthetic agents are generally considered safe in pregnancy. Teeth cleaning/plaque control is considered safe. Dental radiographs are probably safe with use of a lead apron, but should be obtained only when absolutely necessary.

XIII. IS CAFFEINE SAFE DURING PREGNANCY?
Drinking large amounts of caffeine has been associated with increased fetal loss, and women should be counseled on decreasing the amount of caffeine from coffee as well as other sources (tea, colas, chocolate, OTC drugs). In addition, heavy caffeine use may cause caffeine withdrawal in newborns. Most physicians consider drinking low to moderate amounts of caffeine acceptable during pregnancy.

XIV. IS ASPARTAME (NUTRASWEET) SAFE DURING PREGNANCY?
Studies have not shown adverse fetal or maternal effects from aspartame during pregnancy.

XV. IS THERE A PROBLEM WITH VIDEO DISPLAY TERMINALS?
No. They are considered safe during pregnancy.

XVI. ARE INSECTICIDES SAFE?
Pregnant women should avoid use of insecticides and fumigants in the home or in the yard.

XVII. WHAT OTC MEDICATIONS ARE SAFE TO USE?
See Chapter 22, Medications during Pregnancy & Lactation.

XVIII. SHOULD SEAT BELTS BE WORN DURING PREGNANCY?
The leading nonobstetric cause of fetal death is maternal trauma. The use of a diagonal shoulder strap and a lap belt is strongly recommended during pregnancy.

References
AAP and ACOG. Guidelines for perinatal care, 7th Ed. 2012.
HISTORY: Patient is a ___ y/o G__P__AB__ female with a ___ weeks gestation by LMP (and/or) ___ week ultrasound with EDC of __/__/__. She presents to labor and delivery with complaint of **. She (denies/reports) vaginal bleeding or ROM. She reports _____ (positive/decreased/no) fetal movements. Her prenatal course has been complicated by ______ (smoking/alcohol/ drugs/sexually transmitted diseases/multiple gestation/preterm labor, gestational diabetes/PIH/preeclampsia etc.)

**Examples:
1. Contractions which began at __ o’clock, occurring every __ minutes, lasting ___ seconds
2. “My water broke” __ hours ago with ______ (clear, green, bloody, malodorous) fluid
3. Induction of labor for _____ (post-dates, preeclampsia, oligohydramnios, IUGR)

PRENATAL LABS: Blood type and Rh status, antibody screen, HbsAg, HIV, gonorrhea and chlamydia testing, RPR/VDRL, rubella status, Group B strep status, Pap results, H/H, sickle prep if increased risk group, Sullivan test results and 3 hr GTT results if done, Triple Screen results if performed. Note if RhoGAM was given and when

PAST MEDICAL HISTORY
1. Past illness
2. Medications (prenatal vitamins/iron)
3. Allergies
4. Past obstetrical history: List each birth by year, gestational age at delivery, weight and sex of infant, route of delivery, and complications
5. Past surgical history

PHYSICAL EXAM
1. Cervix: dilation/effacement/station
2. Fetal lie, presenting part and position (example vtx, LOA)
3. Fetal monitor show Category I, II or III strip. Note baseline BPM, accelerations, any variables or decelerations. Variability. Reassuring or Nonreassuring
4. Status of amniotic membranes (intact/ruptured) with (clear/meconium stained fluid)

ASSESSMENT: ___ y/o G__P__ female at ___ weeks who presents to L&D for ____ (induction of labor, ROM, active labor/etc). Other problems include ______

PLAN
Admit to Labor and Delivery
Choose one of the following:
1. Expectant Management (or augmentation of labor)
2. Induction of Labor (via Pitocin, Foley bulb, Cytotec, prostaglandin gel, etc.)
Pain management (supportive care, IV medications or epidural)
Pertinent labs (if patient needs type and screen, CBC, etc.)
Additional medications, e.g., antibiotics for positive Group B status, acyclovir for HSV, insulin for type 1 diabetic patients
25. OB Delivery Note

I. EXAMPLE OF AN OB DELIVERY NOTE

Name of Physician
Name of attending or supervising physician (if applicable)
Date/Time

__yo G_P_ now P__ s/p NVSD (LTCS etc) at (time and date) of a term (36 weeker etc) (male or female) infant over intact (2 degree episiotomy etc) perineum. Oxytocin given at delivery of shoulder. Infant suctioned, dried, stimulated and placed on mother's abdomen. Umbilical cord clamped and cut at one minute. (Cord gases sent, Cord sent for cord blood, Cord section saved for fetal blood etc). Active management of the third stage of labor. Intact (or not) 3 (2) vessel cord placenta delivered at (time). Fundus firm at umbilicus (2 cm above or below etc). No complications. EBL ___ ml. (Remember 500 ml is post partum hemorrhage. Sponge and instrument counts verified with nursing and correct. Apgars ___, ___. Infant to level I nursery. Mom in good condition to postpartum.

II. ADDITIONAL INFORMATION THAT MAY NEED TO BE ADDED TO THE NOTE

A. If complication e.g.,
   - Postpartum hemorrhage resolved with manual massage, oxytocin and cytotec PR EBL 800 ml, will check CBC in AM.
   - Shoulder dystocia Duration (e.g., lasting 1 min 30 sec), maneuvers used to resolve (resolved with McRoberts, suprapubic pressure), episiotomy and wood screw. Clavicles intact and no sign of palsy. See nursing notes for additional details
   - Fetal distress or aspiration The cord was clamped x 2 and cut. Infant was handed to NNP or physician in attendance for further resuscitation

B. For repairs:
   - Nth degree laceration repaired with 2-0/3-0 Dexon in usual fashion. Hemostasis complete
26. Postpartum Discharge Instructions

These issues should be discussed with all home-going mothers:

1. No heavy lifting (anything heavier than the baby) or driving for 1–2 weeks. This needs to be individualized as the reason not to drive is that episiotomy pain may cause hesitancy while driving.
2. No vaginal intercourse, tampons or douching for 6 weeks. This allows the vaginal musculature to tighten and the episiotomy to heal.
3. Sitz baths (sitting in a warm bath) may help episiotomy pain.
4. Contraception:
   a. Ask all mothers what type of birth control they will be using. Breast-feeding alone is a poor contraceptive. Depo medroxyprogesterone acetate (DepoProvera) can be started on postpartum day 1. They need to be informed that they may experience a longer duration of postpartum bleeding with the progesterone.
   b. An estrogen-containing contraceptive may decrease milk production and contribute to the normal hypercoagulable state of postpartum patients. An estrogen-containing oral contraceptive may safely be started after 3–4 weeks. For undecided patients, encourage using a condom with or without contraceptive foam until first postpartum visit.
5. Pain medications: Acetaminophen (Tylenol) and Ibuprofen (Motrin) will usually be all that is needed for vaginal deliveries.
6. Call office if temperature > 100.5°, increased abdominal pain, vaginal bleeding, odorous vaginal discharge, breast redness and pain, leg pain or shortness of breath.
7. Prescribe a stool softener, docusate (Colace) 100 mg PO BID. If prescribing narcotics may want to prescribe a senna and colace combination medication.
8. Vaginal bleeding: Patients can expect some lochia for 3–4 weeks postpartum. Anything heavier than a normal menstrual period should be evaluated.
10. Postpartum depression:
   a. Screen for postpartum depression while patient is in the hospital prior to discharge. Also evaluate their support system at home.
   b. Patients should be reevaluated at the infant’s two week visit and again at the mother’s postpartum visit. There are many depression screening tools that can be downloaded for free from the internet.
   c. Postpartum depression includes despondent mood, feelings of inadequacy as a parent, sleep and appetite disturbances, with impaired concentration, and presents in 10–20% of US women within 6 months.
   d. Postpartum blues is a transient state of emotional reactivity (cry easily, irritability, emotionally labile)—occurs in about 50% of women after birth and peaks at 3–5 days after delivery.
   e. Antidepressants commonly prescribed include the serotonin selective reuptake inhibitors (SSRIs). Sertraline (Zoloft) is considered safe with breast feeding. Fluoxetine (Prozac) and Citalopram (Celexa) have occasionally been associated with sleep disturbance in nursing infants. See Chapter 22, Medications During Pregnancy and Lactation.
   f. Women with previous history of postpartum depression are at increased risk for recurrence with subsequent pregnancies.

References:
27. Postpartum Checkup

The following information should be included in the postpartum office visit. The postpartum visit is usually performed 6 weeks after delivery.

**HISTORY**
1. Gravid and Parity
2. Type of delivery (Vaginal, Assisted, VBAC, C-section)
3. Number of weeks postpartum
4. Complication of labor and delivery (maternal and newborn)
5. Episiotomy or lacerations
6. Breast or bottle feeding
7. Fevers
8. Bowel, bladder problems, vaginal discharge
9. Symptoms of postpartum depression, screening with depression screening tool. Also discussion of the possibility of developing depressive/dysthymic symptoms. These symptoms may also be associated with thyroid dysfunction, which is commonly seen in postpartum
10. Bonding with infant. How does the mother hold and interact with the infant? How does the mother describe the infant? (happy, beautiful, or angry, mad)
11. Lochia/menses (date if has already occurred)
12. Resumption of intercourse (if yes, then type of contraception used). Type of birth control desired
13. Assessment of support systems

**PHYSICAL EXAM**
1. Vital signs including BP—(if patient has gestational hypertension, it should be resolved at this time and the blood pressure medications can be stopped)
2. Thyroid-goiter and nodules are commonly found in the intrapartum and postpartum period
3. Breast exam—breast nodules and cancers are sometimes noted during the pregnancy and postpartum period
4. Heart and lung exam
5. Perineum (episiotomy, laceration repair) and vaginal vault
6. Cervix (obtain pap if abnormal during pregnancy, dysphasia may resolve after a pregnancy)
7. Bimanual exam (assess uterine size and adnexa)

**LABORATORY**
1. H/H if anemic prior to labor or postpartum hemorrhage
2. Fasting blood glucose or A1C if gestational diabetes. Mothers with gestational diabetes have a 30% increased chance of developing diabetes in their lifetime. If this is transient, should be resolved at 8 weeks postpartum
3. TSH if indicated by symptoms or exam
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28. CONTRACEPTION

I. ORAL CONTRACEPTIVES (OCs)
OCs act by suppression of ovulation and thickening of cervical mucus

A. Advantages
1. Theoretical and actual failure rates of 0.5% and 3% respectively
2. Decreased risk of ovarian and endometrial cancer by 40% and 50%, respectively
3. Decreased risk of ectopic pregnancy and pelvic inflammatory disease (PID)
4. Lighter menstrual flow, relief of dysmenorrhea, decreased ovarian cysts
5. Decreased endometriosis, PMS symptoms and acne
6. Decreased incidence of fibrocystic breast disease and fibroadenoma
7. Fertility returns within 3 months of discontinuing OCs in most patients
8. Decreased perimenopausal symptoms, such as vasomotor instability (low-dose estrogen)

B. Contraindications (to Estrogen-containing OCs)
1. Absolute
   a. Pregnancy
   b. Thrombophlebitis or thromboembolic disorders past or present
   c. CVA, CAD, or structural heart disease
   d. Breast cancer or Estrogen-dependent cancer (some feel this is a relative contraindication)
   e. Liver disease
2. Relative
   a. Age > 35 and smoker
   b. Hypertension, uncontrolled on appropriate medical therapy
   c. Cardiac, renal, gallbladder disease
   d. Migraines, with focal neurologic symptoms
   e. Postpartum < 21 days or lactation (avoid OCPs until lactation well-established); see I. and J. below
   f. Diabetes, surgery, fracture, severe injury (prolonged bedrest with increased risk of DVT), lactation, significant depression

C. Drug interactions: Patients taking the following drugs will need to use another form of contraception: Rifampin, Phenobarbital, Phenytin (Dilantin), Griseofulvin, Primidone (Mysoline), Carbamazepine (Tegretol), St. John’s Wort, and ATBs (if use ultra-low dose products). OCs can also decrease the hepatic metabolism of certain drugs, resulting in increased toxicity (some Benzodiazepines, β-blockers, Theophylline, TCAs). Pioglitazone (Actos) and Ethosuximide can decrease effectiveness

D. Follow-up: Return 3 months after beginning OCs to have blood pressure checked. Inquire about side effects, spotting, failure to withdrawal bleed (see following tables.) Then follow-up every year. Perform PAP screening and check fasting lipids according to age-related guidelines

E. Initiation of OC’s: Check pregnancy test first and use back-up method of contraception for first 7 days with Quick Start and Sunday Start
1. Quick Start: May be started anytime during cycle but preferred approach is the “Quick Start” where they are started same day as prescription
2. Sunday Start: Begin first Sunday after beginning of menstruation
3. First Day Start: Begin pill on first day of menstruation. No back-up method needed

F. Age > 35
   1. Smokers: Discontinue OCs or change to progesterone only pill
2. If patient is a non-smoker and blood pressure, lipids, and fasting blood sugar are within normal limits, then OCs may be continued until menopause. Use a low dose (20mcg Ethinyl Estradiol) OC if patient > age 40, e.g., Loestrin 1/20
3. Women > age 45 on OCs should have FSH checked every year (on 6th day of a 7-day pill-free interval) and be changed to Estrogen replacement therapy (ERT) when FSH > 30

G. Missed pills
1. 1 missed pill: Take as soon as patient remembers, take next pill on schedule, no back-up required
2. 2 missed pills: Take 2 pills on each of next 2 days and use a back-up for 7 days
3. 3 missed pills: Continue to take pills and use back-up until menstruation

H. Amenorrhea while taking OCs:
1. For 1–2 cycles: Check β-hCG
2. For 3 cycles: Increase estrogen, decrease progestin, or follow

I. Postpartum
1. Progestin-only contraception (pills, DMPA, implants) can be initiated immediately after delivery in nonlactating women (CDC, WHO). There is an increase in volume and duration of vaginal bleeding if progestin-only contraception started prior to 6 weeks
2. Women in the first 6 weeks of postpartum period have a 22-fold to 84-fold increased risk for VTE. Therefore estrogen-containing OCs should not be used in women who are < 6 weeks after delivery, especially in women who had other risk factors for VTE (CDC, WHO)

J. Postpartum and Breast-feeding
1. Progestin-only contraception (pills, DMPA, implants) can be initiated at 6 weeks postpartum in women who are breastfeeding (ACOG, WHO)
2. Estrogen-containing OCs do not cause infant developmental problems but may cause a decrease in milk production. Use of estrogen OCs in women who are > 6 weeks postpartum is reasonable if the benefits outweigh the risks (CDC)

K. Postponing menstruation: Often desired for wedding, vacation. Patient should omit the 7 day hormone-free interval. She should start a new pack the day after finishing the 21 active pills

L. Pregnancy occurring while on OCs: Using OCs during early pregnancy does not appear to increase the risk of fetal deformities. The OC should be stopped after pregnancy is diagnosed

M. Types of oral contraceptives
1. Estrogen-Progestin Combinations:
   a. Two most commonly used Estrogen compounds are Ethinyl Estradiol (EE) or Mestranol. Mestranol is estimated to be 50% less potent than EE
   b. Progestin component in OCs varies in both dose and type, leading to differences in pharmacologic effect. Most OCs contain Norethindrone, Ethinodiol, and Levonorgestrel
   c. Newer progestins: Norgestimate and Desogestrel offer reduced androgenic activity
d. Drospirenone is a progestin derived from spironolactone. It possesses antiandrogenic and antimineralocorticoid activity
   i. The combination of lower androgenicity and diuretic effect may be particularly effective for patients suffering premenstrual dysphoric disorder, nausea, fluid retention, and acne
   ii. Given the potential for hyperkalemia, use with caution in patients with impaired renal or adrenal function. Monitor for interactions with drugs such as ACE inhibitors, ARB, K+ sparing diuretics, and NSAIDs
   iii. The FDA issued safety alert on the possible increased risk of blood clots with drospirenone-containing OCs (1.5 × ) compared to users of other hormonal contraceptives. (FDA Drug Safety Announcement 9/26/12)
   e. Conventional OCs contain 30–35mcg EE and a progestin that is less androgenic (Norgestimate or Desogestrel)
f. Low estrogen (20 or 25 mcg)-progestin combinations are available
g. Regimens
### 28. Contraception

i. Monophasic OCs: constant dose of estrogen and progestin in the active pills per cycle

ii. Biphasic and triphasic OCs: dose of estrogen and progestin vary in the active pills in 2 or 3 phases. These types of OCs attempt to duplicate the pattern of a normal menstrual cycle. Clinically, very little difference is observed between monophasic and multiphasic OCs

iii. Conventional regimen: 28-day cycle (21 days of active pills followed by 7 day medication free)

iv. 24/4 regimen: 24-day on and 4-day off cycle

v. Extended-cycle: 84-days of active pills followed by 7 days of placebo

vi. In some formulations, placebo tablets may be replaced with:
   - **aa. Ferrous fumarate** to facilitate ease of administration (e.g., **Loestrin Fe**)
   - **bb. Levomefolate** to reduce the risk of neural tube defects if pregnancy occurs during or shortly after use (e.g., **Beyaz**)

2. Progestin-only products (“mini-pills”)
   - a. Contain decreased dose of Progestin relative to combination OCs
   - b. Preferred for use during breast-feeding, and for women who have contraindication to estrogens (especially smokers > age 35)
   - c. Have a slightly higher failure rate (1–4%) and may lead to more irregular bleeding
   - d. Best efficacy if taken at same time of day

#### ORAL CONTRACEPTIVE SIDE EFFECT ADJUSTMENTS

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>PROBABLE ETIOLOGY</th>
<th>CHANGE REQUIRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Break through bleeding (BTB) spotting first 10 days</td>
<td>Estrogen deficiency</td>
<td>Increase estrogen*</td>
</tr>
<tr>
<td>BTB or spotting second 10 days</td>
<td>Estrogen and/or progestin deficiency</td>
<td>Increase estrogen* or progestosterone</td>
</tr>
<tr>
<td>Prolonged or heavy menses</td>
<td>Progestin deficiency</td>
<td>Increase progestin</td>
</tr>
<tr>
<td>Delayed onset of menses</td>
<td>Progestin deficiency</td>
<td>Increase progestin</td>
</tr>
<tr>
<td>Shortened menses</td>
<td>Progestin excess</td>
<td>Decrease progestin</td>
</tr>
<tr>
<td>No menses</td>
<td>Progestin excess or estrogen deficiency</td>
<td>Continue one cycle then increase estrogen</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Progestin excess</td>
<td>Decrease progestin</td>
</tr>
<tr>
<td>Hirsutism, loss of scalp hair, acne</td>
<td>Progestin excess</td>
<td>Decrease progestin or change to progestin with low androgenicity</td>
</tr>
<tr>
<td>Cervicitis, candidal vaginitis</td>
<td>Progestin excess</td>
<td>Decrease progestin</td>
</tr>
<tr>
<td>Depression, decreased libido, fatigue</td>
<td>Progestin excess</td>
<td>Decrease progestin</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>Estrogen excess</td>
<td>Decrease estrogen</td>
</tr>
<tr>
<td>Chloasma (skin discoloration)</td>
<td>Estrogen excess</td>
<td>Decrease estrogen</td>
</tr>
<tr>
<td>Uterine cramps</td>
<td>Estrogen excess</td>
<td>Decrease estrogen</td>
</tr>
<tr>
<td>Edema, bloating, breast tenderness and enlargement, headaches</td>
<td>On pills — Estrogen excess</td>
<td>Decrease offending steroid, diuretics</td>
</tr>
<tr>
<td></td>
<td>On placebo week — Progestin excess</td>
<td></td>
</tr>
<tr>
<td>Migraine, blurring of vision</td>
<td>Estrogen excess</td>
<td>Needs further evaluation, consider stopping pills</td>
</tr>
<tr>
<td>Androgenic symptoms</td>
<td>Progestin excess</td>
<td>Change to 3rd generation progestin (desogestrel)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Progestin excess</td>
<td>Change to 3rd generation progestin (desogestrel)</td>
</tr>
</tbody>
</table>

*An easy way to increase the Estrogen without decreasing the Progesterone is to administer Conjugated Estrogen (Premarin) 1.25mg QD x 7 days. This may be attempted no matter where patient is in her cycle*
### Composition of Combination OCs

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Estrogen µg</th>
<th>Progestin mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Androgenic Activity of Progestin Component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monophasic</td>
<td>Brevicon, Mediclon, Necon 0.5/35, Norlut 0.5/35</td>
<td>EE 35</td>
<td>Norethindrone 0.5</td>
</tr>
<tr>
<td></td>
<td>Halron, Ovcon 35, Femcon-Fem 35</td>
<td>EE 35</td>
<td>Norethindrone 0.4</td>
</tr>
<tr>
<td></td>
<td>Ortho-Cyclen, Mononessa, Sprintec</td>
<td>EE 35</td>
<td>Norgestimate 0.25</td>
</tr>
<tr>
<td></td>
<td>Ortho-Leapid, Desogen, Apil</td>
<td>EE 30</td>
<td>Desogestrel 0.15</td>
</tr>
<tr>
<td></td>
<td>Ocella, Yasmin, Safyrala</td>
<td>EE 30</td>
<td>Desopironone 3</td>
</tr>
<tr>
<td></td>
<td>YAZ, Loryna, Giavr, Beya</td>
<td>EE 20</td>
<td>Desopironone 3</td>
</tr>
<tr>
<td>Biphasic low dose</td>
<td>Micrette, Kariva, Aziatre</td>
<td>EE 20-30</td>
<td>Desogestrel 0.13</td>
</tr>
<tr>
<td></td>
<td>Ortho Tri-Cyclen, Trimestene, Tri- Sprintec</td>
<td>EE 35-35-35</td>
<td>Norgestimate 0.18-0.215/0.23</td>
</tr>
<tr>
<td>Triphasic low dose</td>
<td>Cesca, Cyclessa, Velvet</td>
<td>EE 25-25-25</td>
<td>Desogestrel 0.15/0.25/0.35</td>
</tr>
<tr>
<td></td>
<td>Ortho Tri-Cyclen-Lt</td>
<td>EE 25-25-25</td>
<td>Norgestimate 0.18-0.215/0.23</td>
</tr>
<tr>
<td>4-phasic</td>
<td>Yutana, Estradiol valerate</td>
<td>EE 3/2/1</td>
<td>Desogestrel 0.2/0.2</td>
</tr>
</tbody>
</table>

### Medium Androgenic Activity of Progestin Component

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Estrogen µg</th>
<th>Progestin mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monophasic</td>
<td>Zovia 1/50</td>
<td>EE 50</td>
<td>Ethynodiol diacetate 1.0</td>
</tr>
<tr>
<td></td>
<td>Necon 1/50, Naturil 1 + 50</td>
<td>EE 35</td>
<td>Norethindrone 1.0</td>
</tr>
<tr>
<td></td>
<td>Kelron 1/35, Zovia 1/35</td>
<td>EE 35</td>
<td>Ethynodiol diacetate 1.0</td>
</tr>
<tr>
<td></td>
<td>Alyacen 1/35, Ortho-Novum 1/35, Naturil 1 + 50, Necon 1/35, Natrel 1/35</td>
<td>EE 35</td>
<td>Norethindrone 1.0</td>
</tr>
<tr>
<td></td>
<td>Loestrin 21/20, Loestrin Fe 1/20, Loestrin 24 Fe'</td>
<td>EE 20</td>
<td>Norethindrone acetate 1.0</td>
</tr>
<tr>
<td></td>
<td>Aviane, Lestrin, Lutina, Sonya</td>
<td>EE 20</td>
<td>Levonorgestrel 0.1</td>
</tr>
<tr>
<td>Biphasic</td>
<td>Ortho-Novum 10/11, Necon 10/11</td>
<td>EE 35-35</td>
<td>Norethindrone 0.5-1.0</td>
</tr>
<tr>
<td></td>
<td>Lo-Leovistin Fe'</td>
<td>EE 10-10</td>
<td>Norethindrone 1.0</td>
</tr>
<tr>
<td>Biphasic Extended-cycle</td>
<td>Ortho-Novum 7/7, Necon 7/7</td>
<td>EE 35-35-35</td>
<td>Norethindrone 0.5-0.75/1.0</td>
</tr>
<tr>
<td></td>
<td>Tri-Norinyl, Kevinon, Lestena</td>
<td>EE 35-35-35</td>
<td>Norethindrone 0.5-1.0</td>
</tr>
<tr>
<td></td>
<td>Triplan, Imperia, Triova</td>
<td>EE 30/40/30</td>
<td>Levonorgestrel 0.05/0.075/0.125</td>
</tr>
<tr>
<td></td>
<td>Tri-Levlen, Tri-Legent, Estratide Fe'</td>
<td>EE 20/30-35</td>
<td>Norethindrone acetate 1/1</td>
</tr>
</tbody>
</table>

### High Androgenic Activity of Progestin Component

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Estrogen µg</th>
<th>Progestin mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monophasic</td>
<td>Ogestrel, Levonorgestrel</td>
<td>EE 50</td>
<td>Norethindrone 0.5</td>
</tr>
<tr>
<td></td>
<td>Loestrin Fe 1/5/30, Mecongestroin Fe 1/5/30, Loestrin 21/2.5/50</td>
<td>EE 30</td>
<td>Norethindrone acetate 1.5</td>
</tr>
<tr>
<td></td>
<td>Lo-Ovral 28, Lev-Ogestrel, Lo-Ovral 24'</td>
<td>EE 30</td>
<td>Norethindrole 0.3</td>
</tr>
<tr>
<td></td>
<td>Levon, Marissa, Nordesta 28, Poina</td>
<td>EE 30</td>
<td>Levonorgestrel 0.15</td>
</tr>
<tr>
<td>Biphasic Extended-cycle</td>
<td>Sequinsale, Coeurise, Amelia 91-day</td>
<td>EE 30-10*</td>
<td>Levonorgestrel 0.15-0.25*</td>
</tr>
</tbody>
</table>

### Progestin-Only Pills (POPs)

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Estrogen µg</th>
<th>Progestin mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monophasic</td>
<td>Micronor, Nor-QD, Ibrit</td>
<td>None</td>
<td>Norethindrone 0.35</td>
</tr>
</tbody>
</table>

1: Chewable tabs, 21 days active pills followed by 7 days pills containing ferrous fumarate 75mg
2: 21 days of active pills followed by 7 days of pills containing levomefolate calcium 0.451mg
3: EE 20 mcg + desogestrel 0.15mg × 21 days, then 2 days placebo followed by EE 10mg × 5 days
4: 91 days of active pills (EE/progestin) then 7 days of pills containing EE
5: YAZ also has an indication for the treatment of PMDD
6: Additional indication for acne
7: Additional indication for treatment of heavy menstrual bleeding

- Failure rates with the Progestin-only minipill are higher than other OCs (1–4%). They also do not offer protection against functional ovarian cysts
- Ethynodiol, Desogestrel and Norgestimate have a low amount of androgenicity and may be good first line agents for women with acne and hirsutism
- Some clinicians feel that assessing the relative progesterone potency is not clinically useful
II. PROGESTERONE IMPLANTS AND INJECTIONS
A. Depo-Provera (Medroxyprogesterone Acetate) 150mg IM Q 3 months (11–13 weeks)
   1. Failure rate of 0.3% first year; cumulative 5-year 0.9%
   2. Check urine pregnancy test before administering first dose. Should also check urine pregnancy before re-administering Depo-Provera if patient > 1 week late for injection
   3. If first dose is given during menstruation, contraception begins immediately. If not, then use alternate form of contraception until next menses
   4. May give postpartum even if mothers are lactating
   5. Side effects: Irregular bleeding, amenorrhea, weight gain (5–10 lbs), headache, increased risk of bone loss with long-term use, breast tenderness, depression, irritability
   6. If spotting occurs, patient should be informed that irregular bleeding usually disappears after 1yr. Consider giving Premarin 1.25mg QD × 7 days which may be increased to 2.5mg QD × 7 days or 2.5mg QD × 21 days. This therapy should not be continued longer than 1–2 months. If unsuccessful then consider another form of contraception
   7. Disadvantage: Delayed return to fertility, average 10 months
   8. Useful for patients with seizure disorder, sickle-cell anemia (crises reduced by 70%). Also helpful for dysmenorrhea, endometriosis, and menses-related anemia
   9. FDA required a black-box warning that Depo-Provera should not be used long-term because it can cause bone loss. Studies have since shown this to be reversible bone loss that does not increase fracture risk. Long term use in adolescents may affect peak bone mineral density; calcium and Vitamin D supplements are recommended
B. Depo-subQ 104 contains 104mg Medroxyprogesterone. It is given SC Q 3 months. Side effects are similar to that of the IM formulation
C. Implanon: a single-rod implant contains 68 Etonogestrel and releases approximately 40mcg/day. Duration of protection is 3 years. Implanon is being replaced by Nexplanon
D. Nexplanon is radio-opaque implant. It contains the same amount of etonogestrel and is bioequivalent to Implanon; it can also be used for up to 3 years, and is removed in the same way

III. MALE CONDOM
A. Theoretical and actual failure rates: 2% and 10%, respectively. Patients should be instructed in use—the actual failure rate can fall dramatically with correct use
B. Better protection against STDs (including HIV if condoms with nonoxynol-9 are used)
C. Patients should be instructed not to use with oil-based lubricants, such as Vaseline
D. If used with a spermicidal vaginal foam, contraception failure rates approach OCs

IV. FEMALE CONDOM
A. Failure rate 5–20%
B. Difficult to use
C. Protects against STDs
D. Can use any lubricant

V. DIAPHRAGM
A. Theoretical and actual failure rates: 2% and 20% when used with spermicide
B. Provides protection against pelvic infection and cervical dysplasia. Increased risk of UTIs
C. Must be inserted prior to intercourse, but does not need to be removed and reinserted for subsequent intercourse for next 12hrs (do need to use extra spermicide after 6hrs). Cannot be left in longer than 12–18hrs (increased risk of UTIs)
D. Must wait 4–6 weeks postpartum to fit.

VI. PRENATIF CERVICAL CAP
A. Thimble-shaped device, fitted to cervix with small amount of spermicide
B. Advantage: May be used for multiple episodes of intercourse, up to 48hrs, and requires less contraceptive gel than diaphragm
C. Parous cervix may be difficult to fit
D. Pap smear needed prior to fitting, 3 months later, and annually thereafter
VII. COMBINATION HORMONAL PATCH (Ortho Evra)
A. Pregnancy rates equivalent to OCPs
B. 20cm² adhesive patch contains 6mg Norelgestromin and 0.75mg Ethinyl Estradiol
C. Patch placed on trunk or arm once a week—use for 3 weeks, then off for 1 week
D. Side effects: adhesive dermatitis, headache, emotional lability, weight gain (1%)
E. The patch exposes women to a continuous level of estrogen higher than most oral contraceptive pills. Studies found that users could have up to 2 times the risk of developing venous thromboembolism (VTE) than those who take OCs
F. Ortho Evra should not be used by patients who smoke and are over 35 years of age

VIII. HORMONAL VAGINAL CONTRACEPTIVE
Etonogestrel 120mcg per day/Ethinyl Estradiol 15mcg per day (NuvaRing)
A. One ring is inserted on or before day 5 of cycle and left in place for 3 weeks then
  removed for 1 ring-free week
B. If switching from combination OCP, then insert within 7 days of last active pill
C. Vaginitis, leukorrhea, side effects of estrogen and progesterone

IX. VAGINAL SPERMICIDES
A. Failure rates from 3–20% per year
B. Inserted before intercourse and may be used without replacement for repeated acts of intercourse for 12–18hrs
C. Available OTC
D. 2–4% of couples have allergic reactions

X. INTRAUTERINE DEVICE (NONHORMONAL)—PARAGARD
A. Failure rates 1–2%; spontaneous expulsion rate 5%
B. Copper Paragard T380A
C. Implant during menses, mid-cycle to prevent expulsion, or 12 weeks postpartum. Copper T380A should be changed every 10yrs
D. Especially useful in women who have completed child bearing and have only 1 sexual partner. Risk of PID and ectopic pregnancy are increased
E. Menstrual flow and cramping will most likely increase, may prescribe NSAIDs prophylactically

XI. INTRAUTERINE DEVICE (HORMONAL)—MIRENA
A. Failure rate 0.7% cumulative for 5yrs
B. Releases 20mcg Levonorgestrel per day
C. Insert during first 7 days of cycle, approved for 5yrs of use
D. Mechanism—thickens cervical mucus, sperm motility impairment, inhibition of ovulation, inhibition of fertilization
E. Side effects: Mastalgia, headache. No reported weight gain
F. May decrease incidence of dysmenorrhea, menorrhagia, PMS, endometrial hyperplasia
G. Rapid return to fertility: 79% pregnant by 12 months
H. Mirena is recommended for women who have had at least one child
I. Mirena has additional indication for the treatment of heavy menstrual bleeding for women who choose to use IUD as their method of contraception
J. Skyla, a new lower dose version of Mirena has just been approved for the prevention of pregnancy for up to 3 years. It contains 13.5 mg Levonorgestrel and releases 14 mcg/day after 24 days. This rate decreases progressively to 5 mcg/day after 3 years

XII. COITUS INTERRUPTUS
Failure rates 20–25% per year

XIII. FERTILITY BASED AWARENESS (Basal body temperature, calendar)
Failure rates from 2–20% depending on expertise of user

XIV. STERILIZATION
A. Male
  1. Failure rate of only 0.1%

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2. Couple needs to be sure that no more children are desired
3. In office procedure with ‘scalpel-less’ procedure
4. Easy to perform, local anesthesia

B. Female
1. Failure rates depend on procedure used—most effective postpartum
2. Failure rates increase over 10yrs from 0.8% to 4%. Counsel the couple on their certainty of sterilization. Can possibly be reversed, but at a cost of ~$10,000
3. Partial Salpingectomy: part of tube removed and ends tied. Can be open or laparoscopic. Done in the OR with general or regional anesthesia
4. Essure: coil introduced into tubes transcervically with hysteroscope. Office based procedure with local anesthesia
5. Adiana: apply radiofrequency energy to tube then insert silicone matrix. Office based procedure with local anesthesia

XV. NO METHOD
Pregnancy rate of 85–90% per year

XVI. EMERGENCY CONTRACEPTION
A. Administration of drugs to prevent pregnancy in women who have had recent unprotected intercourse (including sexual assault), or to those who have had a failure of another method of contraception (e.g., broken condom)

B. Mechanism of action: May act by inhibiting or delaying ovulation, interfering with fertilization or tubal transport, preventing implantation by altering endometrial receptivity, or possibly causing regression of the corpus luteum

C. Options
1. Copper IUD
   a. Place within 120 hours of unprotected sex
   b. Reduces risk of pregnancy up to 99%
2. Progestin-only pills (Levonorgestrel)
   a. Plan B One-Step: one tablet (1.5 mg Levonorgestrel) as soon as possible within 72 hours of unprotected sexual intercourse
   b. Next Choice: One tablet (0.75 mg Levonorgestrel) as soon as possible within 72 hours of unprotected sexual intercourse; a second 0.75 mg tablet should be taken 12 hours after the first dose
   c. Consider repeating the dose if vomiting occurs within 2 hours of Plan B One Step and 1 hour of Next Choice. If severe vomiting occurs, may consider administering the oral tablets vaginally (ACOG, 2010)
   d. Plan B is available over the counter without age restriction (FDA News Release, June 20, 2013). Next Choice is available without a prescription for ≥17 yr of age
   e. Reduces risk of pregnancy up to 85%
3. Ulipristal (Ella)—a progesterone agonist/antagonist
   a. One tablet (30 mg) taken as soon as possible within 120 hrs (5 days) after unprotected intercourse
   b. Repeat the dose if vomited within 3 hrs of taking Ulipristal
   c. Common adverse reactions (≥25%): headache, abdominal pain, nausea, dysmenorrhea, fatigue and dizziness
   d. Available by prescription
4. Combination Estrogen/Progestin pills
   a. Regimen of Ethinyl Estradiol (100 mcg) and Levonorgestrel (0.5 mg) taken twice, 12 hrs apart. May use combinations of OCs such as 5 orange pills of Aviane or LoSeasonique, 5 white pills of Lutera or Sronyx
   b. Reduces risk of pregnancy 75–80%
   c. Major side effect of nausea and vomiting
   d. Consider use of anti-emetic

CLINICAL PEARLS
• Most cases of condom failure result from inappropriate usage. The number of condoms that break is less than 2 per 100
• The number of women with chlamydia and gonorrhea who later develop infertility ranges from 10–40%
• Correct use of a male (or female) condom can drastically reduce the chance of contracting a sexually transmitted disease.
• Nearly half of all pregnancies in US are unintended.
• Implants and IUDs should be offered as first-line contraceptive options for sexually active adolescents (ACOG new guidelines 2012).

References
CDC. Update to CDC's U.S. medical eligibility criteria for contraceptive use, 2010: Revised recommendations for the use of contraceptive methods during the postpartum period. MMWR. July 8, 2011;60(26):878–83.

Anthony Casey, MD
Ellen Little, MD

29. Fertility Awareness Based Medicine: Creighton Model

I. INTRODUCTION
A. Standardized method of identifying a woman's fertility or infertility based on cervical mucus observations.
B. Works cooperatively with a woman's menstrual and fertility cycle.
C. Combines with Natural Procreative (NaPro) technology for targeted medical and surgical treatments.
D. Avoiding pregnancy: Avoid intercourse on days of fertility
   1. Use effectiveness 96.8%
   2. Method effectiveness 99.5%
E. Achieving pregnancy: Use days of fertility for intercourse
   1. Normal fertility: 98% will conceive in 6 months.
   2. Infertility: Identifies and treats underlying cause of infertility
      a. 80% will conceive with the combined use of Creighton Model and NaPro technology.
      b. Multiple gestations
         i. Creighton Model: 3.2%
         ii. IVF: 10–45% depending on 2–3 embryo transfer.
F. Provides options for treating other common gynecologic medical conditions through NaPro technology, such as endometriosis and PCOS.
II. PHYSIOLOGY OF CERVICAL MUCUS AND FERTILITY
A. Cervical mucus acts as a biological valve, either facilitating or inhibiting sperm motility through the cervix
B. Cervical crypts in endocervical canal produce E-type and G-type mucus
   1. E-type mucus
      a. Stimulated by estrogen, specifically the estrogen peak that stimulates ovulation
      b. Forms channels that facilitate sperm motility through the cervix
      c. Peak type mucus is described as clear, stretchy OR lubricative
      d. Non-peak type mucus is any other mucus
   2. G-type mucus
      a. Stimulated by progesterone in the luteal phase
      b. Increased viscosity makes cervix impenetrable to sperm
C. Peak day is defined as the last day of peak-type mucus during the cycle
   1. Follicular phase is the first day of bleeding until the day before peak day
   2. Luteal phase is Peak Day until the first day of bleeding
D. Women confidently identify the days of fertility and infertility.
   1. Fertile
      a. Days of menstrual flow (unable to detect mucus)
      b. Mucus days through 3 full days post peak
   2. Infertile
      a. Dry days following menstrual flow
      b. 4th day post peak until next menses

II. PATIENT EDUCATION
A. Taught by physician practitioners and allied health professionals
   1. Standard method individualized to each woman
   2. Follow up visits to ensure charting correctly
B. Universal coding allows for international use
C. Check mucus with external vulvar observations, NOT internal exam. Wipe the vaginal opening with tissue from front to back through the perineal body.
   1. 3 steps: SOFT
      a. S-Sensation. Is there lubrication or not? This is an obvious sensation
      b. O-Observe the tissue for mucus
      c. FT-Finger test any available mucus on the tissue
   2. Check before and after using the bathroom and at the end of day.
D. Place a stamp using the recording system at the end of day to identify a day of fertility or infertility. Do this daily throughout entire cycle

III. OPTIMIZING WOMEN’S FERTILITY AND GYNECOLOGIC HEALTH
A. Abnormal bleeding, PMS, PMDD, Post-partum depression
   1. Targeted, cooperative therapy based on detected estrogen and progesterone deficiencies
   2. Method relies on accurate charting, labs and imaging relative to Peak Day
B. Infertility: Includes medical and surgical treatments for PCOS and Endometriosis
C. Prevention of preterm labor, delivery and multiple gestations for subsequent reduction of infant mortality
D. Creighton Model can be used at all times during a woman’s gynecologic life, including adolescence, peri-menopause, infertility, post-pill, breastfeeding, post-abortion and post-sterilization

CLINICAL PEARLS
• There are no taking chances with the Creighton Method: women confidently identify if they are fertile or infertile on any given day
• Creighton Model is a safe, inexpensive method to avoid pregnancy for those with contraindications to contraceptives or with personal preference to avoid artificial means of contraception
• High success rate for those with infertility when combined with NaPro technology
30. Pap Smears

with low multiple gestation rate
• NaPro technology and charting identifies and treats the underlying cause in several gynecologic conditions

References
Hilgers, TW. The medical & surgical practice of NaPro technology. 2004 Pope Paul VI Institute Press, Omaha NE.

Jillian Trizna, DO
David G Stockwell, MD
Miriam Chan, Pharm D

30. Pap Smears: Indications & Interpretation

I. INTRODUCTION
Approximately 50 million women have Pap tests each year and 7% will have an abnormality which requires further testing. Obtaining HPV typing allows clinicians to modify further screening and treatment options. In 2001 the new Bethesda System terminology was introduced. This chapter is based upon this terminology. Approximately 90% of the labs in the US use some form of the Bethesda System

II. INDICATIONS AND SCHEDULE
A. The American College of Obstetrics and Gynecology (ACOG), American Cancer Society (ACS), and U.S. Preventive Services Task Force all have slightly different recommendations regarding onset and frequency of cervical cancer screening
1. USPSTF (updated 2003)
   a. Pap tests every 3 years, beginning within 3 years of onset of sexual activity, or age 21 (whichever comes first)
   b. Discontinue at age 65 if adequate screening has been done and not at high risk for cervical cancer
   c. Discontinue screening in women who have had a hysterectomy for a benign disease
2. ACS (updated 2012)
   a. Screen beginning at age 21, regardless of age of initiation of sexual intercourse or other risk factors
   b. For women ages 21–29, screen every 3 years with cytology alone. For women ages 30–65, screen every 5 years with cytology plus HPV testing (preferred) or every 3 years with cytology alone
   c. Discontinue screening in women 65 years or older if they have had adequate screening (3 consecutive negative cytology results or 2 consecutive negative cytology/HPV results) or hysterectomy for benign disease. If history of CIN2 or 3 or adenocarcinoma in situ, continue routine screening for at least 20 years following regression or appropriate management
3. ACOG (updated 2009)
   a. Avoid screening in women younger than 21 years
   b. Screen every 2 years in women ages 21–29. Screen every 3 years in women ages
Women’s Health

30. Pap Smears

30–65/70 (unless they are HIV+, immunocompromised, CIN2 or 3, or exposed to DES in utero, then screen annually)
c. Discontinue screening in women between ages 65 and 70 years who have had 3 or more negative cytology test results in a row and no abnormal test results in the past 10 years

B. Risk factors for cervical cancer
1. Early first intercourse
2. Large number of lifetime sexual partners
3. History of STDs, especially human papilloma virus (HPV)
4. High-risk sexual partners
5. Cigarette smoking
6. Lack of normal immune response (HIV increases chances of cervical cancer 8–11 times)
7. High parity
8. Low socioeconomic status
9. History of abnormal Pap smear
Note: Smoking and HPV are the only independent risk factors to be consistently shown to have statistical significance in multiple studies

III. RECOMMENDED TECHNIQUE FOR PERFORMING PAP SMEAR
A. Ideally the entire portio should be visualized prior to obtaining smear
B. Vaginal discharge when present in large quantities should be carefully removed so epithelium is not disturbed
C. Portio sample should be obtained first with the spatula and then with the endobrush because of risk of endocervical bleeding interfering with sample collection and drying
D. Sample collection should be uniformly applied and spray fixative applied. Spray fixative should be applied from at least 10 inches away to prevent dispersal and destruction of cells
E. Steps 3 and 4 can be interchanged with using the “broom” which obtains both ecto- and endocervical samples
F. Perform Gonococcus and Chlamydia cultures next (if indicated), then pelvic exam

IV. TECHNIQUES FOR SCREENING
A. ThinPrep (FDA approved) uses fluid-based technology. Process removes multiple contaminants (mucous, small amounts of blood, protein) and allows for a thin even cell layer on slide
B. Advantages: Several studies have demonstrated that ThinPrep and other monolayer systems have lower false negative rates than conventional slide preparations. Studies have also shown a decrease in unsatisfactory specimens
C. HPV typing can be performed from the same ThinPrep container as the Pap smear
D. Disadvantage: There is a slight increase in cost of monolayer preparations over conventional slides

V. PATHOLOGY REPORT AND ACTION: A–D below describe the possible descriptive diagnosis with the 2001 Bethesda System of reporting
A. Negative for intraepithelial lesion or malignancy: This finding may specify non-neoplastic findings including the following. Action should be taken based on the specific result
1. Trichomonas vaginalis
2. Fungal organisms morphologically consistent with Candida species
3. Shift in flora suggestive of bacterial vaginosis
4. Bacteria morphologically consistent with Actinomyces species
5. Cellular changes consistent with herpes simplex virus
6. Reactive cellular changes associated with inflammation (includes typical repair)
7. Radiation
8. Intrauterine contraceptive device
9. Glandular cells status posthysterectomy
10. Atrophy

B. Atypical squamous cells (ASC)
1. This category may be reported as:
   a. Atypical squamous cells of undetermined significance (ASC-US)—or—
   b. Atypical cells, cannot exclude high grade squamous intraepithelial lesion (ASC-H)
2. All ASC is considered suggestive of squamous intraepithelial lesion (SIL); 15–38% of women will have biopsy proven high grade squamous intraepithelial lesion (HSIL) and 0.2–2.7% will have invasive cervical cancer
3. Action for ASC-US:
   a. In women 21 years and older, perform reflex testing for oncogenic HPV types (6, 18 and others) and do colposcopy if positive. If HPV is negative, repeat cytology in 12 months
   b. Instead of HPV testing, another option is to repeat cytology at 6 and 12 months and, if normal, routine screening may be resumed. If either result is ≥ASC, then do colposcopy
4. Action for ASC-H: Colposcopy, without HPV testing

C. Squamous intraepithelial lesion (SIL)—May be low grade SIL (LSIL, LGSIL, HGSIL) or high grade SIL (HSIL)
1. Low-Grade SIL (LSIL): This category includes changes consistent with HPV, mild dysplasia, or CIN 1 (grade 1 cervical intraepithelial neoplasia)
   a. Approximately 80–90% of LSIL will spontaneously regress and 3–16% will progress to a higher grade dysplasia
   b. Action: Colposcopy
   c. Special Populations:
      i. In adolescents (≤20 years) with ASC-US or LSIL, may repeat cytology at 12 months then perform colposcopy if HSIL or higher. Otherwise, repeat cytology again at 12 months and perform colposcopy if ASC-US or higher.
      ii. In post-menopausal women, may perform colposcopy, obtain reflex HPV testing, or repeat cytology in 6 and 12 months
      iii. In pregnant women with LSIL, perform colposcopy (preferred approach for non-adolescent women) or colposcopy may be deferred until at least 6 weeks postpartum
      iv. Biopsies may be obtained if concern for adenocarcinomas Endocervical Curettage (ECC) is contradicted
2. Of the patients with ASCUS with carcinogenic HPV, 15–30% will have HSIL on subsequent Pap test
   a. Action: Colposcopy
3. High Grade Squamous Intraepithelial Lesion (HSIL): HSIL is equivalent to the older classification of moderate to severe dysplasia, CIN 2 or 3, and Carcinoma in Situ (CIS)
   a. 98.8% of women with HSIL have oncogenic subtypes of HPV, therefore testing is unnecessary
   b. Up to 3% of women with HSIL will have invasive cancer
   c. Action
      i. Colposcopy of entire cervix and vagina fornices, with biopsy of all visible lesions and endocervical curettage
      ii. Immediate loop electrosurgical excision procedure (LEEP) (except in pregnant women or adolescents)
      iii. Special Populations: In adolescents (≤20 years), perform colposcopy. Immediate LEEP is an acceptable option
D. Glandular Cell Abnormalities
1. May be reported as:
   a. Atypical glandular cells—either endocervical, endometrial, or not otherwise specified (NOS) as subcategory
   b. Atypical glandular cells, favor neoplastic—either endocervical, endometrial, or not otherwise specified (NOS) as subcategory
   c. Endocervical Carcinoma in Situ (AIS)
   d. Adenocarcinoma
2. Patients with AGUS pap tests have a much higher risk of dysplastic disease. 54% of women will have SIL and up to 9% will have invasive squamous cell of
adenocarcinoma. HPV DNA is present in over 90% of AGC

3. Action:
   a. All AGC categories (except atypical endometrial cells): Colposcopy with cervical biopsies and ECC, testing for high-risk HPV if not already done, and endometrial biopsy in all women
   b. For atypical endometrial cells, perform endometrial and endocervical sampling.
      If there is no endometrial pathology, then perform colposcopy

VI. PREGNANCY AND THE ABNORMAL PAP
A. In pregnancy, the same indications for colposcopy should be followed. If colposcopy is satisfactory and negative for visible lesions, the colposcopy can be repeated postpartum without any further evaluation during the pregnancy. If a lesion is visualized, it should be biopsied. Endocervical curettage (ECC) should NOT be performed during pregnancy. If biopsy negative or LGSIL, then repeat coloscopy can be postponed until 6 weeks postpartum
B. If a patient has HGSIL on Pap with a satisfactory colposcopy or a biopsy consistent with HGSIL, colposcopy should be repeated every trimester until delivery and then postpartum with ECC
C. Microinvasion on a biopsy will require conization and referral
D. Consider referral if cervical biopsy needed in pregnancy

VII. HIV POSITIVE FEMALES
A. If no history of prior cervical disease, the Pap smear should be obtained twice in the first year after diagnosis. If these are both normal, then yearly Pap smears can be performed
B. Once a patient becomes immunocompromised, colposcopy every 6 months should be considered

VIII. TREATMENT OF SQUAMOUS INTRAEPITHELIAL LESIONS
A. Indications for surgical excision (Cone)
   1. Unsatisfactory colposcopic examination (lesion extends into the cervical canal and is not visualized)
   2. Pap and colposcopy do not agree
   3. Diagnosis of microinvasive carcinoma based on punch biopsy
B. Cryosurgery
C. Laser vaporization techniques
D. Loop electrosurgical excision procedure (LEEP)/Large Loop excision of transformation zone (LLETZ): Removal of lesion with tissue diagnosis
Note: After the procedure, all patients will need Pap smears Q3 months × 1yr, Q6 months × 1yr, then Qyr if follow-up Paps are within normal limits

IX. HUMAN PAPILLOMA VIRUS (HPV) VACCINATIONS: HPV is a double stranded DNA virus—there are over 40 types
A. High risk HPV: Oncogenic and is detected in 99% of cervical cancers; e.g., 16, 18
B. Low risk HPV: Responsible for genital warts and condyloma. Ex types 6, 11
C. Affects over 50% of sexually active men and women at some point in their lives. 90% of women with HPV will become HPV negative over a 2 year period. HPV may remain in a dormant state and reactivate years later
D. Two HPV vaccines available: Gardasil (HPV4) and Cervarix (HPV2)—dose below
   1. Common adverse events of HPV vaccine:
      a. Syncope: Sitting or lying down for about 15 minutes after a vaccination may help
      b. Nausea
      c. Headaches
   2. Ideally, HPV vaccine should be given prior to potential HPV exposure through sexual activity; however, persons who are sexually active should still be vaccinated according to the age-based recommendations
   3. HPV vaccine can be given to persons with a history of genital warts, abnormal Pap test, or positive HPV DNA test
4. Cervical cancer screening recommendations are unchanged as the vaccine does not cover all HPV genotypes which cause cancer.

5. HPV vaccines are not recommended for use in pregnant women, data is limited.
   a. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose series should be delayed until completion of pregnancy.
   b. Pregnancy testing is not needed before vaccination.
   c. If a vaccine dose has been administered during pregnancy, no intervention is needed.

6. Gardasil (HPV4), a quadravalent HPV (types 6, 11, 16, 18) vaccine, is indicated to protect ages 9 to 26:
   • Females against cervical, vulvar, and vaginal cancers (HPV types 16 & 18).
   • Both females and males against anal cancer (HPV types 16 & 18); genital warts (HPV types 6 & 11); and precancerous lesions (HPV 6, 11, 16 & 18).
   a. Dosage: 3 dose-series given IM at 0, 2 mo, and 6 mo.
   b. CDC recommends routine HPV vaccination at 11 or 12 years of age. Minimum age: 9 years.
   c. Catch up schedule for 13 to 26 years of age: 3 doses with 1st dose ASAP, 2nd dose given 1–2 mo after the 1st dose and 3rd dose at least 24 wk after the 1st dose.
   d. CDC recommends Gardasil (HPV4) for men who have sex with men through age 26 years who did not get any or all doses when they were younger.

7. Cervarix (HPV2), a bivalent HPV (types 16 & 18) vaccine, is indicated to protect females aged 9 to 25 against cervical cancer (HPV types 16 & 18).
   a. Dosage: 3 dose-series given IM at 0, 1 mo, and 6 mo.
   b. CDC recommends routine HPV vaccination at 11–12 years of age. Minimum age: 9 years.
   c. Catch up schedule: same as HPV4.

**CLINICAL PEARLS**
- Cervical cancer is the 2nd leading cause of female cancer mortality worldwide.
- In 2011, there were an estimated 12,710 new cases of invasive cervical cancer and 4,290 deaths in the US.
- There were 13,000 cases of cervical cancer and 600,000 cases of CIN in 1991. The incidence of cervical cancer has decreased about 80% in the last 50 years.
- Since the introduction of the Pap smear in the US and other developed countries, the incidence and mortality from cervical cancer has declined by 75%.
- As of 2009, the prevalence of HPV in females ages 14–59 was 27%, with the highest prevalence in ages 20–24, where it was 45%.

**References**
31. ABNORMAL UTERINE BLEEDING

I. INTRODUCTION
A. The main goal will be to exclude non-uterine causes of bleeding (mass), then to:
B. Differentiate between ovulatory (heavy regular bleeding) and non-ovulatory (heavy irregular bleeding)
C. This chapter describes the data gathering aspects in sections II.–VI. and then management by age in sections VII.–X. (adolescents, reproductive age women, perimenopausal, post-menopausal)

II. HISTORY
A. Usual Menstrual Pattern: onset of menarche, frequency, volume (number of pads/tampons soaked per day), duration
B. Duration, volume, frequency of abnormal bleeding
C. Previous therapy for abnormal bleeding
D. Sexual history: recent sexual activity, post-coital bleeding, birth control, h/o sexually transmitted infections (STIs)
E. Weight change, exercise, eating disorder, stress, trauma
F. Medications: oral contraceptives, long-acting contraceptives (IUD, Depo-Provera, Nuvaring, Implanon), hormonal replacement therapy, antiepileptics, antipsychotics, anticoagulants
G. Past Medical History: fibroids, polyps, endometriosis, h/o abnormal Pap smears, PCOS, systemic diseases (thyroid, renal, hepatic, coagulopathies), uncontrolled diabetes, radiation therapy

III. TERMINOLOGY
A. Menorrhagia: prolonged (>7 days) or heavy (>80 ml) uterine bleeding (pads/tampons changed at > 3 hour intervals is normal)
B. Metrorrhagia: uterine bleeding occurring at irregular intervals
C. Menometrorrhagia: prolonged or heavy uterine bleeding occurring at irregular intervals
D. Polymenorrhea: uterine bleeding occurring at regular intervals of <21 days
E. Oligomenorrhea: uterine bleeding occurring >35 days
F. Amenorrhea: absence of bleeding for at least 3 usual cycle lengths (see chapter 32, Amenorrhea)

IV. PHYSICAL
A. General Exam: weight, signs of thyroid abnormalities or insulin resistance, surgical scars, hirsutism, acne, ecchymosis, galactorrhea
B. Vaginal Exam: lesions, masses, discharge, atrophy
C. Pelvic Exam: cervical polyps, cervical dilation, cervical motion tenderness, uterine enlargement, adnexal masses

V. DIAGNOSIS
A. Exclude non-uterine causes of bleeding: pregnancy (intrauterine, ectopic, molar), vulva, vagina, cervix, urethra (urethritis), bladder (UTI, cancer), bowel (hemorrhoids, IBD)
B. Differentiate between ovulatory and anovulatory abnormal uterine bleeding (AUB)
1. Ovulatory AUB
   a. Heavy and/or prolonged bleeding that is typically at regular intervals (although menorrhagia or midcycle spotting may occur)
   b. Characteristics of ovulatory cycles: regular cycle length, presence of premenstrual symptoms (pelvic pain, breast tenderness, mood changes, increased thin vaginal discharge), mittelschmerz (unilateral pelvic pain with ovulation), biphasic temperature curve
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c. Causes: Anatomic structural abnormalities (endometrial polyps, fibroids, adenomyosis, cervical neoplasia), bleeding disorder (von Willebrand’s disease, platelet disorder, factor deficiency, leukemia), hypothyroidism, chronic liver or renal disease, copper IUD

2. Anovulatory AUB
   a. Anovulation leads to prolonged estrogen production unopposed by progesterone (no progesterone surge). This results in excessive endometrial proliferation/thickening, endometrial instability, and irregular (sometimes heavy) bleeding with unpredictable cycle length and often spotting
   b. Causes: adolescence, perimenopausal, pregnancy, polycystic ovarian syndrome, thyroid disorder, medication effects, hyperprolactinemia, uncontrolled diabetes, endometrial hyperplasia/cancer, cervical cancer, eating disorder, significant weight changes, stress, excessive exercise
   c. Note: Polycystic Ovarian Syndrome: endocrine disorder usually associated with anovulation, menstrual disorders (irregular bleeding, amenorrhea), infertility, insulin resistance, obesity, increased circulating androgens (acne, hirsutism). Excessive androgens are converted to estrogen in peripheral tissues. Unopposed estrogen state increases risk of endometrial hyperplasia/cancer

VI. LABORATORY
   A. Pregnancy test (urine testing is adequately sensitive and specific)
   B. CBC, TSH, prolactin
   C. Pap smear: If age 21 or older (colposcopy/biopsy needed for patients of all ages if lesion found in pelvic exam)—See chapter 30, Pap Smears
   D. Pelvic cultures (if sexually active): GC, Chlamydia, Trichomonas
   E. Coagulation studies (if sexually active): PT/INR, PTT, vWF Ag/ristocetin cofactor if indicated
   F. Consider LH, FSH, DHEA-S, free testosterone if PCOS is suspected

VII. AUB IN ADOLESCENTS
   A. General
      1. Cycles are often anovulatory and irregular following menarche (up to 80% in the first year after menarche)
      2. Hypothalamic-pituitary-ovarian axis is usually mature within 18 months of menarche
   B. Pelvic exam: Not necessary if within 18 months of menarche and not sexually active
   C. Management
      1. Mild-moderate bleeding: Cycle patients for 6 months on either combined oral contraceptives (COC) or cyclic progestins (see section VIII.B.3 below)
      2. Severe bleeding: Consider further work-up for possible underlying coagulopathy

VIII. AUB IN REPRODUCTIVE AGE WOMEN
   A. Ovulatory AUB
      1. Assess for structural abnormality with transvaginal ultrasound or saline infusion sonohysterography
      2. Note: Measuring endometrial thickness in premenopausal women with AUB is not helpful
      3. Structural causes: hormonal therapy may be attempted, but patient may need definitive therapy (D&C, ablation, embolization, surgery)
   B. Anovulatory AUB
      1. Endometrial biopsy
         a. Women over age 35 with suspected anovulatory bleeding to rule out endometrial hyperplasia/cancer
         b. Consider in women age 18–35 with risk factors for endometrial cancer (chronic anovulation; obesity; diabetes; family history of ovarian, endometrial, breast, or colon cancer; tamoxifen use, estrogen therapy)
      2. Treat underlying conditions if applicable
      3. Hormonal therapy
         a. Combined oral contraceptives (<35 mcg Ethinyl Estradiol): Natazia, a 4-phasic
COC (Estradiol Valerate/Dienogest), has recently received a new indication for the treatment of heavy menstrual bleeding. It is the first and only med with such an indication

b. Levon gestrol IUD (Mirena)
c. Micronized Progesterone (Prometrium) 400mg daily × first 12 days of the month
d. Medroxyprogesterone Acetate (Provera) 10mg daily × first 10–12 days of the month
e. Norethindrone Acetate (Aygestin) 5mg QD × 5–10 days during second half of cycle

4. Non-hormonal therapy
   a. NSAIDs (Ibuprofen, Naproxen)
   b. Lysteda (Tranexamic Acid) 1300mg TID for up to 5 days during monthly menstruation

IX. AUB IN PERIMENOPAUSAL WOMEN (AGE 40 TO MENOPAUSE)
A. Ovulatory AUB—Same as in reproductive women
B. Anovulatory AUB
   1. Can be a physiologic response to declining ovarian function in a perimenopausal woman, but endometrial biopsy is needed to rule out hyperplasia/cancer.
   2. If normal, can prescribe hormonal therapy as described above
   3. Use of oral contraceptives that contain estrogen is contraindicated in smokers age 35 and older
C. Diagnosis of anovulatory AUB vs menopause
   1. If patient has 3 consecutive months of amenorrhea, determine if she is in menopause
      a. Obtain FSH level
         i. If FSH is high (>40 IU/mL), then patient is likely in menopause (although officially diagnosed after 12 months of amenorrhea in absence of other biological or physiological causes)
         ii. If FSH is >25 IU/mL, patient is likely in perimenopause, especially if accompanied by hot flashes, sleep disturbances, mood symptoms, or vaginal dryness
         iii. If FSH is low, the patient has AUB. Perform endometrial biopsy to exclude malignancy
         iv. Can cycle with Provera 10mg QD × 7 days or low dose (20mcg) oral contraceptives to see if patient has withdrawal bleeding
            aa. If no withdrawal bleeding, then repeat in 3 months. If still no withdrawal bleeding, assume she is in menopause
            bb. If there is withdrawal bleeding, then patient is not in menopause. Continue workup for sources of AUB
D. Management
   1. Provera: 10mg QD × 10 days—or—
   2. Prometrium 400mg PO BID × 10 days
   3. Oral contraceptives: Use 20mcg pills

X. AUB IN POST-MENOPAUSAL WOMEN
A. Perform endometrial biopsy as initial test to evaluate endometrium. 5–10% are found to have endometrial thickness. Can consider transvaginal ultrasound as alternative initial test to measure endometrial thickness
1. Results of endometrial biopsy
   a. Hyperplastic without atypia: Treat with Provera 10 mg daily for 14 days per month or daily Megace 40 mg or Mirena IUD. Repeat biopsy in 3–6 months. Refer to gynecologist if hyperplasia persists
   b. Hyperplasia with atypia: refer to gynecologist. Patient likely needs hysteroscopy/D&C. Associated with malignancy 15% of the time
   c. Adenocarcinoma: refer to gynecologist for TAH/BSO
   d. Atrophic: Can begin HRT
2. Endometrial biopsy vs transvaginal ultrasound
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a. Meta-analysis showed that 96% of women with endometrial cancer and 92% of those with endometrial disease, had endometrial stripe thickness of > 5mm whether or not they used HRT

b. If endometrial stripe on ultrasound > 5mm, endometrial sampling should be performed
c. Biopsy is more unfavorable and may be difficult in patients with cervical stenosis

3. Cervical cytology also needs to be performed

B. Patients on HRT

1. 30% of these patients will have uterine pathology
2. Women on continuous HRT may experience breakthrough bleeding due to missed pills, medication interactions, or malabsorption. If bleeding occurs in 2 or more cycles, further evaluation is indicated
3. On continuous HRT, up to 40% have irregular bleeding in first 4–6 months of therapy. Most experts recommend evaluation of abnormal bleeding if it lasts > 6–9 months after initiation of HRT

C. Management for women on HRT

1. If early withdrawal bleeding occurs, increase the progesterone dose
2. If intermenstrual bleeding occurs, increase the estrogen dose
3. If on continuous HRT, try cyclic
4. Try a different type of estrogen

CLINICAL PEARLS

• All post-menopausal bleeding must be worked up as 7% of post-menopausal bleeding is the result of malignancy!
• Consider β-hCG in all pre-menopausal women with abnormal bleeding

References
32. AMENORRHEA

I. INTRODUCTION: First exclude the most common cause: pregnancy. A history and physical including detailed gynecological exam will guide the evaluation and subsequent lab studies.

II. DEFINITION: Amenorrhea (absence of menses) is divided into the following:
   A. Primary: No spontaneous uterine bleeding by age 14 in the absence of the development of secondary sex characteristics or by age 16 in otherwise normal development
   B. Secondary (more common): Absence of menses for 6 months in woman with prior regular menses or for 12 months in women with prior oligomenorrhea

III. HISTORY
   A. Medical
      1. Endocrine or metabolic disorders
      2. Galactorrhea (need to exclude pituitary adenoma)
      3. Past or present serious illnesses
      4. Previous radiation therapy or chemotherapy
      5. Recent weight gain or loss/eating disorder
      6. Psychological disturbance/depression/stress
      7. Athletic training/intense exercise
   B. Menstrual
      1. Age at menarche
      2. Date of last menstrual period
      3. Previous menstrual pattern
      4. Events surrounding the onset of amenorrhea
   C. Reproductive
      1. Contraceptive use
      2. Gynecologic or obstetric procedures
      3. Pregnancies—outcomes, complications
      4. Pubertal development
   D. Family
      1. Age of mother and sister(s) at menarche and menopause
      2. Autoimmune disorders
      3. Congenital anomalies
      4. Endocrinopathies
      5. Infertility
      6. Menstrual dysfunction
      7. Tuberculosis
   E. Medications: Associated with amenorrhea
      1. Drugs that increase prolactin
         a. Antipsychotics: Phenothiazines, Haloperidol (Haldol), Pimozide (Orap), Clozapine (Clozaril)
         b. Antidepressants: Tricyclic antidepressants, Monoamine oxidase inhibitors
         c. Antihypertensives: Calcium channel blockers, Methyldopa (Aldomet), Reserpine
      2. Drugs with estrogenic activity: Digitalis, Marijuana, Flavinoids, Oral contraceptives
      3. Drugs with ovarian toxicity: Busulfan (Myleran), Chlorambucil (Leukeran), Cisplatin (Platinol), Cyclophosphamide (Cytoxan, Neosar), Fluorouracil

IV. PHYSICAL
   A. General: Body habitus and proportion, obesity, body hair extent and distribution
   B. HEENT: Excessive facial hair, acne, funduscopic exam to evaluate for papilledema, visual fields. Assess thyroid for goiter or nodules
   C. Breast development and presence of galactorrhea (fat globules visible per microscope exam)
   D. Abdomen: Striae in nulliparous women (hypercortisolism)
   E. Genitalia: Refer to Tanner Stages
V. LABS
A. Pregnancy test
B. See algorithm below for TSH, Prolactin, FSH, and LH
C. Other labs to consider obtaining to rule out systemic disease include: CBC, Calcium, Phosphorous, Thyroxine, thyroid antibodies, ESR, total protein, RF, ANA

VI. EVALUATION

![Diagram of Pregnancy Test algorithm]

*Refer to text for description of these diagnostic tests

A. Progesterone Challenge Test (PCT)
1. Method: Give Medroxyprogesterone Acetate (MPA) (Provera) 10mg PO QD × 5 days, or Progesterone (Prometrium) 400mg PO BID × 5 days
2. Results: The test is positive if there is any vaginal bleeding within 2–7 days after the fifth tablet. This confirms a diagnosis of anovulation. There is adequate endogenous estrogen, and the outflow tract is patent

B. Estrogen-Progesterone Challenge Test (E-PCT)
1. Method: Give Conjugated Estrogen 1.25mg PO QD × 21 days, add MPA (Provera) 10mg (or Progesterone (Prometrium) 400mg PO BID) days 16–21. Repeat cycle if no bleeding by day 28
2. Results: A positive test indicates menstruation is possible if adequate stimulatory estrogen is available. The workup is depicted in diagram. A negative test requires referral to a gynecologist for further studies

VII. MANAGEMENT
A. Anovulation secondary to inadequate Progesterone (i.e., positive PCT) indicates increased risk of endometrial cancer because of hyperplastic effect of unopposed estrogen. In addition, there may also be increased risk for breast cancer
1. To reduce risk of endometrial disease and to provide cycle regularity, give MPA 10mg PO QD (or Progesterone (Prometrium) 400mg BID) for first 7–10 days of each month
2. If pregnancy is desired, consider ovulation induction
3. If pregnancy is not desired, then give low dose cyclic oral contraceptives

B. Hypoestrogenic women (i.e., negative PCT and positive E-PCT) should be further
Elevated levels are indicative of primary ovarian failure. If onset of amenorrhea is age < 30, chromosomal analysis is indicated.

**CLINICAL PEARLS**

- Normally, the arm span and height measures are similar. If the arm span is 5 cm greater than the height, suspect hypogonadal disease
- Prevalence of secondary amenorrhea is higher in certain subgroups such as college students, ballet dancers, and competitive endurance athletes

**Reference**


**33. Menopause & Hormone Replacement Therapy**

**DEFINITION** (World Health Organization): “The permanent cessation of menstrual periods that occurs naturally or is induced by surgery, chemotherapy or radiation.” Natural menopause is diagnosed after 12 months of amenorrhea. Diagnosis can also be based on symptoms of menopause. Mean age 52 (range 40–58)

**I. SIGNS:** The perimenopause begins with skipped periods, increased or decreased interval between menses, or long or heavy bleeding

**II. SYMPTOMS:** Vasomotor (hot flashes, sweating), insomnia, nervousness, atrophic vaginitis, urinary atrophy (stress or urge incontinence), skin atrophy (wrinkles), osteoporosis, arteriosclerosis. Symptoms last from several months to several years. Some women may be asymptomatic

**III. DIAGNOSIS**

**A. If patient has 3 months of amenorrhea:** Obtain FSH level or give Provera to stimulate withdrawal bleeding

1. Obtain FSH level: Sequential measurements may be helpful
   a. If FSH is high (> 40 mIU/mL), then patient is in menopause. The pituitary is trying to stimulate ovulation, but patient is in menopause/ovarian failure. Consider starting hormone replacement therapy (HRT) if severe menopausal symptoms (see IV below)
   b. If FSH is low (< 40 mIU/mL), then the patient is not in menopause. May be perimenopausal. Cycle with Provera 10 mg QD (or Prometrium 400 mg BID) × 7 days per month if patient wants to induce menses

2. Withdrawal bleeding: Provera 10 mg QD × 7 days
   a. If there is no withdrawal bleeding, then repeat in 3 months. If she still has no withdrawal bleeding, assume she is in menopause. Consider starting HRT if severe menopausal symptoms (see IV below)
   b. If there is withdrawal bleeding, then patient is not in menopause

**B. If patient is having symptoms (hot flashes, etc.) and is not amenorrheic and FSH is elevated (> 20 mIU/mL), then she is in the transitional phase and menopause will most likely occur in the next several years**

1. These patients may be placed on low dose oral contraceptives, such as Loestrin 1/20, for symptom relief. Patients should be free of the following risk factors: hypertension,
hypercholesterolemia, cigarette smoking, previous thromboembolic disorders, cerebrovascular disease or coronary artery disease

2. Cyclic progestins may be used for women who are not candidates for OCP. One approach is *Provera* 10mg daily (or *Prometrium* 400mg BID) for 10 days each month to induce withdrawal bleeding and decrease the risk of endometrial hyperplasia

C. If the patient is on oral contraceptives, measure the FSH on the 6th day of the pill-free interval. If FSH > 40 mIU/mL, then change to HRT

D. If patient has heavy menses (passing clots or social inconvenience) for 3 months, bleeding between menses for 3–4 months, or 3 consecutive months of menses which last longer than 7 days, then perform Pipelle biopsy and/or transvaginal ultrasound. Manifestations of malignancy (bleeding) must not be dismissed as early menopause

IV. MANAGEMENT OF MENOPAUSE

A. Hormone replacement therapy (HRT): Estrogen is by far the most effective way to decrease symptoms of menopause, but recent studies including the *Women’s Health Initiative* (16,000 postmenopausal women on combination HT followed for 5 years) have shown increased risk of breast cancer, stroke, coronary heart disease, pulmonary embolism and dementia. There is a decreased risk of fracture and colon cancer, but risks are thought to outweigh the benefits in patients in their 60’s and 70’s

1. The primary indication for hormone therapy is the treatment of moderate to severe vasomotor symptoms. Potential consequences of severe vasomotor symptoms include diminished sleep quality, irritability, difficulty concentrating, and subsequently reduced quality of life (QOL)

2. According to recommendations from the North American Menopause Society (NAMS), the decision to use HT should be individualized and incorporate the woman’s health and quality of life priorities as well as her personal risk factors, such as risk of venous thrombosis, CHD, stroke, and breast cancer

3. Vasomotor symptoms: All systemic HT products except ultralow-dose estradiol transdermal patch have the FDA indication for this use

4. Vaginal atrophy: Use low-dose local vaginal *estrogen therapy* (ET)

5. **Progestogen** is used to negate the increased risk of endometrial cancer from systemic ET use

   a. All women with an intact uterus who use systemic ET should be prescribed with

      i. **Progestogen**

      ii. Women without a uterus do not need a **Progestogen** when prescribed systemic ET

      iii. **Progestogen** is generally not indicated when low-dose local (vaginal) ET is administered for vaginal atrophy

6. Systemic HT Dosage:

   a. **Estrogen**: Use the lowest effective dose—0.3mg to 0.45mg oral conjugate equine estrogen (*Premarin*), 0.5mg oral micronized 17-beta-estradiol (*Estrace*), or 0.014mg to 0.0375mg transdermal 17-beta-estradiol patch

   b. **Progestin**: starting at the lowest effective doses of 1.5 mg medroxyprogesterone acetate (*Provera*), 0.1mg Norethindrone acetate, 0.5mg Drospirenone, or 100mg micronized *Progesterone*

7. Continuous HT:

   a. *Premarin* 0.3 mg or 0.45 mg QD plus *Provera* 2.5 mg or *Prometrium* 100 mg QD. Can also use *Estradiol* for *Premarin*

   b. Oral Estrogen/Progestin combination products: one tablet daily

      i. *Angeliq* (*Estradiol/Drospirenone* 0.5mg/0.25 mg, 1mg/0.5mg)

      ii. *Activella* (*Estradiol/Norethindrone* 0.5mg/0.1mg, 1mg/0.5mg)

      iii. *Femhrt* (*Ethinyl Estradiol/Norethindrone* 2.5mcg/0.5mg, 5mcg/1mg)

      iv. *Prempro* (*Premarin/Provera* 0.3mg/1.5mg, 0.45mg/1.5mg, 0.625mg/2.5mg)

8. Cyclic HT:

   a. *Premarin* 0.3mg or 0.45mg QD plus *Provera* 2.5 or *Prometrium* 100mg QD on day 1–14 of each month. Can also use micronized *Estradiol* for ET
b. Oral Estrogen/Progestin combination products: one tablet daily
   i. Prefest (Estradiol 1 mg × 3 days then Estradiol 1 mg/Norgestimate 0.9mg × 3 days. This regimen repeats continuously)
   ii. Premphase (CEE 0.625mg day 1–14, then CEE 0.625mg/Provera 5 mg day 15–28)

9. Estradiol transdermal patch. Add Provera in women with a uterus
   a. One patch biweekly: Alora, Estraderm, Vivelle-Dot (0.025, 0.05, 0.075, 0.1mg/24 hr)
   b. One patch weekly: Climara (0.025, 0.0375, 0.05, 0.075mg/24 hr)

10. Transdermal Estrogen/Progestin combination patch:
   a. One patch biweekly: CombiPatch (Estradiol/Norethindrone 0.05mg/0.14mg/day, 0.05mg/0.25mg/day)
   b. One patch weekly: Climara Pro (Estradiol/Levonorgestrel 0.045mg/0.015mg/day)

11. Vaginal atrophy/dyspareunia
   a. Premarin, Estrace, Dienestrol, Ogen vaginal cream (0.01%mg/gm): ½ applicatorful nightly for 7–10 nights, then every other night or twice weekly after restoration of vaginal mucosa
   b. Estring: Estradiol vaginal ring (2mg/ring) that is inserted into upper ⅓ of vaginal vault and replaced every 3 months
   c. Estradiol (Vagifem) 10 mcg vaginal tablet: One tablet, inserted vaginally, once daily for 2 weeks, then twice weekly

B. Nonpharmacologic
   1. Relaxation techniques—Paced breathing, meditation
   2. Smoking cessation, weight loss

C. Antidepressants SSRIs or SNRIs
   1. Fluoxetine (Prozac)
   2. Paroxetine (Paxil)
   3. Citalopram (Celexa)
   4. Venlafaxine (Effexor XL)
   5. Duloxetine (Cymbalta)
   6. Desvenlafaxine (Pristiq)

D. Clonidine: 0.1–0.2mg PO QD or Clonidine Patch (0.1mg/week). Has reduced hot flash frequency in breast cancer survivors, but not other groups. Use limited by hypotension

E. Gabapentin (Neurontin): Benefit in hot flash frequency and sleep, but has greater somnolence, dizziness and rash

F. Progestins
   1. Medroxyprogesterone: 10–20mg PO QD
   2. Megestrol Acetate: 20–40mg PO QD

G. Other therapies
   1. Calcium: 1000–1500mg QD and Vitamin D 3 400–800 IU QD
   2. Exercise and diet
   3. Avoidance of smoking, excessive alcohol, and caffeine
   4. Vitamin E 100–200 IU QD
   5. Dietary supplements:
      a. Black Cohosh
      b. Soy and other phytoestrogens (tofu, soybean, coffee, tea, red clovers, isoflavone supplement)
      c. Flaxseed oil, evening primrose oil
   6. Melatonin for sleep
   7. Other sleep aids: Ambien, Lunesta, Remeron, Trazodone

H. For management of osteoporosis—See Chapter 77, Osteoporosis

I. Patient monitoring for patients on ET/HRT
   1. Annual pap test to age 65 in low risk populations
   2. Annual mammography
   3. Endometrial sampling or vaginal ultrasound in patients with abnormal uterine bleeding
34. Premenstrual Syndrome & Dysmenorrhea

Women's Health

4. Dual-energy x-ray absorptiometry (DEXA) scan to evaluate for osteoporosis if > 65 or with risk factors.
5. Monitor lipid profile periodically.
6. HT should be withdrawn when the patient is no longer experiencing significant symptoms. Use the least amount of HRT for the shortest period of time then attempt to wean off.

CLINICAL PEARLS

- Symptoms most strongly linked to menopause are hot flashes, night sweats, and vaginal dryness and sleep disturbance. Vasomotor symptoms (hot flashes) occur in 30–80% of postmenopausal women. Many women have minimal or no symptoms.
- Menopause which occurs from surgery, radiation or chemo often have more severe symptoms.
- 10% of women stop having their menstrual period by 45–46 yrs of age. 1% enter menopause before age 40. Women live 1/3 to 1/2 of their lives in menopause.
- Late menopause is a risk factor for breast cancer and uterine cancer.

References


Jillian Trizna, DO
David G. Stockwell, MD
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34. The Premenstrual Syndrome & Dysmenorrhea

Comparative features between PMS and Primary Dysmenorrhea

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<th>PMS</th>
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<td>Time of Onset:</td>
<td>10–14 days before menses</td>
<td>1 day before or on 1st day of menses</td>
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<td>Improvement:</td>
<td>Onset of menses</td>
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<td>Childbirth:</td>
<td>Worsens</td>
<td>Improves</td>
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PART I: THE PREMENSTRUAL SYNDROME (PMS)

DEFINITION: A condition characterized by debilitating affective, behavioral, cognitive, and somatic complaints which interferes with normal functioning. Develops in the 7–14 days before menses and subsides with the onset of menstruation.

I. PREVALENCE AND STATISTICS

A. Age of affected women is 25–40
B. Affects about 33% of premenopausal women
C. 40–50% of women presenting to the physician with premenstrual complaints will meet criteria for PMS
D. Premenstrual symptoms affect up to 75% of women and clinically significant PMS occurs in 20–30% of women

II. ETIOLOGY: No specific deficiency or abnormality has been identified. Theories include:
A. Deficiency of progesterone—now mostly disregarded
B. Alterations in ovarian hormone production/derangements in relative amounts of estro-
gen and progesterone—no abnormal hormone levels found
C. Alterations at the hypothalamic or suprahypothalamic level

III. SYMPTOMS AND SIGNS: There are no diagnostic physical signs of PMS
A. Affective: Irritability, emotional lability, anxiety, depression
B. Behavioral: Food cravings, hostility, aggression, altered libido
C. Cognitive: Forgetfulness, poor concentration, confusion
D. Somatic: Bloating, fluid retention, weight gain, headache, mastalgia, fatigue, insomnia

IV. DIAGNOSIS based on the following:
A. Symptom complex consistent with PMS as above
B. Symptoms must occur exclusively in the luteal phase
C. Symptoms must be severe enough to interfere with normal functioning
D. Prospective symptom report over a period of at least 2 or 3 cycles
E. Exclusion of other psychological and physical disorders by detailed history and physical exam

V. MANAGEMENT: No one treatment is effective for everyone with PMS. It is important to educate and reassure the patient, and tailor the treatment to the individual. It may take time to find the best option for each patient
A. Lifestyle changes: Try as initial approach
1. Nutrition
   a. Avoid refined sugar, salt, red meat, alcohol, and caffeine
   b. A good PMS diet consists of 60% complex carbohydrates, 20% protein, 20% fat
   c. Rely more on fish, poultry, whole grains, and legumes for protein, and less on red meats and dairy products
   d. Nutritional supplements may be helpful:
      - Calcium Carbonate—600mg elemental calcium twice daily
      - Vitamin E—400 units/day: May reduce mood symptoms and food cravings
      - Vitamin B6—up to 100mg/day
      - Evening primrose oil may relieve breast tenderness
2. Avoid smoking
3. Aerobic exercise
4. Stress management: Identify stressors first, then look for ways to deal with them
5. Adequate sleep
B. Medications
1. SSRIs: These are effective for relieving tension, irritability, and dysphoria. Fluoxetine (Sarafem), Sertraline (Zoloft) and Paroxetine (Paxil CR) have been approved for the indication of premenstrual dysphoric disorder (PMDD). All SSRIs are probably equally effective
2. Oral contraceptive pills: The simplest method for inducing anovulation. More effective than placebo
4. Danazol: Effective therapy but has adverse side effects
5. Diuretics: Spironolactone has not been consistently shown to be effective
C. Surgery: TAH and BSO is last resort. GnRH agonists should be used first to predict response to oophorectomy

PART II: PRIMARY DYSMENORRHEA
DEFINITION: Primary dysmenorrhea is painful menstruation without detectable pelvic disease. Secondary dysmenorrhea is painful menstruation associated with an anatomic cause (endometriosis, adhesions, fibroids, other anomalies)

I. PREVALENCE: Frequency decreased after age 20. Affects 50–90% of reproductive-aged women
II. ETIOLOGY: Increased endometrial prostaglandin production causing higher uterine tone and decreased blood flow

III. SIGNS AND SYMPTOMS

A. Abdominal cramping: May radiate to the back or inner thighs
   1. Onset usually begins many hours prior to menstruation with most severe cramping occurring on the first day
   2. Cramping may last anywhere from several hours up to 2–3 days
B. Dizziness, headache, flushing
C. Nausea, vomiting, diarrhea
D. Depression

IV. DIAGNOSIS: Exclude pelvic pathology with thorough history and physical exam. Consider cultures and other diagnostic studies as indicated

V. MANAGEMENT

A. Primary dysmenorrhea
   1. NSAIDs are treatment of choice. Begin with onset of bleeding and continue for 2–3 days
   2. Oral contraceptive pills
   3. Exercise, yoga, and sexual activity may also reduce menstrual symptoms
   4. Heat applied to lower abdomen is also effective treatment
B. Secondary dysmenorrhea: Causes often include endometriosis, pelvic inflammatory disease, submucous myoma, IUD use, cervical stenosis. Address underlying cause

CLINICAL PEARLS

- Patients who experience mood swings with PMS can also develop mild to moderate depression, which is known as premenstrual dysphoric disorder (PMDD). Selective serotonin reuptake inhibitors (SSRIs) have been found to be an effective treatment
- Patients who complain of worsening abdominal cramping with each period or who complain of pain not associated with menstruation may have secondary dysmenorrhea (e.g., endometriosis, fibroids)

References

I. NIPPLE DISCHARGE: 3–10% of breast complaints. Under age 60, ~ 7% cancer. Over age 60, ~ 32% cancer (usually intraductal carcinoma)

A. History
1. Duration of symptoms
2. Unilateral or bilateral. Color of discharge (clear, serous, milky, bloody, green). Bilateral milky discharge suggests endocrine etiology; pathologic discharges are usually unilateral and confined to 1 duct
3. Presence of blood (increases chances of malignancy)
4. Medication use (oral contraceptives, phenothiazines, antihypertensives)
5. Lactation/breast-feeding history
6. Spontaneous or with stimulation (spontaneous discharge more common with pathologic discharge)

B. Physical exam: Asymmetry, breast mass, axillary adenopathy, skin changes (peau d’orange), express both nipples for discharge, hemocult the discharge

C. Evaluation
1. If discharge is heme-negative and bilateral, then conservative management with follow-up in 1–2 months. Obtain mammogram if not up to date. Evaluate for endocrine abnormalities if indicated. If the discharge is still present in 1–2 months, then proceed as if it were heme-positive
2. All patients with spontaneous or unilateral nipple discharge should be referred for surgical evaluation regardless if discharge is bloody or clear. If discharge is heme-positive, then consult a surgeon to perform diagnostic mammography followed by possible terminal duct excision
3. Cytology is generally not useful
4. Galactorrhea (milky discharge) is evaluated differently than pathologic or clear discharge. Galactorrhea may be secondary to chest wall trauma, nipple stimulation, or meds. Also may be secondary to hypothyroidism, pituitary adenomas, and amenorrhea syndromes. Surgical referral generally not necessary

II. BREAST PAIN (MASTALGIA)

A. Differential
1. Fibrocystic breast disease
2. Cancer: Cyclical mastalgia (7–17% of patients with cancer reported mastalgia in 1 study)
3. Costochondritis
4. Trauma
5. Mastitis (See Chapter 4, Infant Formula & Breast-Feeding)

B. Physical exam— as above

C. Evaluation
1. If mass is present, see next section
2. If < age 35 and no mass, have patient return for follow up exam in 1–2 months
3. If > age 35 and no mass, then proceed to breast imaging. If negative, have patient follow up in 1–2 months for a recheck

D. Treatment
1. Danazol: Approved by FDA for treatment of breast pain. 100–400mg/day. 75% response rate, but high incidence of side effects
2. Alternatives: Evening primrose oil, caffeine avoidance, Vitamin E may be helpful

III. BREAST MASS

A. History
1. Age of patients  
2. Duration  
3. Change in size  
4. Fluctuation with menstrual cycle  
5. Previous biopsies or masses  

**B. Physical exam**  
1. Cystic or solid  
2. Regular or irregular borders  
3. Movable or fixed  
4. Enlarged lymph nodes  
5. Skin changes; peau d’orange  

**C. Evaluation of solitary breast mass:** Cystic or solid (determine by exam or ultrasound)  
1. If cystic, then proceed to aspiration (22 gauge needle)  
   a. If aspiration is non bloody and mass disappears, follow-up in 4–6 weeks and imaging per American Cancer Society (ACS) guidelines—cytology not necessary  
   b. If aspiration is bloody or mass does not disappear, then breast imaging and referral for biopsy  
2. If solid, then breast imaging and referral for biopsy  

**IV. TESTING**  
A. Needle aspiration  
B. Mammography  
C. Ultrasound  
D. Biopsy  

**V. INDICATIONS FOR OPEN BREAST BIOPSY**  
A. Equivocal cytologic findings on aspiration  
B. Bloody cyst fluid on aspiration  
C. Failure of mass to disappear completely after fluid aspiration  
D. Recurrence of cyst after one or two aspirations  
E. Bloody nipple discharge  
F. Nipple excoriation (Paget’s disease of breast)  
G. Skin edema and erythema suggestive of inflammatory breast carcinoma  

**CLINICAL PEARLS**  
• Mammography is 75–90% sensitive at differentiating between benign and malignant disease. Sensitivity is very dependent on interpreter’s skill  
• The differential diagnosis of a breast mass in a lactating woman includes blocked milk ducts and mastitis. A blocked duct may be relieved by massaging the breast during nursing  

**References**  
I. GENERAL: An estimated 3% of the population 18 to 35 has untreated chlamydia infection and about 5.3% has untreated gonorrhea infection.

II. HISTORY & PHYSICAL

A. History
   1. Discharge: Color, duration of symptoms, new sexual partner
   2. Predisposing factors: Recent use of antibiotics, hx diabetes or HIV, immunosuppressed state, pregnancy, use of corticosteroids
   3. Associated symptoms: Fever, abdominal/pelvic pain, testicular pain

B. Physical exam
   1. Visually inspect for discharge, lesions, skin changes, erythema, warts
   2. Bimanual examination in women—Adnexal or cervical motion tenderness (CMT)
   3. Testicular exam in men—Testicular enlargement, tenderness, masses
   4. Abdominal examination
   5. Rectal exam in men (prostatitis)

III. LABORATORY

A. Gonorrhea and Chlamydia cultures if indicated. If positive, test for syphilis and HIV

B. Appearance
   1. White, cottage cheese, yeast smell: Candida
   2. Green, bubbly, with “strawberry spots” on vaginal walls and cervix: Trichomonas
   3. Grey, low viscosity, adherent to vaginal walls: Bacterial vaginosis

C. Vaginal pH
   1. pH 3.5 to 4.5: Candida
   2. pH > 4.5: Bacterial vaginosis (Gardnerella); pH <4.5, it is unlikely patient has BV
   3. pH > 6: Trichomonas
   4. pH > 7: Atrophic

D. Wet mount (KOH and saline): Apply 2 samples to 2 areas of slide, then place 1 drop of KOH to the first and normal saline to the other. Cover and examine under microscope
   1. Pseudomycelia: Candida (there is a significant false negative rate with wet mounts for Candida. If the wet mount is negative and Candida is suspected, then treat empirically and/or plate specimen on Nickersons agar)
   2. Clue cells, positive “whiff” test: Bacterial vaginosis (Gardnerella)
      a. Clue cells: Epithelial cells appear stippled due to presence of bacteria
      b. “Whiff test”: Bacterial vaginosis infection will give off characteristic fishy odor
         when saturated with KOH. The presence of Lactobacillus or pH < 4.5 excludes the diagnosis of bacterial vaginosis
   3. Motile organisms with flagella: Trichomonas

IV. MANAGEMENT

A. Candida vaginitis: Symptoms: External dysuria and vulvar pruritus, pain, swelling, and redness. Signs: Vulvar edema, fissures, excoriations, or thick curdy vaginal discharge
   1. Oral: Fluconazole (Diflucan): 150mg PO as single dose
   2. Intravaginal
      a. Butoconazole 2% cream: 5g intravaginally × 3 days
      b. Clotrimazole 1% cream: 5g intravaginally × 7–14 days
      c. Clotrimazole: 100mg vaginal tablet, 2 tablets × 3 days
      d. Miconazole 2% cream: 5g intravaginally × 7 days
      e. Miconazole: 100mg vaginal suppository QD × 7 days
      f. Miconazole: 200mg vaginal suppository QD × 3 days
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- **Miconazole**: 1,200mg vaginal suppository once
- **Tioconazole 6.5% ointment**: 5g intravaginally once
- **Terconazole 0.4% cream**: 5g intravaginally × 7 days
- **Terconazole 0.8% cream**: 5g intravaginally × 3 days
- **Terconazole**: 80mg vaginal suppository QD × 3 days

**B. Herpes simplex virus (HSV):** First episode — obtain viral culture to confirm diagnosis. Lesions characterized as grouped vesicles on erythematous base, will eventually ulcerate with crusting.

1. Acute treatment (choose 1)
   - **Acyclovir**: 400mg PO TID × 7–10 days
   - **Acyclovir**: 200mg PO 5 ×/day × 7–10 days
   - **Famciclovir**: 250mg PO TID × 7–10 days
   - **Valacyclovir**: 1g PO BID × 7–10 days

2. Suppressive therapy: Reduces rate of recurrences by 70–80%. Recurrences diminish over time so periodically assess continued need for therapy (choose 1)
   - **Acyclovir**: 400mg PO BID
   - **Famciclovir**: 250mg PO BID
   - **Valacyclovir**: 500mg PO QD
   - **Valacyclovir**: 1g PO QD

**C. Uncomplicated gonococcal infections of the cervix, urethra, and rectum**

1. Recommended regimen
   - **Ceftriaxone**: 250mg in a single intramuscular dose—**plus**—
   - **Azithromycin**: 1g orally in a single dose or **Doxycycline** 100mg orally twice daily for 7 days

2. Alternative regimens
   - If Ceftriaxone is not available:
     - **Cefixime**: 400mg in a single oral dose—**plus**—
     - **Azithromycin**: 1g orally in a single dose or **Doxycycline** 100mg orally twice daily for 7 days—**plus**—
   - Test-of-cure in 1 week

3. If the patient has severe **Ceftriaxone** allergy:
   - **Azithromycin**: 2g in a single oral dose—**plus**—
   - Test-of-cure in 1 week

**D. Bacterial vaginosis (Gardnerella)**

1. Treatment of male partners not useful. Treatment may reduce risk of gonorrhea, Chlamydia, HIV and other viral STDs. No alcohol when taking

2. **Metronidazole**: 500mg PO BID × 7 days

3. Alternative: **Tinidazole**—2g PO × 2 days (do not use if pregnant or breast feeding)

4. Pregnancy: Treatment is recommended for pregnant women in all trimesters (2010 CDC Guidelines)

**E. Trichomoniasis:** Protozoal flagellate which is sexually transmitted. Use **Metronidazole** 2g PO once. **Metronidazole** gel is less efficacious than PO (< 50%). Sex partners should be treated. Pregnancy: Use **Metronidazole** at same 2g one time dose during all trimesters of pregnancy. No alcohol when taking

**F. Epididymitis:** Pain and swelling of the epididymis. Caused by *c. trachomatis* or *N. gonorrheae* in sexually active men < 35

1. For patients with epididymitis likely from gonococcal or chlamydial infection
   - **Ceftriaxone (Rocephin)**: 250mg IM once—**plus**—
   - **Doxycycline**: 100mg PO BID × 10 days

2. For patients with epididymitis likely from enteric organisms (E. Coli) or allergic to above meds
   - **Levofloxacin**: 500mg PO QD × 10 days—**or**—
   - **Ofloxacin**: 300mg PO BID × 10days

**G. Genital warts:** Flat, papular, or pedunculated growths on the genital mucosa. HPV types 16, 18, 31, 33, and 35 are found occasionally in visible genital warts and have been associated with external genital squamous intraepithelial neoplasia (use 1 of therapies listed below)
1. **Podofilox 0.5% solution or gel:** Apply BID × 3 days, no meds for 4 days and may repeat up to 4 cycles
2. **Imiquimod 5% cream:** Once daily at HS TIW for up to 16 weeks. Wash with soap and water 6–10 hours after application
3. **Sinecatechins 15% ointment:** Apply TID 0.5 cm strand of ointment to each wart. Do not use longer than 16 weeks
4. **Cryotherapy:** Liquid nitrogen or cryoprobe—repeat every 1–2 weeks
5. **Podophyllin resin 10%–25%:** Apply weekly and 1) application should be limited to < 0.5 mL of Podophyllin or an area of < 10 cm² of warts per session, and 2) no open lesions or wounds should exist in the area to which treatment is administered
6. **Trichloroacetic Acid (TCA) or Bichloracetic Acid (BCA) 80%–90%:** Weekly application
7. **Surgical removal**
8. **Intralesional interferon**
9. **Laser surgery**

**H. Pelvic inflammatory disease (PID):** See next chapter

**CLINICAL PEARLS**

- Patients with an STD may initially present with a complaint of dysuria
- Genital ulcerations may be caused by syphilis, herpes, chancroid, or lymphogranuloma venereum. Herpes and chancroid are painful, others are not
- Vulvar pruritus is the most common presentation of vulvar dysplasia. If patient has a negative workup for vaginitis then patient should be worked up for vulvar dysplasia by using toluidine blue stain and biopsy or vulvar colposcopy and biopsy
- An early manifestation of HIV may be recurrent vaginal yeast infections

**References**


Centers for Disease Control and Prevention. Update to CDC’s sexually transmitted diseases treatment guidelines, 2006: fluoroquinolones no longer recommended for treatment of gonococcal infections. MMWR 2007;56:332–6. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a3.htm?s_cid=mm6131a3_w
37. Pelvic Inflammatory Disease (PID)

I. GENERAL
   A. One million cases per year in the US
   B. Long term sequelae include infertility, increased risk of ectopic pregnancy, chronic pain

II. RISK FACTORS
   A. Multiple sexual partners
   B. History of STDs
   C. Substance abuse
   D. Frequent vaginal douching
   E. Young age
   F. IUD use

III. HISTORY: Lower abdominal pain, vaginal discharge, vaginal bleeding, dyspareunia, dysuria, fever, nausea/vomiting. Inquire about risk factors listed above

IV. PHYSICAL EXAM: Fever, lower abdominal tenderness (bilateral vs. unilateral), vaginal discharge, cervical motion tenderness, adnexal tenderness

V. CRITERIA FOR DIAGNOSIS OF PID—Note: Initiate treatment in women at risk with any one of the following if an alternate diagnosis cannot be found. The requirement of all 3 to be present results in insufficient sensitivity
   A. Minimum criteria:
      1. Uterine tenderness
      2. Cervical motion tenderness (CMT)
      3. Adnexal tenderness
   B. Supportive – Additional criteria which enhance specificity
      1. Oral temperature >101°F (>38.3°C),
      2. Abnormal cervical or vaginal mucopurulent discharge
      3. Presence of abundant numbers of WBC on saline microscopy of vaginal secretions
      4. Elevated erythrocyte sedimentation rate
      5. Elevated C-reactive protein
      6. Laboratory documentation of cervical infection with*N. gonorrhoeae* or*C. trachomatis*

VI. PATHOGENS: *Chlamydia, N. gonorrhoeae*, Gram negative facultative bacteria (e.g., *E. coli*), anaerobes, *Streptococcus, Mycoplasma, Actinomyces, G. Vaginalis, H. Influenzæ*

VII. INDICATIONS FOR HOSPITALIZATION FOR ACUTE PID
   A. Patient is pregnant
   B. Patient does not respond clinically to oral antimicrobial therapy
   C. Patient is unable to follow or tolerate an outpatient oral regimen
   D. Patient has severe illness, nausea and vomiting, or high fever
   E. Patient has a tubo-ovarian abscess

VIII. MANAGEMENT
   A. Oral Treatment
      1. Recommended regimen
         a. *Ceftriaxone*: 250mg IM in a single dose—plus—
         b. *Doxycycline*: 100mg PO BID × 14 days
            WITH or WITHOUT
         c. *Metronidazole*: 500mg PO BID × 14 days
      2. Alternate regimen
Women's Health 37. Pelvic Inflammatory Disease (PID)

a. **Cefoxitin**: 2g IM in a single dose and **Probenecid**: 1g PO administered concurrently in a single dose—plus—
   b. **Doxycycline**: 100mg PO BID × 14 days
      WITH OR WITHOUT
   c. **Metronidazole**: 500mg PO BID × 14 days

B. Parenteral
   1. Recommended regimen. Note: Oral and IV **Doxycycline** have similar bioavailability and should be given orally if possible
      a. **Cefotetan**: 2g IV Q12 hrs—or—
      b. **Cefoxitin**: 2g IV Q6 hrs—plus—
      c. **Doxycycline**: 100mg BID (PO or IV)
   2. Alternate regimen
      a. **Clindamycin**: 900mg IV Q8 hrs—plus—
      b. **Gentamicin**: Loading dose IV or IM (2mg/kg of body weight), followed by a maintenance dose (1.5mg/kg) Q8 hrs. Single daily dosing may be substituted—plus—**Doxycycline**: 100mg PO to complete 14 day therapy

IX. FOLLOW-UP
A. Within 72hrs: Patients should demonstrate significant clinical improvement within this time. If not, then additional testing or diagnosis needs to be assessed
B. Partner needs to be tested and treated: Test both patient and partner for HIV, syphilis, and counsel on safe sexual practices

CLINICAL PEARLS
- With 1, 2, or 3 incidences of PID, the chance of infertility is 15, 35, and 55%, respectively
- Women with HIV are more likely to have PID from Mycoplasma or streptococcus species as opposed to gonorrhea or Chlamydia
- Risk of ectopic pregnancy is increased 7–10 times after an episode of PID
- Recurrent infection occurs in 20–25% of patients who have had PID
- The major contributing factors in the development of PID with IUDs are the number of sex partners and exposure to sexually transmitted diseases. When PID occurs with a IUD in place, the patient can initially be treated without removing the IUD

References
IV. Preventive Medicine

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Related subject:

HPV vaccine, see PAP Smears: Indications and Interpretation .......... see Chapter 30
38. CANCER STATISTICS, SCREENING & PERIODIC HEALTH EXAMINATIONS

I. GENERAL (all are estimates for 2013)

• TOTAL CANCER DEATHS—1,660,290 new cases of cancer (not including carcinoma in situ) diagnosed in the US with an estimated 580,350 deaths. Cancer is the second leading cause of death in the US, after heart disease. Overall costs of cancer in 2009 (most recent stats) were over $216 billion, including $86.6 billion in direct medical costs plus additional costs of lost productivity of $130 billion.

• Four most common cancers are prostate, lung, breast, and colorectal cancer

• Death rates for cancers are declining

A. PROSTATE CANCER—238,590 new cases of prostate cancer diagnosed with an estimated 29,720 deaths. If discovered at local or regional stage (93% of the time), the 5-year survival rate approaches 100%. The 10-year survival is 98% and 15-year survival is 93%

B. LUNG AND BRONCHUS CANCER—228,190 new cases of lung and bronchus cancer with approximately 159,480 deaths. This is the leading cause of death in American men and women. The 1 year survival increased from 37% in the 1970’s to 44% in 2005–2008. The 5-year survival for all stages is only 16%. Five-year survival for small cell cancer is only 6%

C. BREAST CANCER—232,340 new cases of invasive breast cancer with 40,030 deaths. This is the second leading cause of death in American women. The 5-year survival for invasive breast cancer has improved from 75% in the mid-1970’s to 90% today. The 5-year survival for localized cancer (no lymph node involvement or mets) is 98%

D. COLORECTAL CANCER—For 2013, there will be an estimated 102,480 colon cancer and 40,340 rectal cancer cases with approximately 50,830 total deaths. The 5-year survival rate is 90% with localized disease at diagnosis (39% of colon cancer is localized at diagnosis), 70% with regional spread, and 12% with distant metastasis. Primary initial therapy is surgery.

E. LYMPHOMA—79,030 new cases of lymphoma (non-Hodgkin’s 69,740/Hodgkin 9,290) with 20,200 deaths. Survival for non-Hodgkin’s lymphoma is 81% at 1 year and 68% at 5 years. Hodgkin’s lymphoma has a 1-year survival rate of 92% and 85% at 5 years

F. SKIN CANCER (EXCLUDING SQUAMOUS CELL AND BASAL CELL CANCERS)—76,690 new cases of malignant melanoma with 12,650 deaths. The 5-year survival is 91%. For those with distal stage disease, 5-year survival is 15%

G. BLADDER CANCER—72,570 new cases of bladder cancer with 15,210 deaths. The 5-year survival rate is 96% for invasive, 5-year survival rate is 70%

H. KIDNEY CANCER—65,150 new cases of kidney cancer with 13,680 deaths. One-year and 5-year survival rates are 85% and 71%. If localized when diagnosed (62% of the time), 5-year survival rate is 91%

I. THYROID CANCER—60,220 new cases of thyroid cancer with 15,850 deaths. The 5-year survival is 98%

J. ENDOMETRIAL CANCER—49,560 new cases of uterine cancer with 8,190 deaths. The 5-year survival rate is 95%, 67%, and 16% if the cancer is diagnosed at a local, regional, or distant stage

K. LEUKEMIA—48,610 new cases of leukemia with 23,720 deaths

L. PANCREATIC CANCER—45,220 new cases of pancreatic cancer with 38,460 deaths. The median survival ranges from 4.5 months for advanced disease compared to 24.1 months for the earliest stage

M. ORAL AND PHARYNX CANCER—41,380 new cases of oral cancer with 7,890 deaths. The 5-year survival is 62% for all stages combined with a 10-year survival rate of 51%
N. LIVER CANCER—30,640 new cases of liver cancer (more than 80% are hepatocellular carcinoma) with 21,670 deaths

O. OVARIAN CANCER—For 2013, there will be an estimated 22,240 new cases of ovarian cancer with 14,030 deaths. The 5-year survival is 92% if confined to the ovary (only 15% of new cases), but only 27% if diagnosed with distant metastases

P. CERVICAL CANCER—For 2013, there will be an estimated 12,340 new cases of cervical cancer with 4,030 deaths. The 5 year survival is 91% with localized disease

Q. TESTICULAR CANCER—In 2013, there will be an estimated 7,920 new cases of testicular cancer with 370 deaths

Note: Data compiled from: http://www.cancer.org/acs/groups/content/@epidemiology_surveillance/documents/document/acspe-036845.pdf

II. AMERICAN CANCER SOCIETY GUIDELINES FOR THE EARLY DETECTION OF CANCER (2013)—Note: These guidelines are more conservative than other task force recommendations

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Age</th>
<th>Test/exam</th>
<th>Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>55-74</td>
<td>If in the age group of 55-74 and in fairly good health and have at least a 30 pack-year smoking history AND are still smoking or quit within the last 15 years, consider screening chest CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal2</td>
<td>50</td>
<td>Use one of the following: 1. Flexible sigmoidoscopy – Every 5 years 2. Colonoscopy – every 10 years 3. Double contrast barium enema (DCBE) – every 5 years 4. CO colonoscopy (virtual colonoscopy) 5. Tests that find cancer but not polyps 6. Fecal occult blood test (FOBT) or fecal immunochemical test (FIT) – Annually</td>
<td>Positive tests should be followed up by colonoscopy</td>
<td></td>
</tr>
<tr>
<td>Breast 4</td>
<td>25</td>
<td>Breast self-exam (BSE)</td>
<td>Monthly</td>
<td>No upper age limit for women in good health. Women with positive family history should consider earlier screening.</td>
</tr>
<tr>
<td></td>
<td>20-39</td>
<td>Clinical breast exam (CBE)</td>
<td>Every 3 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>Mammogram and CBE</td>
<td>Annual</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>50</td>
<td>PSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>21</td>
<td>Pap</td>
<td>Perform every 3 years</td>
<td>Women under 21 should not be tested</td>
</tr>
<tr>
<td></td>
<td>30-65</td>
<td>Pap + HPV test (co-testing)</td>
<td>Every 5 years</td>
<td>Women who have certain risk factors such as diethylstilbestrol (DES) exposure before birth, HIV infection, or a weakened immune system due to organ transplant, chemotherapy, or chronic steroid use should continue to be screened annually.</td>
</tr>
<tr>
<td></td>
<td>Over 65</td>
<td>None</td>
<td>If woman has been screened per the previous life schedule, do not screen after 65</td>
<td></td>
</tr>
<tr>
<td>Endometrial</td>
<td>Not recommended for patients at average risk. Ask patients at increased risk (post menopausal) about vag. bleeding or other CA warning signs. Women at high risk should have screening at age 35.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 FOBT should be performed by collecting 2 samples from 3 consecutive at home specimens and not as single test in the office (colonic neoplasms bleed intermittently). Positive results should be followed with colonoscopy.

2 Patients at increased/high risk should have individualized screening (see article):
   - People previously diagnosed as having adenomatous polyps
   - A personal history of curative-intent resection of colorectal cancer
A family history of either colorectal cancer or colorectal adenomas diagnosed in a first-degree relative before age 60
Individuals with inflammatory bowel disease of significant duration
Individuals with 1 of 2 hereditary syndromes that place them at very high risk for colorectal cancer
Women at high risk include those known to carry HNPCC-associated genetic mutations, women who have a substantial likelihood of being a mutation carrier (i.e., a mutation is known to be present in the family), and women without genetic testing results, but who are from families with suspected autosomal dominant predisposition to colon cancer
Women with higher risk due to family history, genetic tendency, or other factors should be screened with MRI in addition to mammograms (less than 2% of women in the US)
If positive, perform colonoscopy


### III. PERIODIC HEALTH EXAMINATIONS AND PREVENTIVE CARE

<table>
<thead>
<tr>
<th>Preventive Service</th>
<th>USPSTF¹</th>
<th>CTF²</th>
<th>Other Organizations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening Tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Recommended for all adults; interval not stated</td>
<td>Fair evidence for inclusion in routine care</td>
<td>Joint National Committee VIII: Recommended for all adults at each clinical encounter</td>
</tr>
<tr>
<td>Serum lipids</td>
<td>Recommended for all middle-aged and older adults and for young adults with multiple risk factors</td>
<td>Insufficient evidence for or against inclusion</td>
<td>National Cholesterol Education Panel Adult Treatment Panel III: Recommended for all adults age 21 and older</td>
</tr>
<tr>
<td>Depression</td>
<td>Recommended (B recommendation)³</td>
<td>Fair evidence for exclusion from routine care</td>
<td></td>
</tr>
<tr>
<td><strong>Counseling</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy Diet</td>
<td>Recommended for patients with increased risk; insufficient evidence for or against in average-risk patients</td>
<td>Fair evidence for inclusion</td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>Recommended</td>
<td>Fair evidence for inclusion</td>
<td></td>
</tr>
<tr>
<td><strong>Immunizations and Chemoprevention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin chemoprevention</td>
<td>Recommended for adults at increased risk for coronary heart disease (CHD)</td>
<td>Insufficient evidence for or against use</td>
<td>American Heart Association: Recommended for adults at increased risk for CHD</td>
</tr>
<tr>
<td>Influenza vaccination</td>
<td>Recommended for all adults 65 and older and for selected high-risk groups</td>
<td>Not addressed</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal vaccination</td>
<td>Recommended for immunocompetent adults older than age 65 or for adults younger than age 65 at increased risk</td>
<td>Insufficient evidence for or against in immunocompetentfree-living adults older than age 55</td>
<td></td>
</tr>
</tbody>
</table>

¹United States Preventive Services Task Force; recommendations available at: http://www.ahrq.gov
²Canadian Task Force on Preventive Health Care; recommendations available at: http://www.ctfphc.org
³The USPSTF recommends that clinicians routinely provide the service to eligible patients. (The USPSTF found at least fair evidence that the service improves important health outcomes and concludes that benefits outweigh harms)

Reference
39. Smoking Cessation

Rob Crane, MD

I. RELEVANCE
A. Cigarette smoking is a leading cause of death in the world today accounting for one fifth of all deaths in the United States. Smoking is estimated to cause over 400,000 annual deaths in smokers themselves and an additional 50,000 deaths in non-smokers exposed to secondhand smoke. There are 44 million Americans actively addicted to smoked nicotine and over 50 million ex-smokers. Approximately 3,000 children and adolescents become regular users of tobacco every day
B. There is a link between cigarette smoking and atherosclerotic vascular disease, COPD, gastritis, skin and connective tissue diseases, impotence, depression, substance abuse and 15 distinct cancers. 50% of continuing smokers will die from related disease losing 10 years from their expected lifespan. 10% of women smoke during their pregnancy resulting in substantial increases in rates of miscarriage, prematurity, stillbirth, infants small for gestational age, poor fetal lung development and behavioral abnormalities
C. Smoking cessation benefits all age groups and extends to those individuals already afflicted with smoking related diagnoses
D. Success in treating nicotine addiction is most likely when a physician actively identifies a smoker, encourages cessation, makes a referral to a cessation expert, and prescribes adjunctive pharmacologic therapy

II. PHARMACOLOGIC INTERVENTIONS
The FDA has approved 2 non-nicotine, prescription drugs and 5 nicotine replacement therapies (NRTs), 3 of which are OTC. Two other drugs are considered second-line. Each has been found to be effective when used alone, but there is enhanced benefit when used in combination with expert counseling

A. First-line agents: Non-nicotine
1. Bupropion Hydrochloride (Zyban), sustained release
   a. Atypical antidepressant that has both dopaminergic and adrenergic actions
   b. Begin treatment 1 week prior to anticipated stop date
   c. Dosage: 150mg PO QD for 3 days then 150mg SR BID or 300mg XL daily
   d. Duration: 7–12 weeks. Maintenance up to 6 months
   e. May be combined with NRT to enhance efficacy in heavily addicted patients
   f. Adverse effects: Insomnia, dry mouth, and lowers seizure threshold
   g. Precautions/Contraindications: History of seizure disorder, anorexia, head trauma or excessive alcohol use. Both Bupropion and Varenicline have a black box warning about neuropsychiatric adverse effects (see below). Pregnancy category C

2. Varenicline (Chantix)
   a. Partial agonist/antagonist of α4β2 nicotinic-cholinergic receptors
   b. Begin treatment 1 week prior to anticipated stop date
   c. Dosage: 0.5mg PO QD × 3 days, 0.5mg BID × 4 days, then 1mg BID. (Prescribe Chantix “Starter Month Box” followed by “Continuing Month Box”)
   d. Duration: 12–24 weeks; efficacy improved with longer duration
   e. Cannot combine with nicotine replacement therapy due to increased adverse reactions (nausea and vomiting)
   f. Adverse reactions: 30% of patients experience nausea. Also common: insomnia, headache, abnormal dreams
   g. Precautions/Contraindications: Black box warning summary: Neuropsychiatric effects. A small percentage of users may experience increases in agitation, hostility, depression and suicidality. Warnings should be issued to all patients and caution should be used in prescribing for those with predisposing mental illness. Pregnancy category: C
   h. Cardiovascular events: A meta-analysis of 15 trials showed that varenicline may be associated with a small increase in the risk of CV events, including MI. FDA
B. First line agents: Nicotine replacement therapy (NRT)

1. Nicotine gum (Nicorette, Nicorette DS, various generics), OTC
   a. Single (2mg) and double strength (4mg) dosages
   b. Use single strength dose for those who smoke < 25 cigarettes/day. Use double strength dose for those who smoke > 25 cigarettes/day
   c. Dosage: 1 piece Q 1–2 hrs, then repeat PRN. Daily maximum is 30 pieces of the single strength and 24 pieces of the double strength
   d. Duration: Minimum 8 pieces QD for 3–6 weeks, then taper for 6 weeks. Maintenance: probably safe for 5 years
   e. Adverse effects: Dyspepsia and mouth soreness
   f. Precautions/Contraindications: None. Pregnancy category: C

2. Nicotine lozenge (Commit), OTC
   a. Similar to gum: 2mg and 4mg doses
   b. Use 2mg dose for those who smoke first cigarette > 30 minutes after awakening and 4mg dose for those who smoke earlier after awakening
   c. Dosage: Dissolve 1 piece in mouth Q 1–2 hrs then repeat PRN 8–24 pieces/day
   d. Duration: 6–24 weeks. Likely similar to nicotine gum for longer duration
   e. Adverse effects: Headache, cough, sore throat, heartburn, nausea
   f. Precautions/Contraindications: None. Pregnancy category: D

3. Nicotine inhaler (Nicotrol)
   a. Inhaler is a white plastic tube with a tapered mouthpiece and a screw-in nicotine ampule that provides a nicotine vapor when puffed. It seems similar to a cigarette and acts as a substitute for some of the behavior features of smoking
   b. Delivers nicotine buccally
   c. Dosage: 6–16 cartridges/day
   d. Duration: 12 weeks. Maintenance up to 6 months
   e. Adverse effects: Local irritation of mouth and throat
   f. Precautions/Contraindications: None. Pregnancy category: D

4. Nicotine nasal spray (Nicotrol NS)
   a. Delivers nicotine more rapidly than gum, inhaler or patch, but less than cigarettes
   b. Peak levels occur within 10 minutes
   c. Dosage: 1–2 sprays each nostril Q 1 hr. Minimum dose: 8/day. Maximum dose: 40/day
   d. Duration: 3–6 months. Maintenance unknown
   e. Adverse effects: Nasal irritation, throat irritation, rhinitis, sneezing, coughing, and watering eyes. Tolerance occurs in the first week
   f. Precautions/Contraindications: None. Pregnancy category: D

   Note: OTC patches are also effective and their use should be encouraged
   a. Apply patch daily to a different site. Wear for 16 hrs/day
   b. Ensure smoking cessation to avoid nicotine toxicity
   c. Dosage: Nicoderm CQ 21mg patch QD × 6 weeks, then 14mg patch QD × 2 weeks, and then 7mg patch QD × 2 weeks
   d. Duration: 8 weeks. Maintenance unknown
   e. Adverse effects: Local skin reaction and insomnia
   f. Precautions/Contraindications: None. Pregnancy category: D

C. Second line agents

1. Clonidine
   a. Dosage: 0.15–0.75mg/day
   b. Duration: 3–10 weeks
   c. Adverse effects: Dry mouth, sedation, drowsiness, and dizziness
   d. Precautions/Contraindications: Rebound hypertension. Pregnancy category: C

2. Nortriptyline
   a. Dosage: 75–100mg/day
   b. Duration: 12 weeks
c. Adverse effects: Dry mouth and sedation
d. Precautions/Contraindications: Risk of arrhythmias. Pregnancy category: D

III. BEHAVIORAL MODIFICATION
Should be used in conjunction with appropriate pharmacotherapies. Modifications should be individualized. As in narcotic or cocaine addiction, refer patient for comprehensive counseling. There are several primary care strategies that may be effective. One example of a simple 4-step plan is: Advise, Assist, Refer, Prescribe (AARP)

A. Advise to quit
1. Recognize that most patients want to quit (>70%) but may feel discouraged
2. Brief intervention by a physician has clear effect
3. Motivational interviewing associated with new findings. Some examples:
   a. “Examining your lungs today makes me worry about early emphysema. I truly think the time has come to quit smoking. What do you think?”
   b. “Smoking is strongly linked with depression and anxiety. Have you noticed that your mood is sometimes unpredictable?”
   c. “Smoking reduces sexual functioning even in younger people, you may want to quit while you still can.”

B. Assist the patient with a quit plan
1. Set a firm quit date. Ideally the date should be within 2–4 weeks
2. Total abstinence is essential. Complete abstinence during the first week increases success rates 10 fold
3. Tell family and friends about quitting. Ask for accountability, support and understanding
4. Remove tobacco products from the environment and encourage a smokefree home
5. Limit or abstain from alcohol since use is highly associated with nicotine relapse

C. Refer for expert counseling
1. Most states have a free expertly-staffed “Quitline”—usually 800-QUIT-NOW
2. Many communities have local “in-person” counseling services through the Cancer Society, Heart or Lung Association or local hospital

D. Prescribe: Adjunctive medications double to quadruple success rates (see above)—Follow up 2 weeks after beginning medications and then monthly × 2

IV. NEW PRODUCTS
The electronic or e-cigarette has emerged as a proposed adjunct to smoking cessation. Typically this is a cigarette shaped tube containing a battery, a heating element and a humectant (glycerol, etc) mixed with nicotine. The liquid is vaporized by the heating element and inhaled. The products are unregulated and produce variable amounts of nicotine and/or small amounts of other toxins. Advocates and promoters cite widespread anecdotal and small study evidence that e-cigarettes reduce cigarette smoking and aid in cessation, but no large-scale controlled studies of safety or efficacy have been published. Critics offer concerns about e-cigarettes as a gateway by young users to cigarette smoking and lack of standards for safety and promotion. There does seem little doubt that compared to regular smoking, use of e-cigarettes does reduce health risk

CLINICAL PEARLS
• Most patients will attempt smoking cessation several times before they are successful
• Most patients initially attempt smoking cessation on their own without any intervention
• Only about 3–5% of smokers achieve long-term success when trying to quit on their own. Success rates increase to 15–30% by using appropriate therapies
• Even brief physician interactions of 3 minutes or less results in about a 10% quit rate. Physician’s advice to quit smoking is an important motivator cited by many smokers
• For every 4–5 patients that physicians encourage to quit smoking, 1 premature death will be prevented
• Nearly 43% of children ages 2 months to 11 years live in homes with at least 1 smoker. Evidence suggests that smoke exposure during childhood is associated with increased illnesses, including upper and lower respiratory diseases, middle ear infections with effusion, asthma, and sudden infant death syndrome
40. **Endocarditis Prophylaxis**

The following recommendations are based on 2007 guidelines from the American Heart Association available online at: [www.circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.183095](http://www.circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.183095)—please note that there are some major changes from previous guidelines as prophylaxis is no longer recommended for most common dental procedures or for patients undergoing a genitourinary or gastrointestinal tract procedure. It is no longer recommended for patients with mitral valve prolapse (MVP).

I. FIRST, WHICH PATIENTS SHOULD RECEIVE PROPHYLAXIS FOR ENDOCARDITIS:

A. Prophylaxis against infective endocarditis is **recommended** for patients with cardiac conditions associated with the highest risk for adverse outcome from endocarditis:
   1. Prosthetic cardiac valve
   2. Previous infective endocarditis (IE)
   3. Cardiac transplantation recipients who develop cardiac valvulopathy
   4. Congenital heart disease (CHD)*
      a. Unrepaired cyanotic CHD, including palliative shunts and conduits
      b. Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†
      c. Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
   
   *Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD
   
   †Prophylaxis is recommended because of endothelialization of prosthetic material

B. Prophylaxis against infective endocarditis is **not recommended** for patients with the following conditions:
   1. Mitral valve prolapse, rheumatic heart disease, bicuspid valve disease, calcified aortic stenosis
   2. Congenital heart conditions such as ventricular septal defect, atrial septal defect, and hypertrophic cardiomyopathy
   3. Isolated secundum atrial septal defect
   4. Patients with physiological, functional, or innocent heart murmurs, including patients with aortic valve sclerosis as defined by focal areas of increased echogenicity and thickening of the leaflets without restriction of motion and a peak velocity less than 2.0 m per second

**References**


Crane RS. The most addictive drug, the most deadly substance: smoking cessation tactics for the busy clinician. Prim Care 2007;34(1):117–35.


Surgeon general reports on smoking. Available at: [http://www.surgeongeneral.gov/tobacco](http://www.surgeongeneral.gov/tobacco)
5. Patients with echocardiographic evidence of physiologic MR in the absence of a murmur and with structurally normal valves
6. Patients with echocardiographic evidence of physiological tricuspid regurgitation (TR) and/or pulmonary regurgitation in the absence of a murmur and with structurally normal valves
7. Patients 6 or more months after successful surgical or percutaneous repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus

II. NEXT, IF PROPHYLAXIS IS RECOMMENDED, WHICH PROCEDURES REQUIRE PROPHYLAXIS:

A. Procedures for which endocarditis prophylaxis is recommended
   1. All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa
      Note: The following procedures and events do not need prophylaxis: routine anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lips or oral mucosa
   2. Respiratory tract procedures involving incision or biopsy of the respiratory mucosa (e.g., tonsillectomy). Note: Studies have not demonstrated a conclusive link and prophylaxis should be considered (class IIb recommendations)

B. Specific procedures for which endocarditis prophylaxis is not recommended
   1. Bronchoscopy
   2. Genitourinary procedures
   3. Gastrointestinal tract procedure (including EGD and colonoscopy)
   4. Ear and body piercing, tattooing
   5. Vaginal delivery and hysterectomy

III. CHOICE OF ANTIBIOTICS—REGIMENS FOR A DENTAL PROCEDURE

<table>
<thead>
<tr>
<th>Regimens for a Dental Procedure</th>
<th>Situation</th>
<th>Agent</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral</td>
<td>Amoxicillin</td>
<td>2 g</td>
<td>50 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Unable to take oral medication</td>
<td>Ampicillin OR Cefazolin or ceftriaxone</td>
<td>2 g IM or IV</td>
<td>50 mg/kg IM or IV</td>
</tr>
<tr>
<td></td>
<td>Allergic to penicillins or ampicillin—oral</td>
<td>Cephalaxin*† OR Clindamycin OR Azithromycin or clarithromycin</td>
<td>2 g</td>
<td>50 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Allergic to penicillins or ampicillin and unable to take oral medication</td>
<td>Cefazolin or ceftriaxone OR Clindamycin</td>
<td>1 g IM or IV</td>
<td>50 mg/kg IM or IV</td>
</tr>
</tbody>
</table>

IM indicates intramuscular; IV, intravenous.
*Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.


Reference
41. TUBERCULOSIS SCREENING

I. TRANSMISSION
   A. TB is spread primarily through respiratory droplets. Respiratory droplets may remain airborne within a room for hours after a cough or sneeze. In 6–12 weeks most people infected with TB develop cell-mediated immunity which halts the spread of infection. The PPD (purified protein derivative of TB) test becomes positive by 12 weeks. Approximately 10% of those infected with TB will develop active TB infection at some time in their life.

II. HIGH RISK POPULATIONS
   A. Contacts of people with infectious TB
   B. IV drug users
   C. Medical Risk Factors/Immunosuppressed: HIV/AIDS, DM, chronic steroid use, immunosuppressive therapies, CRF or hemodialysis, malignancy, silicosis, weight > 10% below ideal body weight, gastrectomy, jejunoileal bypass, CXR with fibrotic lesions consistent with old TB, silicosis, solid organ transplant, head and neck cancer
   D. Residents and employees of high risk congregate settings: Prisons, nursing homes, health care facilities, homeless shelters, residential settings for HIV+ persons
   E. Immigrants from high prevalence countries (most countries in Africa, Asia, Latin America)
   F. Recent TST converters (that is, persons with baseline testing results who have an increase of 10mm or more in the size of the TST reaction within a 2-year period)
   G. Infants and children under the age of 5 who have a positive TB test result

III. SCREENING
   A. All high risk individuals should be screened annually
   B. All pregnant women at high risk should be screened
   C. Exceptions to routine screening include:
      1. Documented skin test positive in past
      2. Prior course of treatment for positive skin test

IV. TUBERCULIN SKIN TEST (TST)
   A. PPD (Mantoux)
      1. Mantoux TB skin test is the standard test
      2. 0.1mL PPD is injected intradermal into the inner forearm. When placed correctly, the injection should produce a wheal of 6–10mm in diameter
      3. The skin test reaction should be read between 48–72 hours after administration
      4. The reaction should be measured and recorded in mm of the induration. The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis). Recording the “positive” or “negative” is not sufficient
   B. Negative skin test: Does not exclude TB infection. A reaction may not occur in patients who are immunocompromised, severe febrile illness, virus vaccinations (MMR, OPV), malnutrition, old age, overwhelming TB infections and HIV disease
   C. Two-step TST (Booster phenomenon)
      1. Explanation: Repeated testing of uninfected individuals does not sensitize them to tuberculin. However, delayed sensitivity to tuberculin (a positive test) may wane over time. Certain individuals who were exposed to TB early in their life may have no reaction many years later (false negative). In these individuals, it is necessary to do 2 tests, 1 week apart. If the second test (performed 1–2 weeks later) is positive, this represents a booster phenomenon (remote infection) and not a recent conversion
      2. Indications: Indicated for the initial screening of residents and employees of long-
term care facilities and others who will be receiving yearly skin testing. It is done to avoid misinterpreting a boosted reaction as a recent infection.

V. CRITERIA FOR A POSITIVE TB SKIN TEST

A. An induration of ≥5mm is considered positive in:
1. HIV-infected persons
2. A recent contact of a person with TB disease
3. Persons with fibrotic changes on chest x-ray consistent with prior TB
4. Patients with organ transplants
5. Persons who are immunosuppressed such as taking >15mg/day of Prednisone ≥1 months, taking TNF-α antagonists

B. An induration of ≥10 mm is considered positive in:
1. Recent immigrants (<5 yrs) from high-prevalence countries
2. Injection drug users
3. Residents and employee of high-risk congregate setting
4. Mycobacteriology lab personnel
5. Persons with clinical conditions that place them at high risk
6. Children <4 yr of age or children and adolescents exposed to adults in high-risk categories

C. An induration of ≥15 mm is considered positive in any person, including persons with no known risk factors for TB

VI. PRIOR BCG VACCINATION

A. History of BCG (Bacille bilié de Calmette-Guérin) vaccination does not alter guidelines for interpreting skin test results

B. Effectiveness of BCG varies from 0–76% in major trials

VII. TB BLOOD TEST

A. Interferon-gamma release assay (IGRA)
1. IGRA detects sensitization to M. tuberculosis by measuring IFN-gamma release in response to antigens representing M tuberculosis. Results can be available within 24 hours
2. 2 IGRA approved by the FDA: QuantiFERON-TB Gold In-Tube test (QFT-GIT) and T-SPOT.TB test (T-Spot)

B. Positive IGRA: the person has been infected with TB. Additional tests are needed to determine if the person has latent TB infection or TB disease

C. Negative IGRA: Latent TB infection or TB disease is not likely

D. IGRA are preferred method of TB infection testing for:
1. People who have received BCG (as a vaccine or for cancer therapy).
2. People who have a difficult time returning for a second visit to have TSTs read

E. Limitation of IGRA:
1. Blood sample must be processed within 8–30 hrs after collection
2. Limited data exist on use in groups such as children <5 yrs of age, persons recently exposed to TB, immunocompromised persons, and those who will be tested repeatedly

VIII. TREATMENT OF LATENT TB INFECTION (LTBI)—PER CDC RECOMMENDATIONS

A. Careful evaluation for active disease must precede initiation of treatment for LTBI. Individuals with LTBI would have a positive TST or IGRA result, normal chest x-ray, and no symptoms or physical findings suggestive of TB disease

B. Decisions to treat latent infection should take into account the individual patient’s risk for the development of active tuberculosis and the risk of therapy

C. There are several treatment regimens available. Selection of appropriate regimen is based on drug-susceptibility results of the presumed source case if known, co-existing medical illness, and potential for drug-drug interactions

D. Directly observed therapy (DOT) for LTBI should be considered for persons who are at especially high risk for TB disease and are suspected of nonadherence or are given an intermittent dosing regimen

E. Isoniazid (INH) regimens: 2 treatment options, 6 mo or 9 mo regimen
Preventive Medicine

41. Tuberculosis Screening

1. The 9-month regimen is preferred because it is more efficacious
2. The 6-month regimen is more cost-effective and results in greater adherence by the patient
3. Every effort should be made to ensure the patients adhere to LTBI treatment for at least 6 mo
4. The preferred regimen for children aged 2–11 yr is 9 months of daily INH
5. INH dose: 10 mg/kg/day, up to 300mg/day

F. Isoniazid and Rifapentine (RPT) regimen
1. This is a directly observed therapy by a health care worker, 12 doses, once-weekly regimen of INH and RPT
2. This regimen is recommended as an option to the standard INH 9-month regimen for otherwise healthy people, ≥12 years of age, who were recently in contact with infectious TB, or who had TST or IGRA for TB infection conversions, or those with chest x-ray findings consistent with healed pulmonary TB.
3. This 12-dose regimen is NOT recommended for children <2 yr of age, people with HIV taking ART, people presumed to be infected with INH or Rifampin-resistant M. tuberculosis, pregnant women or women expecting to become pregnant while taking this regimen

G. Rifampin (RIF) regimen
1. This is a 4-month regimen considered for persons who cannot tolerate INH or who have been exposed to INH-resistant TB
2. This is not indicated for HIV-infected persons taking ART

### LTBI Treatment Regimens

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration</th>
<th>Dose</th>
<th>Frequency</th>
<th>Min. Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>9 mo</td>
<td>Adult: 5 mg/kg</td>
<td>Once daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children: 10-20 mg/kg *</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max dose: 300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid (INH)</td>
<td>9 mo</td>
<td>Adult: 15 mg/kg</td>
<td>Twice weekly</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children: 20-40 mg/kg*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max dose: 900 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid (INH)</td>
<td>6 mo</td>
<td>Adult: 5 mg/kg</td>
<td>Once daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children: Not recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max dose: 300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid (INH)</td>
<td>6 mo</td>
<td>Adult: 5 mg/kg</td>
<td>Twice weekly</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children: Not recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max dose: 900 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid (INH) and Rifampine (RPT)</td>
<td>3 mo</td>
<td>Adults and children ≥12 yo:</td>
<td>Once weekly</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INH: 15 mg/kg, rounded up to nearest 50 or 100 mg; max 900 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RPT: 10-14 kg: 300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.1-25 kg: 450 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>25.1-32 kg: 600 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>32.1-49.9 kg: 750 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥50 kg: 900 mg max</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td>4 mo</td>
<td>Adult: 10 mg/kg#</td>
<td>Daily</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max 600 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The American Academy of Pediatrics (AAP) recommends an INH dosage of 10-15 mg/kg for daily regimen and 20-30 mg/kg for the twice weekly regimen.

^Use Directly Observed Therapy (DOT)

In the US, the recommended regimen for treatment of LTBI in children is a 9-month course of INH. For children who cannot tolerate INH or have had contact with a case patient infected with an INH-resistant but Rifamycin-susceptible organism, the AAP recommends 6 months of daily Rifampin (180 doses) at the dosage of 10-20 mg/kg.

Adapted from CDC and New Jersey Medical School Global Tuberculosis Institute, Latent tuberculosis infection: a guide for primary health care providers. Table 2. http://www.cdc.gov/tb/publications/ltbi/pdf/TargetedLTBI.pdf
IX. ADVERSE EFFECTS OF INH

A. LFT elevation
1. Occurs in 10%–20% of patients taking INH
2. Withheld INH if LFT level >3× the upper limit of normal if associated with symptoms or 5× the upper limit of normal if patient is asymptomatic

B. Hepatitis
1. Occurs in about 0.1% of people taking INH; more common when INH is combined with other hepatotoxic drugs
2. Other risk factors include daily alcohol consumption, underlying liver disease or risks for liver disease, and concurrent use of other medications which are metabolized in the liver

C. Peripheral neuropathy
1. Occurs in <0.2% of people taking INH at conventional doses
2. More common in people with conditions associated with neuropathy such as diabetes, HIV, renal failure, and alcoholism
3. Pyridoxine (Vitamin B<sub>6</sub>) 10–25 mg/day supplementation is recommended in conditions associated with neuropathy, or to prevent neuropathy in pregnant or breastfeeding women

X. ADVERSE EFFECTS OF RIFAMPIN (RIF) AND RIFAPENTINE (RPT)

A. Hepatotoxicity occurs in 0.6% of patients taking RIF. It is more likely when RIF is combined with INH
B. Cutaneous reactions, such as pruritis, can occur in 6% of patients taking RIF—generally self-limited and may not be a true hypersensitivity reaction; continued treatment may be possible
C. Rifamycins (Rifampin, Rifapentine) are rarely associated with hypersensitivity reactions (hypotension, nephritis, or thrombocytopenia)
D. GI symptoms include nausea, anorexia, and abdominal pain
E. Orange discoloration of body fluids is expected and harmless. Advise patients beforehand. Soft contact lenses and dentures may be permanently stained
F. RIF and RPT interact with a number of drugs such as methadone, warfarin, hormonal contraceptives, and phenytoin
G. RIF should not be used in HIV patients taking certain antiretroviral drugs. Rifabutin may substitute RIF in the 4-month regimen. RPT should not be used in HIV patients taking ARTs

XI. SPECIAL CONSIDERATIONS IN THE TREATMENT OF LTBI

A. Those with recent exposure to a person with known or suspected infectious TB should be evaluated immediately for LTBI and TB disease
1. If the TST or IGRA result is positive, treat with a regimen according to drug susceptibility
2. Those who have negative TST or IGRA results should be retested in 8–10 weeks after exposure has ended. However, if the chest x-ray is normal, LTBI treatment should be initiated in TST-negative children ≥5yr of age and in immunocompromised persons of all ages who have negative TST or IGRA results. Treatment should be continued until the results of the second test and other medical evaluation are known. For some high-risk contacts, a full course of LTBI treatment may be recommended. Consult the local TB control program for the management of such contacts
B. HIV-infected persons receiving ART should receive 9-month regimen of INH.
C. Pregnancy
1. Consider immediate treatment for LTBI if the woman is HIV infected or a recent contact, and monitor
2. In the absence of risk factors, wait until after the woman has delivered to avoid administering unnecessary medication during pregnancy
3. INH daily or twice weekly (using DOT) is the preferred regimen
4. Supplement with Pyridoxine (Vitamin B<sub>6</sub>) 10–25mg/d
5. The 12-dose regimen is not recommended
6. There is potential for an increased hepatotoxicity during pregnancy and the first 2–3 months of the post-partum period. Consider delaying treatment until 2–3 months
post-partum unless there is a risk of progression to TB disease
D. Breastfeeding is not contraindicated in women taking INH. **Pyridoxine (Vitamin B6)** 10–25mg/d is recommended for nursing mothers and for breastfed infants
E. Infants and children <5yr of age with LTBI have been recently infected and, therefore at high risk for progression to disease
1. Test adults in close social contact with the child to find the person with infectious TB disease
2. The preferred regimen for children (age 2–11yr) is 9 months of daily INH. The risk of INH-related hepatitis in this population is minimal. Routine LFT monitoring is not necessary unless the child has risk factors for hepatotoxicity
F. Persons with old fibrotic lesions with TST result of ≥5mm of induration or a positive IGRA result and negative culture should be treated with LTBI

**References**

Updated guidelines for using interferon gamma release assays to detect mycobacterium tuberculosis infection—United States 2010. MMWR 59(RR05):1–25.
Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm

Available at http://www.cdc.gov/tb/publications/ltbi/pdf/TargetedLTBI.pdf


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42. EVALUATION OF CHEST PAIN

I. INTRODUCTION
A. One of the most common complaints evaluated in ER, on wards, and in office setting
B. Tables and charts listed below will help to stratify patients into high or low risk groups, and then the decision on how to further evaluate these patients can be made according to the pre-test likelihood of cardiac or other etiology. See Chapter 46, Coronary Artery Disease and Chapter 50 Cardiac Stress Testing for more specific information on evaluation

II. DIFFERENTIAL DIAGNOSIS OF CHEST PAIN
A. Cardiovascular: Ischemic, valvular disease, hypertrophic cardiomyopathy, aortic dissection, hypertensive crisis, pulmonary hypertension
B. Pulmonary: Pulmonary embolus (PE), pneumothorax/tension pneumothorax, pneumonia, asthma, pleurisy
C. Gastrointestinal:
1. Esophageal: Esophageal rupture (Boerhaave’s syndrome), esophageal reflux or spasm, esophageal foreign body, esophagitis (chronic reflux, Barrett’s esophagus, candida, etc.)
2. Peptic ulcer disease/gastritis
3. Mallory-Weiss tear
4. Pancreatitis
5. Cholecystitis/symptomatic cholelithiasis
6. Hepatitis
D. Musculoskeletal: Costochondritis/musculoskeletal chest wall strain, thoracic outlet syndrome, cervical disk disease
E. Psychogenic: Anxiety/panic disorder, depression
F. Other: Herpes zoster, breast disease, post-nasal drip

III. HISTORY: See tables listed below
A. Character/radiation of discomfort (Ask about “chest discomfort” instead of “chest pain”)
1. Dull pressure, squeezing, burning: Consider CAD or esophageal pain (GERD)
2. Radiation of pain to neck/shoulder/jaw: Consider CAD
3. Radiation of pain to the back: Consider aortic dissection, pancreatitis, or perforated peptic ulcer
4. Radiation to the epigastrium: Consider GI etiology, pancreatitis, inferior wall MI, AAA
5. Sharp, stabbing pain: Consider muscular chest wall pain/costochondritis, pleurisy, pericardial pain, or PE
B. Onset
1. Sudden onset: Consider PE, pneumothorax, or aortic dissection
2. Slow onset (building over 2–5 minutes): Consider CAD

C. Activity at onset: Exertion, lifting/moving the body, arguing, eating, coughing

D. Exacerbation/Relief
1. Exacerbated by exercise or stress and relieved by rest: Consider CAD
2. Relieved by Nitroglycerin: Consider CAD or esophageal spasm
3. Exacerbated by movement of body (positional) or deep inspiration: Consider musculoskeletal, pericardial, pleuritic disease, or PE
4. Worse when supine and better with upright position: Consider pericarditis

E. Other symptoms associated with CAD: See tables below
1. Dyspnea
2. Diaphoresis
3. Palpitations
4. Light-headedness
5. Nausea/vomiting
6. Radiation to neck, arm, or jaw
7. Syncope
8. CHF-related symptoms: Orthopnea, paroxysmal nocturnal dyspnea (PND), peripheral/dependent edema

F. Past medical history
1. Determine risk factors for CAD: Known coronary artery disease or vascular disease, family history, smoking, diabetes, hypertension, dyslipidemia, male > 45, female > 55, obesity, sedentary lifestyle
2. Complete past history including childhood illnesses (rheumatic fever)
3. Obtain results of stress tests, cardiac catheterizations, ECHOs, PTCA/STENT, and CABG
4. Current meds including nitrates, anti-hypertensives, β-blockers, and aspirin

IV. PHYSICAL EXAM
A. Vital Signs: Check heart rate and BP, consider BP in both arms and legs (to evaluate for coarctation, dissection, AAA)
B. Neck: Assess for midline trachea, JVD, carotid bruits
C. Lungs: Listen for bilateral and equal breath sounds, rales, wheezes
D. Chest: Palpate for subcutaneous air or tenderness
E. Heart
1. Inspect (for presence of surgical scars)
2. Palpate for parasternal lift, increased LV impulse, point of maximal impulse
3. Auscultate for friction rub, gallops, murmurs, clicks (MVP), distant heart sounds
F. Abdomen: Pulsatile abdominal mass, bruits
G. Extremities: Assess for unilateral leg swelling (DVT), cyanosis, clubbing, or edema; palpate femoral pulses (dissection)

### Clinical Features That Increase the Probability of a Myocardial Infarction in Patients Presenting with Acute Chest Pain

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Likelihood Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain in chest or left arm</td>
<td>2.7*</td>
</tr>
<tr>
<td>Chest pain radiation</td>
<td></td>
</tr>
<tr>
<td>Right shoulder</td>
<td>2.9 (1.4 - 6.0)</td>
</tr>
<tr>
<td>Left arm</td>
<td>2.3 (1.7 - 3.1)</td>
</tr>
<tr>
<td>Both left and right arm</td>
<td>7.1 (3.6 - 14.2)</td>
</tr>
<tr>
<td>Chest pain most important symptom</td>
<td>2.0*</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>1.9 (1.7 - 2.3)</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>2.0 (1.9 - 2.2)</td>
</tr>
<tr>
<td>Third heart sound on auscultation</td>
<td>3.2 (1.8 - 6.5)</td>
</tr>
<tr>
<td>Hypotension (systolic blood pressure ≤80 mm Hg)</td>
<td>3.1 (1.8 - 5.2)</td>
</tr>
<tr>
<td>Pulmonary crackles on auscultation</td>
<td>2.1 (1.4 - 3.1)</td>
</tr>
</tbody>
</table>

*Data not available to calculate confidence intervals.
†In heterogeneous studies the likelihood ratios are reported as ranges.

Clinical Features That Decrease the Probability of a Myocardial Infarction in Patients Presenting with Acute Chest Pain

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Likelihood Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleuritic chest pain</td>
<td>0.2 (0.2 - 0.3)</td>
</tr>
<tr>
<td>Chest pain sharp or stabbing</td>
<td>0.3 (0.2 - 0.5)</td>
</tr>
<tr>
<td>Positional chest pain</td>
<td>0.3 (0.2 - 0.4)</td>
</tr>
<tr>
<td>Chest pain reproduced by palpation</td>
<td>0.2 - 0.4*</td>
</tr>
</tbody>
</table>

*In heterogeneous studies the likelihood ratios are reported as ranges.


V. FIVE LIFE THREATENING CAUSES OF CHEST PAIN

<table>
<thead>
<tr>
<th>Condition</th>
<th>Location of Pain</th>
<th>Quality of Pain</th>
<th>Duration of Pain</th>
<th>Aggravating or Relieving Factors</th>
<th>Signs or Symptoms</th>
<th>Diagnosing the Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction/Unstable Angina</td>
<td>Substernal, may radiate to jaw, neck or shoulder/arm(s)</td>
<td>Pressure, heaviness, squeezing, burning</td>
<td>Builds over several minutes to hours</td>
<td>Worse with exertion and relieved with rest</td>
<td>SOB, diaphoresis, N/V, light-headedness</td>
<td>EKG, cardiac enzymes, stress testing, cardiac cath</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Unilateral</td>
<td>Sharp, pleuritic</td>
<td>Sudden onset</td>
<td>Worse with inspiration</td>
<td>Dyspnea, decreased breath sounds, tracheal deviation, tachypnea</td>
<td>Chest x-ray and physical exam</td>
</tr>
<tr>
<td>Pericarditis (and Tamponade)</td>
<td>Retrosternal and left precordial</td>
<td>Sharp, stabbing, pleuritic</td>
<td>Hours to days</td>
<td>Worse with deep breaths or supine position, better with upright and forward position</td>
<td>Friction rub, pulsus paradoxus, tamponade</td>
<td>EKG, CXR, ECHO</td>
</tr>
<tr>
<td>Pulmonary Embolus</td>
<td>Substernal</td>
<td>Pleuritic</td>
<td>Sudden onset</td>
<td>Worse with breathing</td>
<td>Dyspnea, tachypnea, tachycardia rates, hemoptysis peripheral edema</td>
<td>Pulmonary angiogram, ventilation/perfusion (V/Q) scan (second line),</td>
</tr>
<tr>
<td>Aortic Dissection</td>
<td>Anterior chest with radiation to back</td>
<td>Severe pain, tearing sensation</td>
<td>Sudden onset</td>
<td>Unable to relieve</td>
<td>Lower BP in one arm, decreased femoral pulses, AR murmur, pulsus paradoxus</td>
<td>Chest x-ray, CT, Angiography, TEE</td>
</tr>
</tbody>
</table>

VI. EVALUATING CHEST PAIN

A. There are many clinical prediction rules, but they are user dependent and there is a question if they are better than history and physical exam. Percentage of patients sent home from emergency departments with acute MI has decreased and is now approximately 2%. Any clinical prediction rule (for emergency departments) would have to have a sensitivity of greater than 98%

B. Probably most important aspect of assessment is determination of pretest probability of pain being ischemic in origin. If it is determined that there is a likelihood of pain being ischemic, then subsequent tests (after the ECG and CXR) usually include a stress
42. Evaluation of Chest Pain

Cardiac & Pulmonary Disorders

test and/or cardiac catheterization. See Chapter 46, Coronary Artery Disease and Chapter 50, Cardiac Stress Testing

C. EKG: Important for diagnosing myocardial ischemia or infarction as well as pericardial disease. May rarely show findings consistent with PE (S, Q, T). See table below and also see Chapter 43, ECG Interpretation

D. Chest x-ray: Will aid in diagnosing pneumothorax, assessing cardiac silhouette, and determining a widened mediastinum vs. non cardiac etiologies such as infiltrate, effusion, or rib fracture

E. Laboratory: Initial labs in an emergency department setting include CPK with isoenzymes (CPK-MB peaks at 8–12hrs), troponin I (same peak as CPK-MB but remains elevated for 2–3 days), CBC, chemistry, oxygen saturation, and possibly arterial blood gas

F. Echocardiography: Looking for segmental wall motion abnormalities, pericardial effusion, root size, aortic insufficiency, mitral regurgitation or papillary muscle dysfunction

<table>
<thead>
<tr>
<th>Feature of the Electrocardiogram</th>
<th>Likelihood Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New ST-segment elevation ≥ 1 mm</td>
<td>5.7 - 53.9*</td>
</tr>
<tr>
<td>New Q wave</td>
<td>5.3 - 24.8*</td>
</tr>
<tr>
<td>Any ST-segment elevation</td>
<td>11.2 (7.1 - 17.8)</td>
</tr>
<tr>
<td>New conduction defect</td>
<td>6.3 (2.5 - 15.7)</td>
</tr>
<tr>
<td>New ST-segment depression</td>
<td>3.0 - 5.2*</td>
</tr>
<tr>
<td>Any Q wave</td>
<td>3.9 (2.7 - 5.7)</td>
</tr>
<tr>
<td>Any ST-segment depression</td>
<td>3.2 (2.5 - 4.1)</td>
</tr>
<tr>
<td>T-wave peaking and/or inversion ≥ 1 mm</td>
<td>3.1†</td>
</tr>
<tr>
<td>New T-wave inversion</td>
<td>2.4 - 2.8*</td>
</tr>
<tr>
<td>Any conduction defect</td>
<td>2.7 (1.4 - 5.4)</td>
</tr>
</tbody>
</table>

*Data not available to calculate confidence intervals.
†In heterogeneous studies the likelihood ratios are reported as ranges.


CLINICAL PEARLS

- 10% of acute MI patients state that chest pain is relieved by antacids. No published data supports use of antacids + viscous Lidocaine to “rule out” an MI
- 10–20% of patients who have MI will have either normal EKG or “nonspecific” changes. Patient with good history for myocardial ischemia in light of “normal” EKG still needs to be admitted for cardiac evaluation
- Chewing 1 aspirin in patient suspected of having acute MI is fast, cheap, and benign way to initiate therapy

References
43. ECG INTERPRETATION

Note: All criteria listed below are not required for diagnosis

I. SEQUENCE TO READ ECG
   A. Rate: Rate < 60 = bradycardia, rate > 100 = tachycardia
   B. Rhythm: Sinus, junctional, ventricular
   C. Axis: Normal axis is -30° to 100°
   D. Hypertrophy and heart block: Atrial or ventricular hypertrophy (check P, QRS), heart block (check PR interval, P before each QRS, etc.) and bundle branch block (RBBB, LBBB, LAHB, LPHB)
   E. Ischemia/infarction: Check each lead for Q waves, ST elevation or depression, hyperacute or inverted T waves
   F. Electrolyte or Digoxin disturbances: Check QT, U waves

II. AXIS
   If leads I and II have the largest R waves, or the net of I plus aVF is positive, the axis can be considered normal
   A. Causes of left axis deviation (LAD) (-30 to -120)
      1. Left ventricular hypertrophy (LVH)
      2. Left bundle branch block (LBBB)
      3. Left anterior fascicular block (LAHB)
   B. Causes of right axis deviation (RAD) (100 to 180)
      1. Right ventricular hypertrophy (RVH)
      2. Right bundle branch block (RBBB)
      3. Left posterior fascicular block (LPHB)
      4. COPD, pulmonary emboli (PE), cor pulmonale

III. HYPERTROPHY
   A. Right atrial enlargement (RAE)
      1. ECG diagnosis
         a. Tall P waves in II, III, aVF > 0.12 seconds wide or 3mm tall (P pulmonale)
         b. Large diphasic P wave in V1 with initial component > 1.5mm
         c. P > 0.11 seconds
      2. Differential diagnosis of RAE
         a. Pulmonary HTN (COPD, PE)
         b. Tricuspid or pulmonic valvular dysfunction (TR, TS, PR, PS)
         c. Congenital disorder
   B. Left atrial enlargement (LAE)
      1. ECG diagnosis
         a. P wave in lead I > 0.12 seconds
         b. Terminal negativity of P wave in V1 > 1mm with duration > 0.04 seconds
      2. Differential diagnosis of LAE
         a. Systemic HTN
         b. Aortic or mitral valvular dysfunction (AR, AS, MR, MS)
         c. Left ventricular failure
   C. Right ventricular hypertrophy (RVH)
      1. ECG diagnosis
         a. Right axis deviation > 100°
         b. R > S in right precordium (V1–2) and deep S waves over left precordium (V5–6)
         c. ST depression and inverted T wave in V1–2
         d. Associated RAE
         e. Normal QRS
2. Differential diagnosis of RVH
   a. Pulmonary HTN (COPD, PE)
   b. Pulmonary stenosis, MS, MR, left to right shunt

D. Left ventricular hypertrophy (LVH)

1. ECG diagnosis: The Estes point system for LVH (95% specific, 50% sensitive)
   a. Amplitude (Any of the following) ................................................................. 3
      i. Largest R or S in limb leads ≥ 20mm
      ii. S in V1 or V2 ≥ 25mm
      iii. R in V5 or V6 ≥ 25mm
   b. ST segment changes of strain
      i. Without Digitalis ..................................................................................... 3
      ii. With Digitalis .......................................................................................... 1
   c. LA abnormality .......................................................................................... 3
   d. Left axis deviation ≥ -30º ........................................................................... 2
   e. QRS duration ≥ 0.09 seconds .................................................................... 1
   f. Intrinsicoid deflection* in V1 or V6 > 0.05 seconds .................................... 1

   *Intrinsicoid deflection is the time to the beginning of the rapid fall from the peak of the R

   Probable LVH = 4 total points
   LVH = 5 total points

2. Differential diagnosis of LVH
   a. Systemic arterial HTN
   b. AS, AR
   c. Hypertrophic cardiomyopathy
   d. Coarctation of the aorta

IV. HEART BLOCK

Normal PR = 0.12–0.2 seconds; QRS = 0.08–0.12 seconds; QTc = < 0.37 seconds (males),
< 0.40 seconds (females). QTc = QT (seconds) / √RR (seconds)

Note: Small blocks are 0.04 seconds; large blocks are 0.2 seconds

A. AV block
   1. First degree heart block: PR interval > 0.2 seconds
   2. Second degree heart block
      a. Mobitz I (Wenckebach): PR interval gradually increases until the AV node is not
         conducted and a QRS is dropped
      b. Mobitz II: PR is constant with QRS occasionally dropped
   3. Third degree heart block: Complete heart block with no atrial impulses reaching the
      ventricles. The P waves and the QRS complexes both independently “march out”

B. Bundle branch block
   1. Right bundle branch block (RBBB)
      a. Total QRS > 0.12 seconds (QRS = 0.10–0.11 seconds in incomplete RBBB)
      b. RSR’ in right precordial leads (V1–2)
      c. Terminal broad S in I, V1–2
      d. Right axis deviation (RAD)
   2. Left bundle branch block (LBBB)
      a. Total QRS > 0.12 seconds (QRS = 0.10–0.11 seconds in incomplete LBBB)
      b. Broad R wave in I, V5–6
      c. ST depression and T wave inversion in I, aVL, V5–6
      d. Displacement of the ST segment and T wave in a direction opposite to the major
         QRS deflection
      e. Left axis deviation (LAD)
      f. Absence of Q wave in I, V5–6
      g. Poor R wave progression
   3. Left anterior fascicular block (LAHB)
      a. LAD (QRS axis -30º to -90º)
      b. Small R in II, III, aVF
      c. S in V1–6
      d. Small Q in I, aVL
      e. Normal QRS duration
4. Left posterior fascicular block (LPHB)
   a. RAD (QRS axis > 100°)
   b. Small S in II, III, aVF
   c. Small R in I, aVL
   d. Normal QRS duration
   e. Exclude other causes of RAD: RVH, COPD, lateral MI

V. ISCHEMIA/INFARCTION

A. ECG changes
   1. Ischemia: Horizontal ST segment depression or downsloping ST segment, T waves
      upright or inverted
   2. Injury: Acute ST segment elevation (convex)
   3. Infarction: Q waves (Q waves must be > 25% of succeeding R wave and > 0.04
      seconds)

B. ECG changes by ischemic/infarction location
   1. Inferior MI: Changes in leads II, III, aVF (right coronary artery or circumflex)
   2. Anterior MI: Changes in leads I, V_{1-2}, upright T in V, ST depression V_{1-2} (circumflex artery or
      RCA)
   3. Posterior MI: R wave in V_{1-2}, upright T in V, ST depression V_{1-2} (circumflex artery or
      RCA)
   4. Lateral MI: Changes in leads I, aVL, V_{5-6}
   5. Anterolateral MI: Changes in leads V_{3-6}, aVL
   6. Anteroseptal MI: Changes in leads V_{4-5}
   7. Right ventricular MI: ST elevation in lead V_{4R} seen on a right sided ECG

C. For an excellent table on the features of the electrocardiogram which increase the
   probability of MI, see Chapter 42, Evaluation of Chest Pain, Section VI. F.

VI. DIFFERENTIAL DIAGNOSIS OF SPECIFIC ABNORMALITIES (ST, QT, ETC.)

A. Increased PR interval
   1. AV block
   2. Hypothyroidism
   3. Digitalis effect
   4. Hypothermia

B. Shortened PR interval
   1. Wolff-Parkinson-White (WPW)
   2. AV junctional rhythm with retrograde P wave conduction
   3. Lown-Ganong-Levine (accessory pathway)
   4. HTN

C. Increased QRS interval
   1. Hyperkalemia
   2. Bundle branch block
   3. Hypothermia
   4. Quinidine
   5. Procainamide
   6. Tricyclic overdose

D. ST segment elevation
   1. Q wave MI
   2. Pericarditis (diffuse ST segment elevation)
   3. Ventricular aneurysm (ST segment elevation persists > 2 weeks)
   4. Early repolarization: Seen best in V_{1-2}, no other ECG abnormalities present, cannot be
      distinguished from MI. If patient is > age 30, may need to be admitted to exclude
      MI. Check old ECGs
   5. Prinzmetal’s angina
   6. Nonspecific

E. ST segment depression
   1. Ischemia
   2. Non Q wave MI
3. Ventricular hypertrophy (typically downsloping)
4. Interventricular Conduction Defect (IVCD)
5. Digoxin effect, Quinidine effect
6. Hypokalemia
7. “Reciprocal” changes in MI

F. Prolonged QTc: measured from the beginning of the Q to the end of the T wave (> 0.37 seconds in men and > 0.40 seconds in women — due to delayed repolarization of the ventricular myocardium). \( QTc = QT \div \sqrt{RR} \)
1. Ischemia, CHF
2. Drugs: Quinidine, Procaine, Norpace, Phenothiazines, Tricyclics, Terfenadine, Cisapride
3. Hypocalcemia, hypokalemia, hypomagnesemia
4. Hypothermia
5. Mitral valve prolapse (MVP)
6. Ventricular hypertrophy
7. Intracranial hemorrhage

G. Shortened QTc
1. Hypercalcemia
2. Digoxin

H. Inverted T waves
1. Ischemia
2. Non Q wave MI
3. Chronic pericarditis
4. Ventricular hypertrophy
5. Intraventricular conduction defect (IVCD)
6. Intracranial hemorrhage
7. Hypokalemia
8. Pulmonary embolism (PE)

I. Tall/peaked T waves
1. Hyperkalemia
2. Acute MI
3. Intracranial hemorrhage
4. Normal variant

J. Tall R wave in V1
1. Posterior MI
2. RVH
3. Incomplete RBBB
4. Duchenne’s muscular dystrophy
5. WPW
6. Normal variant (counterclockwise rotation of the heart)

K. RSR' in V1
1. Complete or incomplete RBBB
2. RVH
3. WPW
4. Pectus or straight back deformities
5. Normal variant—occurs in 5% of young people

L. U waves: Considered abnormal when amplitude is > 1.5mm in any lead; best seen in V1
1. Bradycardia
2. Electrolyte imbalance (hypokalemia, hypercalcemia or hypomagnesemia)
3. Drugs (Digitalis, Quinidine, Procainamide, Phenothiazines, Epinephrine)
4. CNS disease
5. LVH
6. Hyperthyroidism
7. Mitral valve prolapse (MVP)
8. Intracranial hemorrhage
9. Negative U waves are suggestive of severe triple vessel disease
M. Poor R wave progression (precordial leads)
   1. COPD
   2. LV dilation
   3. LAHB
   4. Anterior MI

VII. DRUG EFFECTS
A. Digitalis
   1. Digitalis effect: Seen in most patients on Digitalis. Digitalis is often stopped several
days before exercise stress testing so that Digitalis effect (ST depression, T wave
changes) will not be confused with ischemia
      a. Increased PR interval
      b. ST segment depression (downsloping ST segment)
      c. Flattening of T waves, diphasic T, inverted T
      d. Shortening of QT interval
      e. Increase of U wave amplitude
   2. Digitalis toxicity: This is a clinical and not an ECG diagnosis
      a. Evidence of increased automaticity and impaired conduction
      b. Examples: Bradycardia, junctional rhythm, AV block, PAT with 2:1 AV
         block, PVCs, bi-/trigeminy, atrial fib, V. Tach, V. Fib.
B. Quinidine
   1. Quinidine effect: Changes seen on ECG
      a. Wide, notched P
      b. Wide QRS (> 0.12 seconds)
      c. ST depression
      d. Prolonged QTc
      e. U wave
   2. Quinidine toxicity: This is a clinical and not an ECG diagnosis
      a. Widening of QRS (> 0.12 seconds)
      b. AV block, sinus bradycardia, sinus arrest
      c. Ventricular arrhythmias, syncope, sudden death
      d. Torsade de pointes

VIII. ELECTROLYTE ABNORMALITIES
A. Hyperkalemia
   1. Tall, narrow, peaked T waves (hyperacute T waves)
   2. Widening of QRS > 0.10 seconds
   3. Wide, flat P waves
   4. Bradycardia, tachyarrhythmias, AV block, ventricular fibrillation, cardiac arrest
B. Hypokalemia
   1. Flattening and inversion of T wave
   2. Prominent U wave
   3. ST depression
   4. Ventricular ectopy and AV block
C. Hypercalcemia: Decreased QT interval, U waves
D. Hypocalcemia (hypomagnesemia): Increased QT interval

IX. ECG CHANGES ASSOCIATED WITH VARIOUS CONDITIONS
A. Pulmonary embolism (PE): Sinus tachycardia, S in lead I, Q in lead III, inverted T in
   lead III, RAD, ST segment decreased in lead II, transient RBBB, T wave inversion in
   right precordial leads, right atrial enlargement. Note: the most common is a normal ECG
B. Chronic lung disease: RAD, RVL, right atrial enlargement, low voltage, multifocal atrial
tachycardia (MAT), right atrial enlargement
C. Pericardial effusion: Sinus tachycardia, electrical alternans, low voltage (< 5mm), ST
   segment elevation
D. LV strain: Depressed and wavy ST segment in V,
E. RV strain: Depressed and wavy ST segment in V,
F. Wolff-Parkinson-White syndrome (WPW): PR < 0.12, QRS > 0.11, delta wave, ST/T changes, associated with paroxysmal tachycardia
G. Ventricular aneurysm: Persistent ST elevation (> 2 weeks) after MI (usually anterior MI)
H. Early repolarization/normal variant: QRS slurs into ST with high J point and concave up ST segment, most common in lateral and inferior leads
I. Pericarditis: Diffuse ST segment elevation (concave) present in all leads except aVR and V, PR segment depression, QRS changes are absent
J. Hypothermia: Prolonged PR, prolonged QT, sinus bradycardia syndrome
K. Sick sinus syndrome: Severe sinus bradycardia, sinus arrest, bradycardia alternating with tachycardia, chronic atrial fibrillation, AV junctional escape rhythm

CLINICAL PEARLS
• Reciprocal changes for inferior infarctions may involve I, aVL. Reciprocal changes for a lateral MI may involve II, III, aVF
• Approximately 15% of normal individuals may have a Q wave and/or T wave inversion in lead III
• Q waves may be normal in lead III, V, and sometimes V,

References
44. HYPERLIPIDEMIA

Note: See Chapter 128 for nutrition information concerning hyperlipidemia patients

I. SIGNIFICANCE
A. A major modifiable risk factor for coronary heart disease, which is the leading cause of death for both women and men in the US
B. An approximation of efficacy of therapy is that there is a 1% reduction in risk of coronary artery disease (CAD) for every 1% decrease in LDL

II. ETIOLOGY
A. Total cholesterol is influenced by genetic predisposition, concomitant disease, certain meds, and lifestyle
B. Genetic connection: Autosomal dominant familial hypercholesterolemia—present in 1 in 500 patients with myocardial infarction

III. 2013 ACC/AHA GUIDELINE ON THE TREATMENT OF BLOOD CHOLESTEROL TO REDUCE ATHEROSCLEROTIC CARDIOVASCULAR RISK IN ADULTS
A. General concepts
1. There is a consistent reduction in atherosclerotic cardiovascular disease (ASCVD) events from 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) therapy in secondary and primary prevention populations, with the exception of no ASCVD event reduction in those with New York Heart Association (NYHA) class II-IV heart failure or receiving maintenance hemodialysis
2. A heart healthy diet, regular exercise, avoidance of tobacco products, and maintenance of a healthy weight are the foundations of ASCVD risk reduction
3. The panel was not able to find a reduction in ASCVD outcomes by titrating cholesterol lowering therapy
4. The panel was not able to find a reduction in ASCVD outcomes by the use of Niacin to additionally lower non-HDL cholesterol once an LDL target was achieved
5. Note: This new approach abandons the previous approach of “treat-to-goal.” The panel recommends using current RCT evidence to reduce ASCVD events by using the maximum tolerated statin therapy for those groups shown to benefit (see below)
B. Groups that benefit from Statin therapy (4 main groups where the benefit outweighs the risk)
1. Individuals with clinical ASCVD (acute coronary syndromes (ACS), history of myocardial infarction (MI), stable or unstable angina, coronary or arterial revascularization, stroke, TIA or peripheral arterial disease from ASCVD)
2. Primary elevations of LDL–C >190mg/dL
3. Diabetic aged 40 to 75 years with LDL–C 70 to 189mg/dL and without clinical ASCVD
4. Individuals without clinical ASCVD or diabetes with LDL–C 70 to 189mg/dL and estimated 10-year ASCVD risk >7.5%. See risk calculator at: http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp

See figure below for algorithmic approach to initiation of therapy
MAJOR RECOMMENDATIONS FOR STATIN THERAPY FOR ASCVD PREVENTION

ASCVD Statin Benefit Groups
Heart healthy lifestyle habits are the foundation of ASCVD prevention. In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL–C 70-189 mg/dL.

Definitions of High- and Moderate-Intensity Statin Therapy
(See Table 5)

LDL–C ≥190 mg/dL

Yes

High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

No

Diabetes
Type 1 or 2
Age 40-75 y

Yes

Moderate-intensity statin

Estimate 10-y ASCVD Risk with Pooled Cohort Equations*

≥7.5% estimated 10-y ASCVD risk and age 40-75 y

Yes

Moderate-to-high intensity statin

No

ASCVD prevention benefit of statin therapy may be less clear in other groups
In selected individuals, consider additional factors influencing ASCVD risk† and potential ASCVD risk benefits and adverse effects, drug-drug interactions, and patient preferences for statin treatment.

ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcium; and LDL–C, low-density lipoprotein cholesterol.

*Percent reduction in LDL–C can be used as an indication of response and adherence to therapy, but is not in itself a treatment goal.

†The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes.

‡ Primary LDL–C=160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years of age in a first degree male relative or <65 years of age in a first degree female relative, highsensitivity C-reactive protein >2 mg/L, CAC score >300 Agatston units or >75 percentile for age, sex, and ethnicity, ankle-brachial index <0.9, or elevated lifetime risk of ASCVD.


C. Recommendations based on risk group
1. Individuals with clinical ASCVD
   a. High-intensity statin therapy if < 75 years of age
   b. If over 75, evaluate potential for benefit vs. risk of side effects or drug-drug interactions
2. Primary elevations of LDL–C >190 mg/dL
   a. Evaluate for secondary causes of hyperlipidemia
      i. Diet
      ii. Drugs elevated LDL-C: Diuretics, cyclosporine, glucocorticoids, amiodarone, Drugs elevated: TG: Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, raloxifene, tamoxifen, beta blockers (not carvedilol), thiazides
      iii. Diseases elevated LDL-C: Biliary obstruction, nephrotic syndrome; diseases elevated TG: nephrotic syndrome, chronic renal failure, lipodystrophies
      iv. Disorders of metabolism: elevated LCL-C: Hypothyroidism, obesity, pregnancy; elevated TG: diabetes (poorly controlled), hypothyroidism, obesity, pregnancy
   b. High-intensity statin therapy
3. Diabetics aged 40 to 75 years with LDL–C 70 to 189 mg/dL and without clinical ASCVD
   a. Moderate dose statin therapy
   b. High dose statin therapy if ASCVD risk is > 7.5%
4. Individuals without clinical ASCVD or diabetes with LDL–C 70 to 189 mg/dL and estimated 10-year ASCVD risk >7.5%. Use moderate to high dose statin therapy

<table>
<thead>
<tr>
<th>High- Moderate- and Low-Intensity Statin Therapy</th>
<th>(Used in the RCTs reviewed by the Expert Panel)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-Intensity Statin Therapy</td>
<td>Moderate-Intensity Statin Therapy</td>
</tr>
<tr>
<td>Daily dose lowers LDL–C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL–C on average, by approximately 30% to &lt;50%</td>
</tr>
<tr>
<td>Atorvastatin (40†)–80 mg</td>
<td>Atorvastatin 10 (20) mg</td>
</tr>
<tr>
<td>Rosuvastatin 20 (40) mg</td>
<td>Rosuvastatin (5) 10 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20–40 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40 (80) mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin X L 80 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg bid</td>
</tr>
</tbody>
</table>

Specific statins and doses are noted in bold that were evaluated in RCTs (17,18,46-48,64-67,69-78) included in CQ1, CQ2 and the CTT 2010 meta-analysis included in CQ3 (20). All of these RCTs demonstrated a reduction in major cardiovascular events. Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in italics.

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in...
44. Hyperlipidemia

Cardiac & Pulmonary Disorders

Clinical practice. There might be a biologic basis for a less-than-average response.

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (47).

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

bid indicates twice daily; FDA, Food and Drug Administration; IDEAL, Incremental Decrease through Aggressive Lipid Lowering study; LDL–C, low-density lipoprotein cholesterol; and RCTs, randomized controlled trials.


D. Initiation of therapy in patients with ASCVD and without ASCVD

1. Initiating statin therapy in individuals with clinical ASCVD

<table>
<thead>
<tr>
<th>Fast lipid panel*</th>
<th>ALT</th>
<th>CK (if indicated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider evaluation for other secondary causes (Table 6) or conditions that may influence statin safety (Table 8, Rec 1).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Evaluate and Treat Laboratory Abnormailties

1. Triglycerides ≥500 mg/dL
2. LDL–C ≥190 mg/dL
   - Secondary causes (Table 6)
   - If primary, screen family for FH
3. Unexplained ALT >3X ULN

Aged <75 y

- Without contraindications, conditions or drug-drug interactions influencing statin safety, or a history of statin intolerance

Initiate high-intensity statin therapy
Counsel on healthy lifestyle habits

Aged ≥75 y

- OR
- With conditions or drug-drug interactions influencing statin safety, or a history of statin intolerance

Initiate moderate-intensity statin therapy
Counsel on healthy lifestyle habits

Monitor statin therapy (Next Figure)

*Fasting lipid panel preferred. In a nonfasting individual, a nonfasting non-HDL–C >220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are >500 mg/dL, a fasting lipid panel is required.

†It is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, and to consider patient preferences in initiating or continuing a moderate- or high-intensity statin, in individuals with ASCVD >75 years of age.

ALT indicates alanine transaminase; ASCVD indicates atherosclerotic cardiovascular disease; CK, creatine kinase; FH, familial hypercholesterolemia; LDL–C, low-density lipoprotein cholesterol; and ULN, upper limit of normal.

2. Initiating statin therapy in individuals without clinical ASCVD

**No Clinical ASCVD**
- Not currently on cholesterol-lowering drugs
- Initial evaluation prior to statin initiation
  - Fasting lipid panel*
  - ALT
  - Hemoglobin A1c (if diabetes status unknown)
  - CK (if indicated)
  - Consider evaluation for other secondary causes (Table 6) or conditions that may influence statin safety (Table 8, Rec 1)

**Evaluate and Treat Laboratory Abnormalities**
- Triglycerides ≤500 mg/dL
- LDL-C ≤190 mg/dL
- Secondary causes (Table 6)
- If primary, screen family for FH
- Unexplained ALT >3X ULN

**Assign to statin benefit group** (Figure 2)
- Counsel on healthy lifestyle habits

**Diabetes and age 40-75 yr**
- LDL-C ≥190 mg/dL
- OR
- LDL-C 70-189 mg/dL

**Estimate 10-y ASCVD risk† with Pooled Cohort Equations**
- ≥7.5% 10-y ASCVD risk
- 5%-<7.5% 10-y ASCVD risk
- <5% 10-y ASCVD risk

**Clinicians and patients should engage in a discussion of the potential for:**
1. ASCVD risk reduction benefits
2. Adverse effects
3. Drug-drug interactions
4. Patient preferences

**Initiate statin therapy** (Figure 2)
- Re-emphasize healthy lifestyle habits

**Monitor statin therapy** (Figure 5)

---

*Fasting lipid panel preferred. In a nonfasting individual, a nonfasting non-HDL-C >220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are >500mg/dL, a fasting lipid panel is required.


‡These factors may include primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years of age in a first degree male relative or <65 years of age in a first degree female relative, sensitivity-C-reactive protein ≥2 mg/L ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity (For additional information, see http://www.mesa-
nhlbi.org/CACReference.aspx), ABI <0.9, or lifetime risk of ASCVD. Additional factors that may aid in individual risk assessment may be identified in the future.

1) Potential ASCVD risk reduction benefits (e.g., absolute risk reduction from moderate- or high-intensity statin therapy can be approximated by using the estimated 10-year ASCVD risk and the relative risk reduction of ~30% for moderate-intensity statin or ~45% for high-intensity statin therapy. 2) Potential adverse effects. The excess risk of diabetes is the main consideration in ~0.1 excess case per 100 individuals treated with a moderate-intensity statin for 1 year and ~0.3 excess cases per 100 individuals treated with a high-intensity statin treated patients for 1 year. Note: a case of diabetes is not considered equivalent to a fatal or nonfatal MI or stroke. Both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin should be evaluated in Table 8, Safety Rec 8.

ABI indicates ankle-brachial index; ALT, alanine transaminase; ASCVD indicates atherosclerotic cardiovascular disease; CK, creatine kinase; FH, familial hypercholesterolemia; LDL.C, low-density lipoprotein cholesterol; and ULN, upper limit of normal.


E. Monitoring response to statin therapy

1. To determine adherence to therapy, obtain a second lipid panel (total cholesterol, triglycerides, HDL and LDL) 4–12 week after initiation of statin therapy. Thereafter every 3–12 months as clinically indicated

Reference


Daniel M. Neides, MD
Miriam Chan, PharmD
Michael B. Weinstock, MD

45. Hypertension

(Recommendations based on JNC-VIII Guidelines)

Note: See Chapter 128 for nutrition information concerning hypertension patients

I. INTRODUCTION

A. Hypertension (HTN) affects 50 million people in the US and 1 billion people worldwide

B. There is a continuous, consistent relationship between blood pressure (BP) and risk of cardiovascular disease (CVD) which is independent of other risk factors

C. The risk of CVD begins at 15/75 and doubles with each incremental rise of 20 (systolic)/10(diastolic) in patients 40–70

D. Systolic BP (SBP) is more important CVD risk factor than diastolic BP (DBP) in patients > 50

E. Antihypertensive therapy is associated with a 35–40% decreased incidence of stroke, a 20–25% decreased incidence of myocardial infarction, and a 50% decreased incidence of heart failure

F. HTN is the most common diagnosis in the US with 35 million office visits/yr. 30% of people with HTN are unaware of their diagnosis

II. HISTORY

A. Previous history of HTN with previous levels and previous therapies attempted (note if these therapies were successful or not). Adverse effects of previous therapies, including
45. Hypertension

allergic reactions

B. Symptoms of morbidity related to HTN including coronary artery disease, heart failure, cerebrovascular disease, peripheral vascular disease, dyslipidemia, renal disease, and diabetes mellitus

C. Symptoms suggestive of secondary hypertension (see VI. below)

D. Recent changes in weight, physical activity, smoking or other tobacco use, intake of sodium, alcohol, saturated fat, and caffeine

E. Prescribed and over-the-counter meds, herbal remedies, and illicit drugs

F. Other factors which may affect adherence with medication regimen including psychosocial and environmental factors such as employment status, educational levels, understanding of HTN, and importance of control

G. Family history of conditions listed in II. B. above

III. PHYSICAL EXAM

A. General: 2 or more blood pressure measurements at least 2 minutes apart with the patient seated, measurement in the other arm (if values are different, take the higher of the 2), weight, height, waist circumference

B. Neck: Thyroid enlargement or nodules, carotid bruits, JVD

C. Eyes: Funduscopic exam for hypertensive retinopathy, papilledema

D. Lungs: Crackles or other signs of heart failure

E. CV: Rhythm, rate, gallop, murmur

F. Abdomen: Bruits (renal artery stenosis), abdominal aneurysm, truncal obesity or striae, enlarged kidneys, masses

G. Extremities: Edema, pulses in the extremities (coarctation), femoral bruits

H. Neuro: Focal deficits consistent with previous CVA

IV. EVALUATION

A. The goals of evaluating a patient with elevated blood pressure include an accurate diagnosis of hypertension, determination of cardiovascular risk, detection of target organ damage (heart, kidney and brain) and the diagnosis of secondary causes of hypertension (see section VI)

B. Accurate diagnosis of hypertension

1. Measurement
   a. Patient: seated quietly for 5 minutes prior to testing with back supported, legs uncrossed with feet on the floor, arm supported at heart level. No caffeine, strenuous activity or nicotine within 30 minutes
   b. Cuff: bladder encircles 80% of arm circumference and is placed on the patient’s uncovered arm 2 cm above the elbow crease just snug enough to allow two fingers to slide under the cuff. Midline of the cuff bladder is over the brachial artery

2. Hypertension diagnosis in the office: 140/90 or greater, based on the average of 2 or more readings taken during at least 2 separate visits

3. Ambulatory measurement
   a. Indications
      i. Suspected “white coat HTN”
      ii. Apparent drug resistance
      iii. Hypotensive symptoms with meds
      iv. Episodic hypertension
      v. Autonomic dysfunction
   b. Technique
      i. Home BP measurement with an automated upper arm cuff twice daily for one week with proper technique. Readings 135/85 or greater indicate the need for treatment
      ii. 24-hour ambulatory monitoring: considered when average home readings are 125/76-134/84, episodic HTN, hypotensive symptoms with medication, suspected white coat HTN

C. Routine laboratory and diagnostic testing
   1. Creatinine: to detect chronic kidney disease
   2. Potassium: unprovoked hypokalemia suggests hyperaldosteronism

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3. Calcium: elevated in hyperparathyroidism
4. Hematocrit
5. Urinalysis - Includes dip UA with micro if needed or albumin to creatinine ratio. A ratio of 30–300 mcg/mg indicates microalbuminuria, a sign of chronic kidney disease and a cardiovascular risk factor
6. Fasting lipid panel: cardiovascular risk
7. EKG: detect LVH (low sensitivity; high specificity), ischemic heart disease

D. Optional evaluation
1. Uric acid in patients with suspected gout
2. PTH if hyperparathyroidism is suspected (high calcium, history of stones/osteoporosis)
3. Spot urine protein to creatinine ratio if macroalbuminuria (>300 mcg/mg). Consider nephrology evaluation with a ratio of greater than 1 (equal to 24 hour protein excretion of > 1 g/day)
4. Echocardiogram: more sensitive at detecting LVH and should be done if symptoms and or signs of valvular heart disease or heart failure

V. CLASSIFICATIONS AND MANAGEMENT OF BLOOD PRESSURE

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mmHg</th>
<th>DBP mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>&gt;160</td>
<td>or &gt;100</td>
</tr>
</tbody>
</table>

VI. SECONDARY HYPERTENSION—CONSIDER EVALUATION WITH:
A. Patients whose age, history or physical exam, severity of hypertension, or initial lab findings suggest a secondary cause. Examples:
1. Abdominal bruits—RAS
2. Paroxysms of HTN accompanied by headache, palpitations perspiration—Pheochromocytoma
3. Abdominal or flank masses—Polycystic kidneys
4. Delayed or absent femoral pulses—Coarctation of the aorta
5. Truncal obesity with abdominal striae—Cushing’s or steroid therapy
6. Unprovoked hypokalemia—Primary aldosteronism. Primary aldosteronism should also be worked up in cases of resistant hypertension regardless of potassium level, since this is a relatively common cause of secondary hypertension and unproved hypokalemia is only present in 30% of patients with this condition
7. Hypercalcemia—Hyperparathyroidism
8. Elevated creatinine—Renal parenchymal disease

B. Other causes of secondary HTN: Sleep apnea, drug-induced or drug-related thyroid disease, oral contraceptives, drug or alcohol-related sympathomimetics (decongestants, anoretics)

C. Poor response to conventional anti-HTN meds after an adequate trial
D. HTN which has suddenly worsened (well controlled hypertension has begun to increase)
E. Patients with severe HTN or sudden onset of HTN
F. Patients who have renal failure after administration of ACE inhibitors/Angiotensin II receptor antagonists

VII. MANAGEMENT OF HYPERTENSION
A. Lifestyle modifications

Chart on next page
### Lifestyle Modifications to Manage Hypertension **†**

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate SBP Reduction (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight (body mass index 18.5–24.9 kg/m²)</td>
<td>5–20 mmHg/10 kg weight loss</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat.</td>
<td>8–14 mmHg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).</td>
<td>2–8 mmHg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week).</td>
<td>4–9 mmHg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>Limit consumption to no more than 2 drinks (1 oz or 30 mL ethanol, e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men and to no more than 1 drink per day in women and lighter weight persons.</td>
<td>2–4 mmHg</td>
</tr>
</tbody>
</table>

**DASH,** Dietary Approaches to Stop Hypertension.
* For overall cardiovascular risk reduction, stop smoking.
† The effects of implementing these modifications are dose and time dependent, and could be greater for some individuals.


### B. Drug therapy: Recommendations based on JNC 8 Guidelines

1. Patient groups to be treated with pharmacotherapy

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>BP Threshold for Drug Therapy (mm Hg)</th>
<th>BP Goal (mm Hg)</th>
<th>Recommendation Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population aged &lt;60 yr</td>
<td>≥140/90</td>
<td>&lt;140/90</td>
<td>A</td>
</tr>
<tr>
<td>General population &lt;60 yr</td>
<td>SBP ≥140 or DBP ≥90</td>
<td>SBP &lt;140 or DBP &lt;90</td>
<td>A (ages 30-59 yr in regard to DBP) E (ages 18-29 yrs in regard to DBP and &lt;60 yr in regard to SBP)</td>
</tr>
<tr>
<td>Patients aged ≥8 yr with CKD</td>
<td>≥140/90</td>
<td>&lt;140/90</td>
<td>E</td>
</tr>
<tr>
<td>Patients aged ≥8 yr with diabetes</td>
<td>≥140/90</td>
<td>&lt;140/90</td>
<td>E</td>
</tr>
</tbody>
</table>

*If treatment results in SBP<140 and is well tolerated by the patients without any adverse events, no treatment adjustment is needed. (Grade E).
A=Strong recommendation, B=Moderate recommendation, C=Weak recommendation, D=Recommendation against, E=Expert opinion

### C. Medication Selection

1. The 4 recommended drug classes for initial drug therapy are Thiazides-type diuretic (HCTZ, Chlorothalidone, Indapamide), CCB, ACEI, and ARB
2. β-blockers are no longer recommended as first-line therapy because they have worse CV outcomes data than the recommended agents
3. Specific populations
   - General nonblack population including those with diabetes: Start with Thiazides, CCB, ACEI or ARB (Grade B)
     a. Patients with CAD or heart failure were not reviewed in this recommendation.
   - General black population including those with diabetes: Start with Thiazides or CCB (Grade B for general black population, but grade C for black diabetic patients)
4. Therapeutic strategy (Grade E):
   • If BP goal not achieved in 1 mo: increase dose or add a second drug from one of
     the recommended drug classes. Select either a Thiazide, CCB, ACEI, or ARB.
     Do not use ACEI and ARB together
   • If BP not at goal with 2 drugs, add and titrate a third drug. Choose a drug outside
     the classes recommended above only if these options are exhausted. Refer to a
     hypertension specialist if needed

<table>
<thead>
<tr>
<th>Evidence-Based Dosing for Antihypertensive Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive Medication</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Ace Inhibitors</td>
</tr>
<tr>
<td>Captopril</td>
</tr>
<tr>
<td>Enalapril</td>
</tr>
<tr>
<td>Lisinopril</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
</tr>
<tr>
<td>Eprosartan</td>
</tr>
<tr>
<td>Candesartan</td>
</tr>
<tr>
<td>Losartan</td>
</tr>
<tr>
<td>Valsartan</td>
</tr>
<tr>
<td>Irbesartan</td>
</tr>
<tr>
<td>β-Blockers</td>
</tr>
<tr>
<td>Atenolol</td>
</tr>
<tr>
<td>Metoprolol</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>Amlodipine</td>
</tr>
<tr>
<td>Diltiazem extended release</td>
</tr>
<tr>
<td>Nitrendipine</td>
</tr>
<tr>
<td>Thiazide-type diuretics</td>
</tr>
<tr>
<td>Bendroflumethiazide</td>
</tr>
<tr>
<td>Chlorthalidone</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
</tr>
<tr>
<td>Indapamide</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; RCT, randomized controlled trial.

*Current recommended evidence-based dose that balances efficacy and safety is 25-50 mg daily.


D. Algorithm for treatment of hypertension

Algorithm on next page
Adult aged ≥18 years with hypertension

Implement lifestyle interventions (continue throughout management).

Set blood pressure goal and initiate blood pressure lowering medication based on age, diabetes, and chronic kidney disease (CKD).

General population (no diabetes or CKD)

Diabetes or CKD present

Age <60 years

Blood pressure goal
SBP <140 mm Hg
DBP <90 mm Hg

Blood pressure goal
SBP <140 mm Hg
DBP <90 mm Hg

Blood pressure goal
SBP <140 mm Hg
DBP <90 mm Hg

Blood pressure goal
SBP <140 mm Hg
DBP <90 mm Hg

All ages
Diabetes present
No CKD

All ages
CKD present with or without diabetes

Nonblack

Black

Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination.

Select a drug treatment titration strategy
A. Maximize first medication before adding second or
B. Add second medication before reaching maximum dose of first medication or
C. Start with 2 medication classes separately or as fixed-dose combination.

At goal blood pressure?
Yes

Reinforce medication and lifestyle adherence. For strategies A and B, add and titrate thiazide-type diuretic or ACEI or ARB or CCB (use medication class not previously selected and avoid combined use of ACEI and ARB). For strategy C, titrate doses of initial medications to maximum.

At goal blood pressure?
Yes

Reinforce medication and lifestyle adherence. Add and titrate thiazide-type diuretic or ACEI or ARB or CCB (use medication class not previously selected and avoid combined use of ACEI and ARB).

At goal blood pressure?
Yes

Reinforce medication and lifestyle adherence. Add additional medication class (e.g., ß-blocker, aldosterone antagonist, or others) and/or refer to physician with expertise in hypertension management.

At goal blood pressure?
Yes

Continue current treatment and monitoring.

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and CCB, calcium channel blocker.

a ACEIs and ARBs should not be used in combination.

b If blood pressure fails to be maintained at goal, reenter the algorithm where appropriate based on the current individual therapeutic plan.
45. Hypertension

CLINICAL PEARLS

- HTN is “the silent killer” and the goal of treatment is prevention of cardiovascular disease, stroke, nephropathy, and retinopathy
- Compliance is a major factor in treating HTN. Therapy should be individualized
- Patients started on ACE inhibitors should have BP checked in 1 week and serum K+ checked in 1 week
- Patients with hypertension and unexplained hypokalemia (K < 3.5) have 50% incidence of primary hyperaldosteronism (Conn’s syndrome). Approximately 0.5% of HTN is caused by Conn’s syndrome
- No direct relationship has been found between caffeine intake and HTN
- About 5% of women on oral contraceptives will have a rise in BP to > 140/90
- Short acting calcium channel blockers should not be used in the management of HTN
- Low dose aspirin should not be used with uncontrolled HTN as risk of hemorrhagic stroke is increased

References

46. CORONARY ARTERY DISEASE

Note: This chapter is for management of patients with known coronary artery disease. For diagnosis of patients with chest pain or evaluation with stress testing, see Chapters 42 and 50

I. ETIOLOGY:
Clinical manifestations are usually caused by fissuring, hemorrhage, and thrombosis of plaque in epicardial coronary arteries (plaque rupture). Plaque is comprised of subintimal collections of abnormal fat, cells, and debris

II. CLINICAL PRESENTATION
A. When ischemic cardiac events are transient, the patient may experience angina pectoris; if prolonged, can lead to myocardial necrosis and scarring with or without the clinical picture of MI
B. Patients can also present with cardiomegaly and heart failure secondary to ischemic damage of left ventricle

III. HISTORY
A. Description of pain: Character (tightness, squeezing, pressure), location, radiation (neck, shoulder(s), arm(s), jaw), onset, duration, exacerbating and relieving factors. May be more important to ask about chest discomfort rather than pain. Ask about chest pain/discomfort with exertion
B. Associated symptoms: Dyspnea, diaphoresis, dizziness, syncope, palpitations, nausea with or without vomiting, peripheral edema, orthopnea, paroxysmal nocturnal dyspnea. Negative symptoms include pain associated with motion or deep breathing and positional pain, pain on palpation, or sharp pain
Note: Pericarditis is worse when supine and relieved when sitting forward
C. Cardiac risk factors
1. Absolute: Family history, smoking, diabetes, hypertension, hyperlipidemia (LDL > 130, HDL < 35), Age (male > 45, female > 55)
2. Relative: Obesity, sedentary lifestyle, stress, postmenopausal state
3. Other: History of cerebrovascular, peripheral vascular disease
D. History of heart disease: CAD/MI, arrhythmia, valvular disease, previous heart catheterization or stress test, PTCA or CABG. Obtain old EKGs
E. 5 questions recommended to be asked during follow up of patients with angina:
1. Have you decreased your physical activity since the last visit?
2. Have your anginal symptoms increased?
3. How are you tolerating therapy?
4. How successful have you been at reducing risk factors?
5. Have you developed any comorbid illness which may worsen your angina?

IV. PHYSICAL EXAM
A. Vital signs: Blood pressure, heart rate and rhythm, respiratory rate, oxygen saturation
B. HEENT: Hypertensive or diabetic retinopathy, JVD, carotid bruit, thyromegaly
C. Lungs: Rales, pleural effusions
D. Cardiovascular: Arrhythmia, murmur, rub, gallop, click, abnormal apical impulse
E. Abdomen: Hepatomegaly (CHF/hepatojugular reflux)
F. Extremities: Cyanosis, clubbing, edema, shiny hairless legs (PVD)
G. Skin: Xanthomas, diabetic skin changes

V. EVALUATION
A. Laboratory
1. Lipid profiles: See Chapter 44, Hyperlipidemia
2. Cardiac enzymes: For patient whose ambulatory presentation suggests acute MI (concerning symptoms lasting longer than 15–20 minutes), cardiac enzymes should be ordered in an acute care setting. Troponin level peaks in 2–4 hrs and falls in 10–14 days. CPK peaks at 6–8 hrs and then falls within 24 hrs
3. Other: Thyroid panel

B. Chest XR: The presence of cardiomegaly, LV aneurysm, or pulmonary edema is associated with poorer long term prognosis

C. EKG
1. Normal EKG does not exclude the diagnosis of CAD; 12-lead EKG recorded at rest is normal in approximately half of patients with angina pectoris
2. With angina ST segments are usually depressed, but may be elevated in early stages of acute MI and in Prinzmetal’s angina
3. T-wave and ST segment changes are nonspecific and may occur in pericardial, valvular, and myocardial disease, or with anxiety, changes in posture, meds, or esophageal disease

D. Echocardiography: To assess LV function in patients with history of MI, pathological Q waves, signs or symptoms of heart failure, systolic murmur suggesting mitral regurgitation, or patient with complex ventricular arrhythmias

E. Cardiac stress testing (radionuclide or echocardiography): See Chapter 50, Cardiac Stress Testing. Indications for patients with diagnosis of myocardial ischemia:
1. Patient with significant change in cardiac symptoms to identify extent, severity, and location of ischemia
2. ECG abnormalities including WPW, paced rhythm, > 1 mm resting ST depression, LBBB
3. After cardiac catheterization to identify if ischemia is present in the distribution of the coronary lesion identified

F. Coronary angiography: Indications for patients with diagnosis of myocardial ischemia
1. Patients with a significant change in symptoms or with severe angina despite medical therapy
2. Patients with high risk criteria on noninvasive testing regardless of angina severity
3. Clinical characteristics which indicate high likelihood of severe CAD or high probability of left main or triple vessel disease
4. Non-diagnostic noninvasive testing
5. Patients who have survived sudden cardiac death or serious ventricular arrhythmia
6. Patients with angina and heart failure
7. Patients suspected of having a non-atherosclerotic cause of myocardial ischemia (coronary artery anomaly, Kawasaki disease, primary coronary artery dissection, radiation induced vasculopathy)
8. Suspected coronary artery vasospasm

VI. MANAGEMENT
A. Correction of reversible risk factors (smoking, hypertension, hyperlipidemia, uncontrolled diabetes, obesity, sedentary lifestyle, stress). See related chapters for diagnosis and management

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cardiovascular event reduction (%)</th>
<th>Total mortality reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation</td>
<td>—</td>
<td>43</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>42</td>
<td>30</td>
</tr>
<tr>
<td>Exercise</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Blood pressure control</td>
<td>21</td>
<td>12</td>
</tr>
</tbody>
</table>
B. Minimize meds which may exacerbate angina including sympathomimetics, thyroid meds 
C. Treat associated conditions which may exacerbate angina including hypoxemia, anemia, diabetes, valvular heart disease 
D. Exercise training program (may result in reduction of ischemia, improvement in lipids and blood glucose, and decrease in obesity) and weight reduction in obese patients 
E. Anti-platelet meds
   1. Aspirin: 75–325mg PO QD. Associated with 33% decrease in risk of adverse cardiac events 
   2. Clopidogrel (Plavix): 75mg PO QD. Should be used in those who failed ASA, cannot tolerate ASA, or are allergic to ASA 
   3. Ticagrelor (Brilinta): 90mg BID. Indicated for treatment of ACS with aspirin 
   4. Prasugrel (Effient): 10mg QD. With aspirin, for treatment of ACS in patients treated with PCI 
F. β-blockers
   1. Metoprolol (Lopressor): Start dose at 50mg BID, titrate to a target dose of 100mg BID 
   2. Atenolol (Tenormin): 50mg PO BID or 100mg PO QD 
   3. Timolol (Blocadren): 10mg PO BID 
   4. Carvedilol (Coreg): Start dose at 6.25mg BID, titrate to a target dose of 25mg BID 
   5. Propranolol (Inderal): 60–80mg PO TID 
   6. Avoid β-blockers with intrinsic sympathomimetic activity like Acebutolol, Pindolol, Labetalol 
G. Calcium channel blockers: Decrease coronary resistance and increase coronary blood flow. Use in patients with contraindications or unacceptable side effects of β-blockers or in combination with β-blockers when initial therapy with β-blockers is not effective. 
   Note: Do not use short acting dihydropyridine calcium antagonists as they may increase cardiac events 
   1. Amlodipine (Norvasc): 5mg PO QD initially, may increase to 10mg QD 
   2. Nicardipine (Cardene): 20mg PO TID initially, may increase to 120mg in 3 divided doses 
   3. Nifedipine (Adalat CC): 30mg PO QD, maximum 90mg QD; (Procardia XL) 30–60mg PO QD, maximum 90mg QD 
   4. Diltiazem (Cardizem SR): 60–120mg BID; (Cardizem CD) 120–300mg QD; (Dilacor XR) 180–240mg PO QD initially, maximum 480mg QD 
   5. Verapamil (Calan SR): 180mg PO QAM initially, maximum 480mg QD, elderly or small patients immediate-release 40 mg TID; (Isoptin SR) 120–180mg PO QAM initially, maximum 240mg Q12hrs 
   Note: Nifedipine is the most likely to cause reflex tachycardia 
H. Nitrates: Have been shown to improve exercise tolerance, time to onset of angina and work well in combination with β-blockers and calcium channel antagonists. Nitrates do not decrease mortality 
   1. Short acting: Nitroglycerin spray (0.4mg) or SL NTG 1/150 grain (0.4mg), 1/100 grain (0.6mg), or 1/200 grain (0.3mg)—1 SL QS minutes × 3 PRN angina. Should be taken 5 minutes before any activity likely to precipitate angina. If pain persists after 3 doses, patient should be evaluated in ER to rule out MI. Patients who require more doses of nitrates or who are not responding as well as they had previously should be re-evaluated 
   2. Long acting
      a. Transdermal NTG: 0.1, 0.2, 0.4, 0.6mg/hr—should be removed for 8hrs per day 
      b. Isosorbide Dinitrate (Isordil): 20–80mg PO TID 
      c. Isosorbide Mononitrate: 
         i. Imdur: (Extended release): initiate at 30mg QAM and titrate dose to 120mg QAM 
         ii. Ismo (Immediate release): 20mg BID, with the 2 doses given 7 hrs apart 
   3. NTG deteriorates with exposure to air, moisture, and sunlight. If sublingual administration does not cause a slight burning/tingling, NTG may be inactive 
I. Ranolazine (Ranexa)
46. Coronary Artery Disease  

1. Indicated for treatment of chronic angina
2. Dosage: Start at 500mg BID. Increase to 1000mg BID as PRN
3. Common side effects: dizziness, headache, constipation, nausea
4. Can prolong QT interval in a dose-related manner
5. Increase BP (approx. 15mm Hg) in patients with severe renal impairment. Monitor renal function in patient with CrCl<60mL/min
6. Drug interactions:
   a. CYP3A inhibitors (e.g., Diltiazem, Verapamil, Erythromycin): Limit Ranexa to 500mg BID
   b. CYP3A substrates: reduce dose of these drugs (e.g., Lovastatin, Cyclosporine, Tacrolimus, Sirolimus). Limit Simvastatin to 20mg QD
   c. CYP2D6 substrates (e.g., TCAs, antidepressants, antipsychotics): reduce dose of these drugs
   d. Digoxin: reduce dosage
   e. Metformin: Limit to 1700mg QD

J. Combination therapy: Meds may be additive in effect. Exercise caution in giving a β-blocker and negative chronotropic calcium channel blocker as this has a greater chance of leading to heart block. Particularly potent combination may be a β-blocker and a calcium channel blocker with a small amount of negative chronotropic effect

K. Follow-up every 4–12 months

VII. MEDICAL THERAPY VS. REvascularization

A. With stable angina, medical therapy is comparable to angioplasty. Medical therapy reduces the risk on MI and angioplasty results in more rapid relief of symptoms. Patients with left main stenosis > 70% and multivessel CAD with proximal LAD stenosis > 70% have better survival with CABG

B. Indications for revascularization procedures (PTCA, STENT, CABG)
   1. Failed medical therapy (intolerable symptoms despite maximal medical therapy)
   2. Left main coronary artery stenosis > 50% (with or without symptoms)
   3. Triple vessel disease and LV dysfunction (EF < 50% or previous MI)
   4. 2 vessel disease with significant proximal LAD CAD and either EF < 50% or ischemia on noninvasive testing
   5. Unstable angina symptomatic on stress testing despite maximal medical therapy
   6. Post-MI patient continuing to have angina or ischemia
   7. Relative indications include patients with anatomically critical lesions (> 90%), especially in the LAD, or physiologic evidence of severe ischemia by stress testing or ambulatory monitoring

C. PTCA vs. CABG: 2 main comparative trials are the Bypass Angioplasty Revascularization Investigation (BARI) and the Emory Angioplasty versus Surgery Trial (EAST). They showed similar 5yr survival in all patients except diabetics who had a survival advantage with CABG (with multiple severe lesions)

CLINICAL PEARLS

- Patients who are low risk and do not have indications for CABG have a 1% annual mortality
- Most patients who die suddenly from ischemic heart disease do so as a result of ischemia-induced malignant ventricular tachycardia
- In variant (Prinzmetal's) angina, the chest discomfort characteristically occurs at rest or awakens the patient from sleep. Condition is caused by focal spasm of proximal coronary arteries
- PTCA is more effective than medical therapy for the relief of angina in patients with single-vessel coronary artery disease
- Cholesterol (HDL, LDL and cholesterol) are falsely lowered and TG increased after an acute MI
47. Heart Failure

I. DEFINITION

A. Dysfunction of the myocardium resulting from decreased cardiac output. The dysfunction may be:
   1. Systolic—Dilated, eccentrically hypertrophied ventricle with EF < 45%
   2. Diastolic—Thick walled, concentrically hypertrophied ventricle with normal or small cavity, EF > 50%

B. Disease progression in systolic dysfunction may be slowed or reversed by appropriate management. Survival is only 57% at 5 years

II. ETIOLOGY—Disease progression can often be slowed with treatment of reversible causes

A. Ischemic cardiomyopathy (secondary to CAD)
B. Hypertensive cardiomyopathy
C. Valvular dysfunction
D. Toxic cardiomyopathy (alcohol, cocaine, radiation)
E. Endocrine: DM, thyroid, pheochromocytoma
F. Myocarditis
G. Drug induced—Chemotherapy drugs, cyclooxygenase 1 and 2 inhibitors, glitazones, glucocorticoids, androgens, estrogens
H. Hypo/hyperthyroid
I. Renal—Renal failure, nephrotic syndrome, glomerulonephritis
J. Pulmonary—Pulmonary hypertension, sleep apnea, cor pulmonale, pulmonary embolism
K. Other: Infiltrative disease (sarcoidosis, hemochromatosis, amyloidosis), TB, hereditary, congenital/ASD, VSD

III. HISTORY

A. Symptoms of pulmonary edema—Dyspnea with or without exertion, orthopnea, paroxysmal nocturnal dyspnea (PND), chronic non-productive cough (may be worse when supine)
IV. PHYSICAL
A. Vitals: Tachypnea, tachycardia, hypotension
B. Neck: Jugular venous distention, assessment of thyroid gland
C. Pulmonary: Rales (may be difficult to hear in patients with COPD because of decreased lung parenchyma), decreased breath sounds secondary to pleural effusions, wheeze
D. CV: Murmurs, gallop rhythm, parasternal lift (RVH secondary to pulmonary HTN), displaced left ventricular impulse (LV dilation/hypertrophy), distended jugular veins, dependent pitting edema (pretibial, sacral), hepatojugular reflux
E. Other: Hepatic congestion, diaphoresis

V. LABORATORY AND OTHER TESTING
A. Labs
1. Potassium if on diuretics
2. Consider thyroid function testing if etiology is not known
3. Digoxin level (if relevant)
4. B-type natriuretic peptide (BNP)—Hormone produced by the cardiac ventricle when it is exposed to increased wall stress such as due to volume overload
   a. Levels below 100 pg/mL unlikely to have heart failure and greater than 400 pg/mL likely to have heart failure
   b. Cannot be used to differentiate systolic from diastolic failure
B. Chest x-ray: Cardiomegaly, “fluffy” peri-hilar infiltrates (pulmonary edema), pleural effusion (bilateral or right sided), pulmonary venous congestion
C. ECG: Check for evidence of old MI, arrhythmia, bundle branch block (BBB), left ventricular hypertrophy (LVH), left atrial enlargement (LAE), right atrial enlargement (RAE)
D. ECHO: Suggested for patients with a new diagnosis of CHF to differentiate systolic from diastolic dysfunction, evaluate valvular function, and to check for pulmonary hypertension. ECHO will reveal wall motion abnormalities, old MI, ventricular and atrial hypertrophy or dilation, valvular dysfunction, shunts and pericardial effusion
E. Cardiac catheterization: For patients presenting in heart failure with ischemia or angina, or none of the above but suspected to have coronary artery disease, unless the patient is not eligible for revascularization

VI. NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION OF CARDIAC LIMITATION
Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or anginal pain
Class II: Slight limitation of physical activity. Ordinary physical activity results in symptoms
Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms
Class IV: Unable to engage in any physical activity without discomfort. Symptoms may be present even at rest

VII. MANAGEMENT OF HEART FAILURE WITH SYSTOLIC DYSFUNCTION
(Note: see VIII for management of diastolic dysfunction)
Stage C HF/HFrEF: evidence-based, guideline-directed medical therapy. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; HF/HFrEF, heart failure with reduced ejection fraction; Hydral-Nitrates, hydralazine and isosorbide dinitrate; LOE, Level of Evidence; and NYHA, New York Heart Association.


A. Correct reversible causes: Although CHF might not improve with correction, progression can often be slowed (CAD, EtOH, HTN, hemochromatosis, etc.)

B. Diet: For patients with reduced left ventricular ejection fraction (LVEF) and fluid retention, restrict sodium and fluid intake and consider diuretics such as Furosemide (Lasix) 20mg PO QD. Monitor potassium.

C. Activity should include a regular exercise program such as walking 20–30 minutes a day 4–5 times per week as tolerated

D. Medications for HFrEF (heart failure with reduced EF)
   1. Angiotensin converting enzyme inhibitors (ACEIs)
      a. First line drugs that should be used in all patients with HFrEF to prevent symptomatic HF and reduce mortality (20%). (Level of evidence A)
      b. Mechanism: Work by inhibiting the conversion of angiotensin I to angiotensin II in the rennin-angiotensin-aldosterone system. This leads to decrease in vasoconstriction (normally mediated by angiotensin II) and decrease in sodium retention (normally mediated by aldosterone)
      c. Start with a low dose and titrate up the dose especially in patients with low blood pressure, hypovolemia, perrenal azotemia and hyponatremia
      d. Commonly used ACEIs:
         i. Captopril (Capoten): Start 6.25mg TID, max 50mg TID
         ii. Enalapril (Vasotec): Start 2.5mg BID, max 10–20mg BID
         iii. Fosinopril (Monopril): Start 5–10mg QD, max 40mg QD
         iv. Lisinopril (Prinivil): 2.5–5mg QD, max 20–40mg QD
47. Heart Failure
Cardiac & Pulmonary Disorders

v. Quinapril (Accupril): 5mg BID, max 20mg BID
vi. Ramipril (Altace): 1.25–2.5 mg QD, max 10mg QD
vii. Trandolapril (Mavik): Start 1mg QD, max 4mg QD
e. Adverse effects:
   i. Cough (5–20%, women>men, blacks, Asian >whites)—if the patient is not able to tolerate the cough, may switch to an ARB
   ii. Hypotension (diuretic use or volume depletion)
   iii. Hyperkalemia (esp. when also taking K+ sparing or K+ suppl)—monitor K+
   iv. Renal failure- monitor SCr & K+ at baseline & after 1 wk
v. Rash
vi. Angioedema (0.1–0.2%, higher in blacks)
vii. Loss of taste
viii. Fetal malformations in 2nd and 3rd trimesters
ix. Drug interactions: NSAIDs, K+
x. Bilateral renal artery stenosis

2. Angiotensin receptor blockers (ARBs)
a. Use as alternative to ACEI when ACEI is contraindicated or in patients who are ACEI intolerant. ARBs are not more efficacious than ACEIs and should not be added to a regimen which includes an ACEI. (LOE:A)
b. Mechanism: inhibit the formation of angiotensin II
c. Commonly used ARBs:
   i. Candesartan (Atacand): Start 4–8mg QD, max 32mg QD
   ii. Losartan (Cozaar): 25–50mg QD, max 50–150mg QD
   iii. Valsartan (Diovan): Start 20–40mg BID, max 160mg BID
d. Side effects: same as ACEIs except low risk for cough

3. β-blockers
a. Recommended for all stable patients in all classes of heart failure (LOE: A)
b. Three proven to reduce risk of death, i.e., Bisoprolol, Carvedilol, and sustained release Metoprolol Succinate
   i. Bisoprolol (Ziac): Start 1.25mg QD, max 10mg QD
   ii. Carvedilol (Coreg): Start 3.125mg BID, titrate dose by doubling the dose every 2 wks, max 50mg BID
   iii. Carvedilol (Coreg CR): start at 10mg QD, max 80mg QD
   iv. Metoprolol succinate XR (Toprol XL): Start 12.5–25mg QD, max 200mg QD
c. Do not initiate when a patient is decompensated or volume overloaded as initiation is associated with a transient decline in cardiac output
d. Taper dose over 1–2 weeks to discontinue

4. Diuretics
a. Recommended in patients with HFrEF who have evidence of fluid retention to improve symptoms (LOE: C)
b. Loop diuretics: effective in CrCl<30mL/min
   i. Furosemide (Lasix): Start at 20–40mg QD or BID, max 600mg
   ii. Bumetanide (Bumex): Start as 0.5–1mg QD or BID, max 10mg QD
   iii. Torsemide (Demadex): Start 10–20mg QD, max 200mg

5. Hydralazine and Isosorbide Dinitrate (IDN) combination
a. The combination is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III-IV HFrEF receiving optimal therapy with ACEI and β-blockers, unless contraindicated (LOE:A)
i. BiDi: a fixed-dose combination of 37.5mg Hydralazine/20mg IDN: start 1 tab TID, max 2 tabs TID
b. The combination can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated (LOE: B)
i. Start Hydralazine 25–50mg and IDN 20–30mg 3 or 4 times daily, max Hydralazine 300mg/day and IDN 120mg/day give both drugs in divided doses
ii. Side effects include tachycardia, orthostatic hypotension, edema, GI toxicity, lupus-like reaction
6. Aldosterone receptor antagonists
   a. Recommended in patients with NYHA class II-IV HF and who have LVEF ≤35% to reduce morbidity and mortality (LOE:A)
      i. Patients with NYHA class II HF should have a history of prior CV hospitalization or elevated plasma BNP
      ii. SCr ≤2.5mg/dL in men or ≤2mg/dL in women (or est GFR >30mL/min/1.73m²)
      iii. Serum K+ <5mEq/L
      iv. Monitor K+, renal function and diuretic dosing at therapy initiation and follow closely thereafter
   b. Recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF ≤40% who develop symptoms of HF or have a history of diabetes (LOE:B)
   c. Spironolactone (Aldactone): Start 12.5–25mg QD, max 25mg QD or BID
e. Eplerenone (Inspra): Start 25mg QD, max 50mg QD

7. Digoxin
   a. Can be beneficial in patients with HFrEF to decrease hospitalizations for HF (LOE:B)
   b. Digoxin (Lanoxin): 0.125–0.25mg QD
c. Monitor serum digoxin levels, renal function, and serum K+ as needed

8. Aspirin: 81mg QD should be given if patient has CAD, dilated cardiomyopathy, atrial fibrillation or valvular dysfunction

9. Medications which are harmful and should be stopped
   a. Nonsteroidal anti-inflammatory drugs (NSAIDS)
   b. Most antiarrhythmic drugs
   c. Most calcium channel blocking drugs

VIII. MANAGEMENT OF HEART FAILURE WITH DIASTOLIC DYSFUNCTION
A. Unlike systolic dysfunction, there are no clearly effective treatments for diastolic dysfunction
B. The goal of therapy is to slow the rate to allow time for ventricular filling. Few meds are available to treat diastolic dysfunction, and they should be used with caution
1. β-blockers
   a. Propranolol (Inderal): 60–80mg PO TID–QID
   b. Metoprolol (Lopressor): 50–100mg PO BID
   c. Timolol (Blocadren): 10mg PO BID
d. Atenolol (Tenormin): 50mg PO BID or 100mg PO QD
2. Calcium channel blockers
   a. Diltiazem (Cardizem, Cardizem SR, Cardizem CD, Dilacor XR): 60mg PO TID initially, may increase to 360mg QD in 3 divided doses
   b. Verapamil (Calan, Isoptin, Calan SR, Isoptin SR, Verelan): 80mg PO TID initially, may increase to 480mg in 3 divided doses
C. Diuretics for symptoms

CLINICAL PEARLS
- The most common cause of right heart failure is left heart failure
- Mortality of diastolic dysfunction is similar to systolic dysfunction
- Frequent causes of CHF exacerbations are medication non-compliance or change in diet (salt)
- Patients who are bedridden will manifest their edema as sacral (dependent) edema as opposed to edema of the lower extremities
- Patients with stable CHF should continue to exercise as tolerated

References
48. Atrial Fibrillation

Irregular supraventricular tachyarrhythmia caused by simultaneous discharges from multiple atrial foci. If the AV node does not block, or if accessory pathways are present there may be a rapid ventricular response (pulse > 100)

II. INCIDENCE
A. Most common chronic disturbance of heart rhythm
B. Incidence increases with age: 50–59: 0.5%; 60–69: 3.8%; 70+: 9%
C. Chronic disease: Recurrence rate is extremely high, even if treated aggressively with DC or pharmacologic cardioversion

III. ETIOLOGY
A. Cardiac
1. Valvular
2. Post-surgical—Cardiothoracic surgery
3. Heart failure
4. Hypertension with LV hypertrophy
5. Myocardial ischemia/infarction
6. Pericarditis/myocarditis
7. Infiltrative (amyloid, etc.)
8. Wolf-Parkinson-White (WPW)
9. Congenital
B. Non-cardiac
1. Pulmonary—Cor pulmonale, pneumonia, pulmonary embolism (PE), sleep apnea
2. Alcohol (alcoholism, holiday heart)
3. Medications and drugs of abuse—Theophylline, sympathomimetics, antidepressants, Digoxin, Atropine eye drops
4. Electrolyte abnormalities
5. Fever/hypothermia
6. Thyrotoxicosis/hypothyroidism
C. Lone atrial fibrillation

IV. HISTORY
A. New onset vs. persistent or paroxysmal
B. Chest discomfort, palpitations
C. Dyspnea, fatigue, lightheadedness
D. Weight loss, sleeplessness, rapid speech, tremor (thyrotoxicosis)
E. Alcohol history: Acute ingestion (holiday heart) vs. alcoholism (alcoholic cardiomyopathy)
F. Medications
G. History of ischemic, valvular or other heart disease

V. PHYSICAL EXAM
A. Vital signs: temperature, O₂ saturation, pulse, blood pressure, and respiration
B. Neck: JVD, thyromegaly  
C. Pulmonary: Wheezing, rhonchi  
D. CV: Friction rub, murmur, gallop, variation in loudness of first heart sound

VI. OTHER TESTS  
A. Laboratory: Thyroid studies, serial cardiac enzymes with initial onset, electrolytes  
B. ECG: Irregularly irregular rhythm with absence of P waves (special attention to Lead II). Check for rapid rate, LVL, bundle-branch block, pre-excitation  
C. CXR: Heart size, lung disease  
D. Echocardiogram (transesophageal or transthoracic): To evaluate valves, atrial size, hypo-akinesis, thrombus, pericardial effusion

VII. MANAGEMENT  
A. Rate Control—Goal of 80 beats per minute at rest and 110 minutes with exercise  
1. β-blockers—First line therapy  
   a. Metoprolol (Lopressor): 25–100mg PO BID  
   b. Atenolol (Timolol): 25–100mg PO QD  
   c. Propranolol (Inderal): 80–360mg PO divided BID  
2. Calcium channel blockers  
   a. Diltiazem—120–360mg PO QD (use long acting formulation. Onset 2–4hrs)  
   b. Verapamil—120–360mg PO QD (use long acting formulation. Onset 1–2hrs)  
3. Digitalis (Digoxin)—Not first line  
B. Rhythm control  
1. Cardioversion  
   a. Anticoagulation for 3 weeks prior and 4 weeks post-cardioversion to prevent thromboembolism. Note: Thrombi can form within 48hrs onset of afib. Patients with paroxysmal afib are at particularly high risk for thromboembolism  
   b. Electrical  
   c. Chemical—limited by long term lack of effectiveness of meds in addition to risk of ventricular arrhythmias. Meds include Ibutilide (Corvert), Flecainide (Tambocor), Dofetilide (Tikosyn), Sotalol (Betapace), Propafenone (Rythmol), and Amiodarone (Cordarone), Dronedarone (Multaq)  
2. AV nodal ablation/pacing  
3. Afib ablation  
C. Anticoagulation—Indicated for patients with persistent or paroxysmal afib. Overall stroke risk is 5% per year  
1. Estimation of risk/recommended therapy

<table>
<thead>
<tr>
<th>Risk of Stroke Stratified by CHADS2 Score</th>
<th>Adjusted stroke rate (95% CI)</th>
<th>Risk level</th>
<th>Recommended therapy</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.8 (2.0–3.8)</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4.0 (3.1–5.1)</td>
<td>Moderate</td>
<td>Warfarin (Coumadin); target INR of 2–3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5.9 (4.6–7.3)</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8.5 (6.3–11.1)</td>
<td>High</td>
<td>Warfarin; target INR of 2–3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>12.5 (6.2–17.5)</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>18.2 (10.5–27.4)</td>
<td>High</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CHADS2, = congestive heart failure; hypertension; age ≥75 years; diabetes mellitus; stroke or transient ischemic attack.

To assess risk of stroke, add 1 point for each risk factor, except for the stroke and TIA risk factors, which count 2 points each.
2. Aspirin
   a. Reduces risk of stroke 21%
   b. Indicated for low risk patients
   c. Dose 81–325mg PO QD
3. Anti-coagulants
   a. Reduce stroke risk about 68%
   b. Indicated for moderate and high risk patients (see CHADS score above)
   c. Warfarin (Coumadin) acts by inhibiting the synthesis of vitamin K-dependent clotting factors (Factor II, VII, IX, and X, and protein C and S)
      - Adjust dose to achieve therapeutic INR 2–3
      - Risk of bleeding
      - High potential for drug interactions
   d. Dabigatran (Pradaxa), a direct thrombin inhibitor indicated for non-valvular AF
      - 150mg BID for CrCl >30mL/min; 75mg BID for CrCl 15–30mL/min
      - Most common adverse reactions are gastritis-like symptoms and bleeding
   e. Rivaroxaban (Xarelto), a factor Xa inhibitor indicated for non-valvular AF
      But also has indications for treatment of DVT and prophylaxis of DVT in patients undergoing knee or hip surgery
      - Dosing for AF: 20mg QD for CrCl >50mL/min; 15mg QD for CrCl 15–50mL/min
      - Take with evening meal
      - Most common adverse reaction: bleeding
      - Potential for drug interactions with drugs metabolized by CYP3A4 and P-gp
   f. Apixaban (Eliquis), a factor Xa inhibitor indicated for non-valvular AF
      - Recommended dose: 5mg BID
      - In patients with at least 2 of the following: age ≥80 yr, weight ≤60 kg, or Scr ≥1.5mg/dL: 2.5mg BID
      - Most common adverse reaction: bleeding
      - Potential for drug interactions with drugs metabolized by CYP3A4 and P-gp

D. Definitive therapy
1. Surgical therapies
   a. Disruption of abnormal conduction pathways in the atria
2. Ablation
   a. Patients with paroxysmal afib or persistent afib
   b. More effective: 60% success rate first ablation, 80% success rate second ablation

CLINICAL PEARLS
- 70–80% of patients with new onset atrial fibrillation will spontaneously convert to NSR within the first 24hrs
- The sooner atrial fibrillation is converted, the better the chances of success
- The loss of coordinated atrial contraction that occurs with atrial fibrillation causes a 10–20% decrease in cardiac output at a normal rate, and a reduction in diastolic filling time when the response is rapid < 100–120
- In the presence of atrial fibrillation without mechanical valves, anticoagulation can be interrupted for up to 1 week for surgical procedures

References
49. AMBULATORY POST-MI MANAGEMENT

I. IDENTIFY PATIENTS AT HIGH RISK FOR FUTURE EVENTS POST-MYOCARDIAL INFARCTION (MI): Patients at high risk, consider cardiology referral and cardiac catheterization

A. Poor left ventricular (LV) function (EF < 45%): By ECHO or cardiac catheterization. Patients with an EF of 20–44% have a 12% 1-yr mortality

B. Recurrent ischemia post-MI

C. Multiple cardiac risk factors: Post-MI patients with 4 risk factors have ~ 60% 2-yr mortality

D. Location and extent of infarct: Anterior infarct has highest 1-yr mortality

E. Ventricular arrhythmias: If a patient has > 10 PVCs/hr compared to < 1 PVC/hr, the 1-yr mortality is 18% compared to 3% (indication of poor LV function)

F. Number of vessels with atherosclerotic disease: 1-yr mortality is increased from 2% to 12% with triple vessel disease compared to single vessel disease

II. DIAGNOSTIC TESTING

Most patients will have at least 1 of these 3 tests before hospital discharge

A. Stress testing: Submaximal testing 4–6 days post-MI or symptom limited at 10–14 days. See Chapter 50, Cardiac Stress Testing. This should be followed with a maximal stress test 3–6 weeks post-MI. If either is positive, cardiac catheterization should be strongly considered

B. Cardiac ECHO: To assess LV function and ejection fraction, wall motion, valves, septal defects, papillary muscle function. If the prehospital discharge ECHO shows LV dysfunction (EF < 45%), patients should be strongly considered for cardiac catheterization

C. Cardiac catheterization: The gold standard test recommended for patients at high risk of future events or if above tests are positive

III. INDICATIONS FOR CARDIAC CATHETERIZATION/STATISTICS

Of 100 patients admitted with acute MI:

A. 20 patients will have severe ischemia or severe pump failure during their hospital admission. Recommendation: Cardiac catheterization

B. 20 patients will become symptomatic during a submaximal stress test prior to hospital discharge. Recommendation: Cardiac catheterization

C. 10 patients will become symptomatic during maximal stress testing 3–6 weeks post-discharge. Recommendation: Cardiac catheterization

D. The remaining 50 patients will be at low risk with a 0–5% 1-yr mortality. One half of the remaining 50 patients will undergo cardiac catheterization within 1yr. Medical management and risk factor modification should be aggressively pursued

IV. MANAGEMENT

A. Risk factor modification post-MI: Strongly encourage treatment, compliance, and/or behavioral modification of the following risk factors. Patients with 4 risk factors have a 2-yr mortality which is 60% compared to 5% in patients with 1 risk factor (see related chapters)

1. Smoking

2. Hypertension: Reduction of mortality by 20% with successful reduction of blood pressure

3. Diabetes: Presence of diabetes increases 1-yr mortality post-MI by 25%

4. High cholesterol: Target LDL post-MI is < 70mg/dL

5. Sedentary lifestyle, obesity, depression

B. Cardiac rehabilitation: Most post-MI patients will benefit, although the extent of rehabilitation will have to be tailored to a patient’s specific situation. Mortality may be decreased by up to 25% with participation in cardiac rehab

C. Medical management post-MI (Meds with proven efficacy to decrease mortality
include aspirin, Clopidogrel (Plavix), β-blockers, ACE inhibitors, and HMG-CoA reductase inhibitors/statins

1. **Aspirin**: Indicated for all patients unless allergic. Peptic ulcer disease is not a contraindication
   a. The ISIS 2 trial showed that Aspirin reduced vascular death by 23% and reduced nonfatal infarctions by 49% post-MI
   b. Aspirin would save 5,000 lives/yr if given to all post-MI patients, yet as many as 28% of post-MI patients do not receive it. Aspirin has an approximate cost of $13 per life saved (dose: 81mg/day)
   c. Consider **Clopidogrel (Plavix)** 75mg/day for one year or indefinitely if aspirin contraindicated

2. **β-blockers**
   a. The β-blocker Heart Attack Trial (BHAT) showed that β-blockers (which reduce the heart rate) reduced sudden death by 32%, recurrent infarction by 27%, and overall cardiac mortality by 22% post-MI. The benefit is more pronounced in patients with co-morbid factors of angina, prior heart failure or arrhythmia
   b. Should be administered within hours post-MI
   c. Avoid Labetalol and intrinsic sympathomimetics such as Acebutolol and Pindolol

3. **Angiotensin converting enzyme (ACE) inhibitors**: Studies suggest a reduction in incidence of sudden cardiac death and nonfatal subsequent infarctions following myocardial infarction. ACC/AHA guidelines recommend that ACE inhibitors should be started within 24hrs post-MI and continued 4–6 weeks in patients without LV dysfunction and at least 3 years in patients with LV dysfunction. Use ARBs in patients who are ACE inhibitors-intolerant and who have signs of heart failure or LVEF < 40

4. **Statins**
   a. The goal for post-MI patients with hypercholesterolemia is LDL< 70mg/dL
   b. For further guidelines and drug doses/side effects, etc., see Chapter 44, Hyperlipidemia

5. **Anticoagulants**: Indicated when there are other conditions that would benefit from treatment with oral anticoagulation (example: atrial fibrillation)

6. **Nitrates**: If a patient has to use PRN nitrates post-MI, strong consideration should be given to cardiac catheterization if it has not been performed

7. **Calcium channel blockers**
   a. Should not be used for secondary prevention post-MI except possibly in non-Q-wave MI where the EF has been preserved and there is no evidence of CHF
   b. **Nifedipine** should not be used post-MI as it has been shown to increase mortality

8. **Antiarrhythmics**: Although effective at suppressing ventricular ectopy, the CAST study showed that certain antiarrhythmics increased mortality post-MI. Therefore, they should not be routinely used post-MI

**CLINICAL PEARLS**

- In first year after an acute myocardial infarction (MI), mortality ranges from 6–19%. Subsequent mortality is 3–4%/yr
- There is early evidence that stopping a statin on admission to the hospital for acute MI increases mortality

**References**
Muhlestein JB. Post-hospitalization management of high-risk coronary patients. Am J Cardiol 2000;85:13B–20B.
Chen J, et al. Beta-blocker therapy for secondary prevention of myocardial infarction in elderly diabetic patients. Results from the National Cooperative Cardiovascular Project. J Am Coll...
50. CARDIAC STRESS TESTING

I. INDICATIONS FOR EXERCISE STRESS TESTING
(Those listed below do not address patients who have had a recent MI). Before ordering the test, assess the pretest and posttest likelihood of a positive result. If a positive test on an asymptomatic patient will be dismissed as a false positive, then do not perform the test. If a patient with symptoms suggestive of angina and multiple risk factors has a negative test and cardiac catheterization will be performed anyway, consider proceeding directly to the catheterization.

A. Initial evaluation in patients with suspected or known CAD
B. Patients with suspected or known CAD with a significant change in clinical status
C. Low risk unstable angina patients who have been symptom free for 8–12 hrs
D. Intermediate risk unstable angina patients with normal cardiac markers for 12 hrs after onset of symptoms and normal repeat ECG
E. Stable patients undergoing periodic monitoring to guide treatment
F. Asymptomatic patients with diabetes mellitus who plan to start vigorous exercise
G. Asymptomatic men > 45 and women > 55 who:
   1. Plan to start vigorous exercise
   2. Are in occupations where impairment might endanger public safety
   3. Are at high risk for CAD due to other diseases (PVD, CRF)
H. Chronic aortic regurgitation with equivocal symptoms, before participation in exercise, before valve replacement
I. Evaluation of exercise capacity in patients with valvular heart disease

II. AMERICAN HEART ASSOCIATION GUIDELINES
A. Absolute contraindications to exercise testing
   1. Acute myocardial infarction (within 2 days)
   2. High-risk unstable angina
   3. Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
   4. Symptomatic severe aortic stenosis
   5. Uncontrolled symptomatic heart failure
   6. Acute pulmonary embolus or pulmonary infarction
   7. Acute myocarditis or pericarditis
   8. Acute aortic dissection
B. Relative contraindications to exercise testing
   1. Left main coronary stenosis
   2. Moderate stenotic valvular heart disease
   3. Electrolyte abnormalities
   4. Severe arterial hypertension (suggested definition: systolic blood pressure > 200 mm Hg and/or diastolic blood pressure > 100 mm Hg)
   5. Tachyarrhythmias or bradyarrhythmias
   6. Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
   7. Mental or physical impairment leading to inability to exercise adequately
   8. High-degree atrioventricular block
50. Cardiac Stress Testing

C. Pretest probability of coronary artery disease by age, gender and symptoms

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Gender</th>
<th>Typical/Definite Angina Pectoris</th>
<th>Atypical/Probable Angina Pectoris</th>
<th>Nonanginal Chest Pain</th>
<th>Asymptomatic</th>
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<tbody>
<tr>
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<td>Low</td>
<td>Very low</td>
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<tr>
<td></td>
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<td>Very low</td>
<td>Very low</td>
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<tr>
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<td>60–69</td>
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<td>Women</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
</tbody>
</table>


III. TYPES OF EXERCISE AND OTHER TESTS

A. Exercise EKG: Exercise EKG alone without the addition of an imaging procedure is useful for differentiating low- and high-risk patients with chest pain. The demonstration of 1.0mm or more of horizontal or downsloping ST segment depression at low exercise heart rates or workloads is a significant predictor of an adverse outcome. A very rapid heart rate recovery immediately after exercise was associated with a lower risk of cardiovascular disease events in the Framingham study.
1. Advantages: Inexpensive, fast, objective assessment of exercise-induced symptoms
2. Disadvantages: Requires ability to exercise, reduced accuracy in patients with abnormal baseline EKG, does not localize disease
3. Can be non-diagnostic in many situations: Resting ST-T wave abnormalities, LVH, pre-excitation, Digoxin therapy, female gender (stress ECHO more cost-effective), mitral valve prolapse, LBBB, ventricular pacer
4. Sensitivity 50–67% and specificity 72–90%

B. Stress ECHO: A positive test is based on the stress-induced presence of a regional decrease in wall motion, a regional decrease in wall thickening, or regional compensatory hyperkinesis. Cardiac stress may be induced with exercise or with pharmacologic agents. Dobutamine is the preferred pharmacologic agent due to its greater effect on wall motion.
1. Advantages: No radiation exposure, less expensive/time-consuming than nuclear scans, able to localize disease, results are immediately available, can assess valvular and aortic disease
2. Disadvantages: Interpretation is subjective, slightly lower sensitivity for CAD than SPECT scanning, not a feasible test in 5–10% due to obesity or COPD

C. SPECT perfusion imaging: The major prognostic variables on stress perfusion images predictive of future cardiac events are:
• A defect size >20% of the left ventricle
50. Cardiac Stress Testing

- Multiple perfusion abnormalities in 2 or more coronary supply regions suggestive of multivessel CAD
- Defect reversibility reflective of inducible ischemia in multiple myocardial segments, even in the distribution of one major coronary artery
- A large number of nonreversible defects
- Transient left ventricular cavity dilation from stress to rest images
- A resting left ventricular ejection fraction of less than 40% measured on gated SPECT

1. Advantages: Localization of disease, better able to identify “borderzone” ischemia, quantification of EF, can be combined with pharmacologic stress (vasodilators such as Adenosine or Persantine have less side effects than Dobutamine)

2. Disadvantages: More expensive than stress ECHO, more time-intensive, radiation exposure, inability to assess valvular/aortic/pericardial disease

3. Nuclear imaging is the preferred modality for patients with expected suboptimal ECHO windows, or with LBBB or pacer. Also preferred in those patients with prior revascularization or prior MI

4. Sensitivity and specificity about 83–85% and specificity about 70–90%

D. Electron Beam Computed Tomography (EBCT)

1. Coronary calcium is a surrogate marker for coronary atherosclerotic plaque. In the coronary arteries, calcifications occur almost exclusively in the context of atherosclerotic changes

2. Within a coronary vessel or larger segment of the vessel, the quantity of coronary calcium correlates moderately closely with the extent of atherosclerotic plaque

3. In the vast majority of patients with acute coronary syndromes, coronary calcium can be detected, and the amount of calcium in these patients is substantially greater than in matched control subjects without coronary artery disease

4. The complete absence of coronary calcium makes the presence of significant coronary luminal obstruction highly unlikely

5. Several cohort studies have shown that the presence of coronary calcium demonstrated by EBT in asymptomatic individuals is a prognostic parameter with high predictive power regarding the development of cardiac events during the following 3–5 years

6. Individuals who seem to be at intermediate risk for coronary events (0.6–2.0% annual risk) based on traditional risk factor analysis will be most likely to profit from noninvasive testing for subclinical atherosclerosis, such as the assessment of coronary calcification

E. Cardiac MRI

1. Currently useful for an assessment of congenital heart disease and diseases of the aorta and pericardium

2. When compared with cardiac catheterization, MRI has both advantages and disadvantages
   a. Disadvantages:
      i. Noninvasive
      ii. Like Doppler echocardiography, it is unable to measure pressure directly
      iii. It cannot readily measure oxygen saturation
   b. Advantages
      i. Noninvasiveness
      ii. Ability to measure flow and to map velocities through obstructive lesions
      iii. Ability to obtain tomographic views of complex three-dimensional anatomy. In cases where shunting or stenoses of large vessels are concerned especially when these are combined with anatomical deformation, magnetic resonance with velocity mapping can offer the surgeon more comprehensive information, more safely and more economically than the catheter laboratory

CLINICAL PEARLS

- Failure to achieve 80–85% of predicted maximum heart rate (or rate adjusted to MET level) is associated with 84% increase in all cause mortality over the next 2 years
- Abnormal heart rate recovery is associated with increased all cause mortality at 6 years
51. Shortness of Breath

A. Upper airway causes
   1. Tracheal obstruction (cancer, foreign body, mucous plug)
   2. Infectious: epiglottitis, croup
   3. Angioedema/anaphylaxis
   4. Retropharyngeal abscess

B. Pulmonary causes
   1. Obstructive lung disease (COPD: asthma, chronic bronchitis, emphysema)
   2. Infection (pneumonia, bronchitis, TB)
   3. Pneumothorax
   4. Pulmonary embolism, fat, air, or amniotic fluid embolism
   5. Pleural effusion
   6. Lung masses, metastatic disease
   7. Restrictive lung diseases
      a. Extrathoracic: Chest wall restriction (kyphoscoliosis, obesity, ascites), diaphragmatic dysfunction, abdominal distention, pregnancy
      b. Intrathoracic: Infiltrate, infiltrative process (sarcoidosis, amyloidosis, pulmonary fibrosis), pneumonectomy, parenchymal process
   8. Pulmonary hypertension
   9. Adult respiratory distress syndrome (ARDS)
   10. Carbon monoxide toxicity
   11. Cystic fibrosis

C. Cardiac causes
   1. Congestive heart failure (pulmonary edema)
   2. Acute MI/anginal equivalent/myocardial ischemia
Cardiac & Pulmonary Disorders

51. Shortness of Breath

3. Cardiac arrhythmias (atrial fibrillation, ventricular tachycardia)
4. Cardiac valvular disease
5. Pericarditis/pericardial tamponade/myocarditis
6. Hypertensive crisis

D. Systemic causes
1. Noncardiogenic pulmonary edema: Drug OD, pancreatitis, trauma, sepsis, inhalation of toxic chemicals
2. Anemia
3. Diabetic ketoacidosis (DKA)/metabolic acidosis
4. Gastroesophageal reflux (GERD)
5. Hyper-/hypothyroidism
6. Deconditioning
7. Carbon monoxide poisoning, methemoglobinemia

E. Central causes
1. Panic disorder/anxiety
2. Acute hyperventilation
3. Cheyne-Stokes (rapid breathing): Seen in coma from intracerebral pathology
4. CNS/systemic neuromuscular disorders, such as CVA, phrenic nerve paralysis, Guillain Barre, tick paralysis, botulism
5. Multiple sclerosis
6. Phrenic nerve dysfunction
7. Sleep apnea

II. HISTORY

A. History of Present Illness (HOPI)
1. General: Fever, night sweats, or weight loss
2. ENT: Sore throat, dysphonia, dysphagia, acuity of onset, drooling/inability to handle secretions, recent pharyngitis
3. Respiratory
   a. SOB: Acuity of onset and duration of symptoms, exacerbaters, and relievers, relation to exertion or environmental exposure, relation to chest discomfort, associated orthopnea/paroxysmal nocturnal dyspnea
   b. Other: Cough (productive vs. dry, duration, exacerbaters, and time of day), hemoptysis
4. Cardio: Chest discomfort, heart racing, or palpitations
5. Extremities: Peripheral edema
6. Other: Work and travel exposures, anxiety/depression

B. Past Medical/Surgical History
1. Previous diagnoses of shortness of breath, cardiac or pulmonary disease, CAD risk factors, history of diabetes, history of previous DVT/PE, prolonged immobility, or oral contraceptive use
2. Recent infections
3. Medications
4. Smoking history
5. Home oxygen use

III. PHYSICAL EXAMINATION

A. Vital signs: Fever, tachypnea, tachycardia/bradycardia, hypotension, oxygen saturation
B. HEENT: Assess JVD, tracheal deviation, periorbital cyanosis, glossal deviation, peritonsillar/tracheal deviation, other upper airway obstruction
C. Chest: Rales/crackles, rhonchi, increased A-P chest wall diameter (COPD), dullness to percussion/decreased breath sounds, wheezing (asthma, pulmonary edema, foreign body), stridor, palpable crepitus
D. Cardiac: Gallop, murmur, rub, distant heart sounds (pericardial tamponade), loud P2 (pulmonary HTN), jugular venous distention (JVD)
E. Extremities: Clubbing, cyanosis, edema, unilateral edematous or tender leg (DVT)

IV. TESTS
51. Shortness of Breath

A. Radiology:
   1. Obtain PA and lateral CXR
   2. Pleural effusions are best seen at the costophrenic angle on the lateral film
   3. Pneumonia is a clinical diagnosis as CXR findings of pneumonia may lag behind clinical findings
   4. Assess for pneumothorax, heart size, rib fracture, mediastinal widening/deviation, or free air under the diaphragm
   5. Lateral neck films should be considered to evaluate for upper airway compromise

B. ABG:
   Assess pH, pO₂, pCO₂

C. ECG:
   Should be performed in any patient > 30 and all patients with history of CAD or diabetes with undiagnosed dyspnea. In addition to signs of ischemia/infarction and arrhythmias, look for signs of pericarditis, pericardial effusion/tamponade, pulmonary embolism, and COPD

D. Pulse oximetry: Measures oxygenation only. Rest and exercise oximetry may reveal oxygen desaturation (early finding in interstitial lung disease and pulmonary HTN, pneumocystis pneumonia.) The pulse oximetry may be limited by nail polish, hypothermia, severe vasoconstriction, carboxyhemoglobin, or methemoglobinemia, shock

E. Pulmonary function testing
   1. Indications
      a. Evaluation of pulmonary dysfunction: Obstructive vs. restrictive impairment
      b. Evaluation of dyspnea and cough
      c. Evaluation of response to therapy
      d. To determine if there is bronchial reactivity: Methacholine challenge
      e. To determine if there is a reversible component to obstructive lung disease
      f. Preoperative evaluation in selected patients (see Chapter 107, Preoperative Evaluation)
      g. Evaluation of upper airway obstruction with a flow-volume loop
   2. Examples of changes in PFTs with various pulmonary disorders:

<table>
<thead>
<tr>
<th>Tests</th>
<th>Obstructive†</th>
<th>Empysema</th>
<th>Restrictive‡</th>
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<tbody>
<tr>
<td>FEV₁ (Liters)</td>
<td>↓ ↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>FVC (Liters)</td>
<td>↓ ↓</td>
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<tr>
<td>FEV₁ / FEV%</td>
<td>↓ ↓</td>
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<tr>
<td>RV (Liters)</td>
<td>↑ ↑</td>
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<tr>
<td>TLC (Liters)</td>
<td>Normal or ↑</td>
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<tr>
<td>DLCO</td>
<td>Normal or ↑</td>
<td>↓ ↓</td>
<td>Normal or ↓</td>
</tr>
</tbody>
</table>

† For examples of obstructive/restrictive lung diseases, see Section I, Differential Diagnosis
FEV₁ (forced expiratory volume in 1 second), FVC (functional residual capacity), RV (residual volume), TLC (total lung capacity), DLCO (diffusing capacity of carbon monoxide)


F. Chest CT: Used primarily as a follow-up of abnormal CXR

G. Ventilation-perfusion scan/helical CT/pulmonary angiography: See below for evaluation for PE

H. Laboratory:
   Based on history and physical
   1. CBC (elevated WBC, anemia, etc.), electrolytes, BUN/creatinine, glucose
   2. Thyroid functions tests
   3. Alpha-anti-trypsin

I. Bronchoscopy indications
   1. Evaluation of hemothysis
   2. Diagnosis and staging of bronchogenic carcinoma, biopsy of tracheal or 2nd–4th generation bronchial tumors
   3. Diagnosis of lung infiltrates and certain pulmonary infections including PCP and TB
   4. Removal of foreign bodies

J. Cardiopulmonary exercise testing: If clinical presentation suggests cardiac etiology or if workup is negative

V. EVALUATION FOR PULMONARY EMBOLUS

A. Estimated 650,000 cases/yr in the US with 200,000 deaths
B. Deep venous thrombosis (DVT) is the etiology in 80–90% of cases.
C. The classic triad of dyspnea, hemoptysis, and pleuritic chest pain occurs in < 20% of patients. See table below for signs and symptoms in patients with PE.
D. ECG: Sinus tachycardia is the most common finding, plus new RBBB, p-pulmonale, S1Q3T3 (rarely), and 40% have non-specific ST-T wave changes.
E. CXR: Usually normal or with non-specific findings. May have infiltrate or atelectasis in 50%. Beware of a normal CXR in the setting of dyspnea and hypoxia. Hampton’s hump (a wedge shaped pleural based infiltrate) and Westermark’s sign (relative oligemia distal to engorged pulmonary arteries with massive PE) are uncommon.
F. ABG: PaO₂ may be normal but is often decreased, may see hypocapnia or increased A-a gradient (see Chapter 123, Formulas). Not helpful in outpatient setting.
G. Laboratory: D-Dimer should be used in conjunction with the estimated pretest probability of PE. Best reserved for ED setting.
1. ELISA test has a sensitivity of 98% and a specificity of 30–40% and can be used to exclude PE (especially in a low-risk patient).
H. CT pulmonary angiography: Gold standard for diagnosis of PE. Will also screen for other pulmonary etiologies of symptoms.
I. Ventilation Perfusion (V/Q) scan: Reserved for patients for whom CT pulmonary angiography is contraindicated (allergy to contrast, increased risk of contrast induced nephropathy). False positives are increased in patients who have an infiltrate on CXR, preexisting cardiopulmonary disease, and history of previous PE. Will give 1 of 4 different categories including:
1. Normal: No perfusion defects
2. Low probability: < 20% chance of PE
3. Intermediate probability: 20–80% chance of PE
4. High probability: > 80% chance of PE

<table>
<thead>
<tr>
<th>Symptoms and Signs of 327 Patients with Angiographically Proven PE</th>
<th>Total Series, %</th>
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</thead>
<tbody>
<tr>
<td>Symptom</td>
<td>Total Series, %</td>
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<tr>
<td>Chest pain</td>
<td>88</td>
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<tr>
<td>Pleuritic</td>
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<td>Non-pleuritic</td>
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<td>Dyspnea</td>
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<tr>
<td>Apprehension</td>
<td>59</td>
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<tr>
<td>Cough</td>
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<td>Hemoptysis</td>
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<tr>
<td>Sweats</td>
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<td>Sign</td>
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<td>Respirations &gt; 16/min</td>
<td>92</td>
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<tr>
<td>Rales</td>
<td>58</td>
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<tr>
<td>P2 &gt; S2</td>
<td>53</td>
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<tr>
<td>Pulse &gt; 100/min</td>
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<tr>
<td>Temperature &gt; 37.8°C</td>
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<tr>
<td>Phlebitis</td>
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<tr>
<td>Gallop</td>
<td>34</td>
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<tr>
<td>Diaphoresis</td>
<td>36</td>
</tr>
<tr>
<td>Edema</td>
<td>24</td>
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<tr>
<td>Edema</td>
<td></td>
</tr>
<tr>
<td>Murmur</td>
<td>23</td>
</tr>
</tbody>
</table>


CLINICAL PEARLS
- Tachypnea is the most common sign of pneumonia in the elderly
- Virchow’s triad includes venous stasis, hypercoagulability, and endothelial damage and are factors contributing to the development of DVT
- In immunocompromised patients, dyspnea is often the initial manifestation of Pneumocystis pneumonia
- Steroids should be given early to asthmatics to minimize their chances of hospital admission
- Note that orthopnea may be seen in patients with severe dyspnea regardless of etiology as diaphragmatic mechanics are improved in the upright position

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52. Community-Acquired Pneumonia

I. DEFINITION
A. An acute infection of the pulmonary parenchyma associated with:
   1. Symptoms of acute infection—and——
   2. Physical examination and clinical findings consistent with pneumonia and/or presence of an acute infiltrate on CXR
B. Pneumonia is considered nosocomial (not community-acquired) if the patient has been hospitalized or treated in an ECF for 14 days prior to presentation of current illness

II. SIGNIFICANCE
A. Up to 5.6 million cases/yr with as many as 1.1 million hospitalizations
B. Annual incidence in children < 5 is 34–40 cases/1000 in Europe and North America
C. Annual incidence of pneumonia in patients > 65 is approx. 1%
D. Combination of community acquired pneumonia (CAP) and influenza ranks as the sixth leading cause of death in the US. Mortality has remained fairly consistent at approx. 25% over the last 4 decades, despite advances in ATBs and critical care medicine. Mortality in outpatients is less than 1%

III. ETIOLOGY
A. Neonate: Group B Streptococcus, Listeria monocytogenes, Gram negative enteric bacteria, (E.Coli, Klebsiella), Chlamydia trachomatis (neonate to 3 months), Viral pathogens, (CMV, HSV, Rubella)
B. < 1 year: Viral pathogens, (RSV, parainfluenza, influenza, adenovirus, rhinovirus), Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus
C. > 1 year: Streptococcus pneumoniae, Haemophilus influenzae. Staphylococcus aureus, Viral pathogens, (influenza, parainfluenza, adenovirus, rhinovirus), Chlamydia pneumoniae, Mycoplasma (school-age children)
D. Adult: Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Mycoplasma pneumoniae, Gram-negative bacilli, viruses, Staphylococcus pneumoniae, Legionella pneumoniae, Chlamydia pneumoniae, Mycobacterium tuberculosis, Pneumocystis carinii

References
Cardiac & Pulmonary Disorders 52. Community-Acquired Pneumonia

E. Elderly, ECF resident: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, Anaerobic organisms, (in cases of suspected/possible aspiration), MSSA, MRSA


IV. DIAGNOSIS

A. History

1. Symptoms
   a. General: Fever/chills/rigors, fatigue, generalized malaise
   b. Respiratory: Cough—productive or nonproductive, dyspnea, pleuritic chest pain
   c. Musculoskeletal: Myalgia/arthralgia

2. Timing and temporal relationship of preceding symptoms
   a. Sudden onset: Indicative of “classic” pneumococcal pneumonia
   b. Preceding influenza pneumonia: “Classic” precedent to staphylococcal pneumonia

3. Risk Factors for pneumonia: Extremes of age, smoker, severe illness or immunocompromised state, ECF resident, EtOH abuse, HIV/AIDS, aspiration risk factors

B. Physical examination

1. Vitals signs: Febrile, tachypneic, tachycardic, check for hypoxia
2. Assess hydration: Mucous membranes, skin turgor, urine output
3. Lung exam
   a. Inspection: Retractions, accessory muscle use, asymmetry in inspiration secondary to splinting
   b. Auscultation
      i. Rales (Crackles) most common finding in CAP
      ii. Rhonchi
      iii. Bronchial breath sounds due to consolidation
      iv. Whispered pectoriloquy, present at consolidation
      v. Egophony, present at consolidation
   c. Palpation
      i. Tactile fremitus presents at consolidation
      ii. Percussion asymmetry present secondary to consolidation (dull over consolidation)

4. Additional findings to lead diagnosis and therapy
   a. Signs of immunocompromised state (lymphadenopathy, thrush, Kaposi’s sarcoma, wasting)
   b. Signs of malignancy (as above plus weight loss, smoking history, clubbing)

C. Radiographic findings

1. Recommended for all patients suspected of pneumonia
2. Helps to predict severity of disease: Multilobar infiltrates and pleural effusions are associated with increased mortality
3. CXR may be falsely negative in dehydrated patients
4. “Classic” findings
   a. Lobar infiltrate: Most commonly associated with *Streptococcus pneumoniae*
   b. Pleural effusion: Streptococcal, staphylococcal, or anaerobic infection
   c. Nodular or reticular infiltrates: *Mycoplasma* or Chlamydial atypical organisms
   d. Cavity with air-fluid level: Anaerobic lung abscess
   e. Upper-lobe cavitary lesion: *Mycobacterium tuberculosis*
   f. Diffuse bilateral infiltrates: *Pneumocystis carinii* pneumonia, viral

D. Laboratory evaluation

1. Oxygenation
   a. Pulse oximetry: Admit patients with hypoxia
   b. Arterial blood gas: Consider ordering in patients with history of COPD, suspicion of pulmonary embolus, or hypoxia. \( \text{pO}_2 < 60\text{mmHg} \) is predictive of increased mortality

2. Sputum stain/culture: Often not useful in ambulatory CAP, because of high number
of negative gram stains and cultures
3. Blood culture: Not necessary for outpatient therapy. Only 5–14% of hospitalized patients with CAP will have positive blood cultures and do not usually result in a change in therapy
4. CBC: Leukocyte count should not guide diagnosis or treatment—it has not been shown to affect mortality
5. Electrolytes
   a. Hyponatremia occurs with CAP, most commonly with *Legionella pneumonia*. 
      
   b. HIV status: Check in any patient with risk factors or suspected opportunistic pneumonia, (PCP, fungal, etc.)
6. Legionella and pneumococcal antigen—obtain with severe CAP, risk factors

V. ADMISSION CRITERIA—Consider admission for the following:
A. There are various prognostic models including the CURB-65 criteria (Confusion, Uremia, Respiratory rate, low Blood pressure, age ≥ 65) and the Pneumonia Severity Index (PSI)—see below
B. Should be guided by clinical judgment and a determination if patient is able to reliably follow outpatient recommendations

VI. OUTPATIENT MANAGEMENT OF ADULTS
A. Previously healthy and no use of antimicrobials within the previous 3 months
   1. **Macrolide** (strong recommendation)—Azithromycin (Zithromax), Clarithromycin (Biaxin) or Erythromycin
   2. **Doxycycline** (weak recommendation)
B. Presence of comorbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)
   1. A respiratory Fluoroquinolone (Moxifloxacin, Gemifloxacin, or **Levoﬂoxacin** [750 mg]) (strong recommendation)
   2. A β-lactam (Amoxicillin 1g TID or Augmentin XR 2g BID) plus **Macrolide** (strong recommendation; level 1 evidence)
      a. Alternative to β-lactam: Ceftriaxone, Cefpodoxime, Cefuroxime (500mg BID)
      b. Alternative to **Macrolide**: Doxycycline
C. In regions with a high rate (>25%) of infection with high-level Macrolide-resistant *Streptococcus pneumoniae*, consider use of alternative agents listed above in (B) for patients without comorbidities (moderate recommendation)
D. Both Fluoroquinolones and Macrolides have the potential for QTc prolongation that may lead to torsades de points
   1. Recent data showed that Azithromycin and Levoﬂoxacin were associated with the risk of cardiovascular death when compared to Amoxicillin, Ciprofloxacin, and placebo
   2. When choosing an antibiotic, consider the risk particularly in patients with existing QT prolongation, hypokalemia, hypomagnesemia, bradycardia, or concurrent antiarrhythmic drug therapy
E. For therapy of influenza (viral etiology of pneumonia) see VII. D. below

VII. VIRAL ETIOLOGY OF PNEUMONIA
A. **Influenza**: Responsible for 25,000 to 50,000 deaths annually in the US, predominantly in the elderly and in patients with underlying cardiopulmonary or metabolic diseases. Influenza-associated pneumonia should be considered in high-risk patients with underlying disease and in residents of chronic care facilities during October through May, especially in patients who haven’t been vaccinated
B. Respiratory Syncytial Virus (RSV): Though considered mainly an infection in pediatric populations, can lead to serious lower respiratory tract infections in adults during the
C. Severe Acute Respiratory Syndrome (SARS): The cause of rapidly progressive respiratory insufficiency with case fatality rate of 4–15%

1. Caused by the SARS-associated coronavirus (SARS-CoV)
2. Should be considered in any patient who, within the past 10 days, has traveled (including transit in an airport) to an area with documented or suspected SARS or close contact with a person known or suspected to have SARS
3. Signs and symptoms of SARS include: temperature >100.4° F (>38° C) and 1 or more clinical findings of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, or hypoxia), particularly if there is radiographic evidence of pneumonia or clinical evidence of the respiratory distress syndrome without another identifiable cause

D. Indications for therapy
1. Children less than 2 years old
2. Children less than 19 years old taking long-term aspirin
3. Patients over 65
4. Morbidly obese
5. Pregnant women up to 2 weeks post-partum
6. Persons of American Indian/Alaska Native heritage
7. Residents of nursing homes and other chronic care facilities
8. Immunosuppressed patients
9. Patients requiring hospitalization
10. Note: Healthy persons with uncomplicated influenza do not require treatment

Antiviral Drugs for Seasonal Influenza: 2013-2014

<table>
<thead>
<tr>
<th>Drug Formulations</th>
<th>Adult Dosage</th>
<th>Pediatric Dosage</th>
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<tbody>
<tr>
<td>Oseltamivir – Tamiflu® (Genentech)</td>
<td>30, 45, 75 mg capsules; 6 mg/mL oral suspension</td>
<td>75 mg PO once/d</td>
</tr>
<tr>
<td>Zanamivir – Relenza® (GSK)</td>
<td>5 mg blister for inhalation</td>
<td>2 inhalations (10 mg) once/d</td>
</tr>
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</table>

1. For post-exposure prophylaxis in households, a 10-day course is recommended. For prophylaxis of exposures in institutions, the drug should be taken for at least 2 weeks and continued for 1 week after the end of the outbreak. For prophylaxis during community outbreaks, oseltamivir has been shown to be effective and safe when taken for up to 42 days, and zanamivir for up to 28 days. Some experts would use twice-daily therapeutic doses for post-exposure prophylaxis in highly immunocompromised persons.
2. Hospitalized, critically ill, or immunocompromised patients may require longer treatment.
3. Approximate wholesale acquisition cost (WAC) for 5 days’ treatment at adult dosages. Source: Analy$ource® Monthly (Selected from FDB MedKnowledge™) January 5, 2014. Reprinted with permission by FDB, Inc. All rights reserved. ©2014. www.fdbhealth.com/policies/drug-pricing-policy. Actual retail prices may be higher.
4. In patients with GCI 10-30 mL/min, the dose should be 75 mg every other day or 30 mg once/d for prophylaxis and 75 mg once/d for treatment.
5. In adults with pneumonia or severe lower respiratory tract disease, some experts recommend 150 mg bid x 10 days for treatment (off-label).
6. Dose for children ≤1 yr old: ≤15 kg: 30 mg; 16-23 kg: 45 mg; 24-49 kg: 60 mg; ≥50 kg: 75 mg (once daily for prophylaxis and twice daily for treatment). Although not FDA-approved for prophylaxis for children <1 year, the ACIP and CDC recommend that children 3 months to <1 year old receive 3 mg/kg once/d. The FDA-approved dose for treatment of infants ≥2 weeks to <1 year old is 3 mg/kg bid. The American Academy of Pediatrics recommends 3.5 mg/kg once daily for prophylaxis and twice daily for treatment for infants 6-11 months old.
7. Not recommended for use in patients with underlying respiratory disease such as asthma or COPD.
8. Available in a carton containing 5 rotadisks (each rotadisk contains four 5-mg blisters of the active drug in a lactose carrier) and a Diskhaler inhalation device. Zanamivir should not be used in a nebulizer.

VIII. OUTPATIENT FOLLOW-UP
A. Advise patient to call or return to office for fever > 102°, worsening shortness of breath, inability to swallow meds or remain hydrated, chest pain, hemoptysis, or failure to improve after 2 days of therapy
B. Follow-up CXR not necessary: CXR findings may take weeks or months to return to normal.
Follow-up CXR is warranted if suspicion of underlying pathology (e.g., malignancy)

IX. PREVENTION

A. Pneumococcal polysaccharide antigen vaccine: Risk for acquiring complications of pneumonia is reduced by 2/3 following vaccination, indicated for:
   1. Asplenic patients
   2. Immune-competent patients > 65
   3. Diabetes
   4. COPD
   5. Chronic renal failure
   6. Malignancy
   7. CAD and CHF
   8. Chronic liver disease
   9. HIV/AIDS
   10. Consider in any chronic, debilitating illness

B. Pneumococcal conjugate vaccine in pediatric population—effective in decreasing pediatric pneumococcal pneumonia

C. Influenza vaccine: Indicated yearly for all patients at risk for pneumonia

CLINICAL PEARLS

- *Pneumococcus* remains the number-1 agent of bacterial pneumonia in children and adults
- Presence of dementia or confusion in an elderly patient increases the likelihood of a chest film being positive for pneumonia. Dementia/confusion may be the only symptom in elderly patients with pneumonia
- Most common pneumonia in patients with HIV is pneumococcal pneumonia. Ask about risk factors and evaluate for signs of HIV including thrush, oral hairy leukoplakia, seborrheic dermatitis
- Treat early—delay in ATB therapy associated with increased mortality
- Treat empirically: Gram stains are not helpful
- The most common mechanism by which the lung is inoculated with pathogenic organisms is through microaspiration of oropharyngeal contents, a process that occurs in otherwise healthy individuals during sleep

References


Available at: www.journals.uchicago.edu/doi/pdf/10.1086/511159


53. Asthma in Adults

(Based on 2007 NAAEP expert panel report)

I. GENERAL
   A. Affects 5% of the population, resulting in almost 500,000 admissions/yr and 5,000 deaths/yr
   B. Death rates are highest for blacks 15–24yrs

II. PATHOGENESIS AND LONG TERM CONTROL
   A. Chronic inflammatory condition resulting in airway obstruction and airway hyperresponsiveness to various stimuli (see below)
   B. Asthma may be precipitated by sinusitis, gastroesophageal reflux, URIs, exercise, post nasal drip, or exposure to tobacco smoke
   C. Asthma changes over time
   D. 4 factors to consider in long term control of asthma
      1. Assessment and monitoring
      2. Control of factors contributing to asthma
      3. Pharmacologic therapy
      4. Patient education

III. HISTORY
   A. Symptoms: Wheezing, cough (may be the only manifestation), shortness of breath, chest tightness, nocturnal symptoms
   B. Duration of symptoms
   C. Frequency of symptoms (how many days/nights per week or month)
   D. Medications attempted in the past and response to meds
   E. Exacerbating factors: Smoking, household with dust/mites, cockroaches, exercise
   F. Associated medical conditions: Atopic dermatitis, allergic rhinitis, Aspirin/NSAID allergy
   G. Family history: Asthma, allergy, sinusitis, rhinitis

IV. PHYSICAL EXAM
   A. General: Pulse, respiratory rate, temperature
   B. ENT: Nasal mucosa swelling, increased nasal secretions, nasal polyps, vocal wheezing
   C. Respiratory: Tachypnea, retractions, wheezing (may elicit by having patient perform a forced expiration), hyperexpansion of thorax, rhonchi
   D. Skin: Eczema, atopic dermatitis

V. DIFFERENTIAL DIAGNOSIS
   A. Upper airway disorders: Vocal cord paralysis or dysfunction, foreign body aspiration, upper airway mass, tracheal narrowing, tracheomalacia, airway edema (angioedema/inhalation)
   B. Lower airway disorders: COPD, bronchiectasis, cystic fibrosis, eosinophilic pneumonia, bronchiolitis obliterans
   C. Systemic vasculitides: Churg-Strauss syndrome
   D. Psychiatric disorders: Conversion disorder, emotional laryngeal wheezing

VI. DIAGNOSIS
   A. History of episodic symptoms of airway obstruction including wheezing, shortness of breath, tightness in chest, or cough
   B. Reversibility of airway obstruction
      1. Spirometry
         a. Performed before and after inhaled bronchodilator therapy
         b. Establish obstruction: FEV₁ < 80% predicted or FEV₁/FVC ratio < 65% predicted
         c. Establish reversibility: FEV₁ increases > 12% or 200mL after use of a short-acting inhaled β₂-agonist
      2. Peak expiratory flow meters: There is variability depending on which is used, but good correlation to follow and assess the severity of symptoms. 20% variability from morning to afternoon suggests asthma
VII. MANAGEMENT

A. Stepwise approach for adults and children ≥ 12 years of age

**Intermittent Asthma**
Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

### Step 1
**Preferred:** SABA PRN

### Step 2
**Preferred:** Low-dose ICS
**Alternative:** Cromolyn, LTRA, Nedocromil, or Theophylline

### Step 3
**Preferred:** Low-dose ICS + LABA
**Alternative:** Medium-dose ICS + either LTRA, Theophylline, or Zileuton

### Step 4
**Preferred:** Medium-dose ICS + LABA
**Alternative:** Medium-dose ICS + either LTRA, Theophylline, or Zileuton

### Step 5
**Preferred:** High-dose ICS + LABA
**Alternative:** Medium-dose ICS + either LTRA, Theophylline, or Zileuton

### Step 6
**Preferred:** High-dose ICS + LABA + oral corticosteroid
**Alternative:** High-dose ICS + LABA + oral corticosteroid + Omalizumab for patients who have allergies

Quick-Relief Medication for All Patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA > 2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

Key:
Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, inhaled corticosteroid; LABA, long-acting inhaled beta2-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta2-agonist

Notes:
The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Zileuton is a less desirable alternative due to limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.
- In step 6, before oral corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.
- Step 1, 2, and 3 preferred therapies are based on Evidence A; step 3 alternative therapy is based on Evidence B for LABA, Evidence B for theophylline, and Evidence D for zileuton. Step 4 preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and theophylline and Evidence D zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on (EPR—2 1997) and Evidence B for omalizumab.
- Immunotherapy for steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

### Usual Dosages for Long-Term Control Medications*

<table>
<thead>
<tr>
<th>Medication</th>
<th>≥ 12 years of Age and Adults</th>
<th>Potential Adverse Effects</th>
<th>Comments (not all inclusive)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhaled Corticosteroids</strong></td>
<td></td>
<td>Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis.</td>
<td>For long-term treatment of severe persistent asthma, administer single dose in a.m. either daily or on alternate days (alternate-day therapy may produce less adrenal suppression).</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>7.5–60 mg daily in a single dose in a.m. or qod as needed for control</td>
<td>Tachycardia, skeletal muscle tremor, hypokalemia, prolongation of QTc interval in overdose.</td>
<td>Short courses or “bursts” are effective for establishing control when initiating therapy or during a period of gradual deterioration.</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5 mg tablets, 5 mg/5 cc, 15 mg/5 cc</td>
<td>A diminished bronchoprotective effect may occur within 1 week of chronic therapy. Clinical significance has not been established.</td>
<td>There is no evidence that tapering the dose following improvement in symptom control and pulmonary function prevents relapse.</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc</td>
<td>Potential risk of uncommon, severe, life-threatening or fatal exacerbation; see text for additional discussion regarding safety of LABAs.</td>
<td>For patients unable to tolerate the liquid preparations, dexamethasone syrup at 0.4 mg/kg/day may be an alternative. Studies are limited, however, and the longer duration of activity increases the risk of adrenal suppression.</td>
</tr>
</tbody>
</table>

### Inhaled Long-Acting Beta 2 Agonists (LABAs)

<table>
<thead>
<tr>
<th>Medication</th>
<th>(Apply to both LABAs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol DPI 50 mcg/ blister</td>
<td>Tachycardia, skeletal muscle tremor, hypokalemia, prolongation of QTc interval in overdose.</td>
</tr>
<tr>
<td>Formoterol DPI 12 mcg/ single-use capsule</td>
<td>A diminished bronchoprotective effect may occur within 1 week of chronic therapy. Clinical significance has not been established.</td>
</tr>
</tbody>
</table>

**Key:** DPI, dry powder inhaler; EIB, exercise-induced broncospasm; HFA, hydrofluoroalkane; ICS, inhaled corticosteroids; IgE, immunoglobulin E; MDI, metered-dose inhaler; NA, not available (either not approved, no data available, or safety and efficacy not established for this age group); SABA, short-acting beta-agonist

*Note: Dosages are provided for those products that have been approved by the U.S. Food and Drug Administration or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.

(Chart continued on next page)
<table>
<thead>
<tr>
<th>Medication</th>
<th>≥ 12 Years of Age and Adults</th>
<th>Potential Adverse Effects</th>
<th>Comments (not all inclusive)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combined Medication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone/Salmeterol</td>
<td>DPI 100 mcg/50 mcg, 250 mcg/50 mcg, or 500 mcg/50 mcg</td>
<td>1 inhalation bid, dose depends on level of severity or control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HFA 45 mcg/21 mcg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>115 mcg/21 mcg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>230 mcg/21 mcg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45 mcg/21 mcg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>115 mcg/21 mcg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>230 mcg/21 mcg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide/Formoterol</td>
<td>HFA MDI 80 mcg/4.5 mcg</td>
<td>2 puffs bid, dose depends on level of severity or control</td>
<td>See notes for ICS and LABA.</td>
</tr>
<tr>
<td></td>
<td>160 mcg/4.5 mcg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DPI 100/50 DPI or 45/21 HFA for patients who have asthma not controlled on low- to medium-dose ICS.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>250/50 DPI or 115/21 HFA for patients who have asthma not controlled on medium to high dose ICS.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>There have been no clinical trials in children &lt;4 years of age.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Most children &lt;4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not blow into inhaler after dose is activated.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Currently approved for use in youths ≥12 years of age. Dose for children 5–12 years of age based on clinical trials using DPI with slightly different delivery characteristics.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>80/4.5 for patients who have asthma not controlled on low- to medium-dose ICS.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>160/4.5 for patients who have asthma not controlled on medium- to high-dose ICS.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>There have been no clinical trials in children &lt;4 years of age.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cough and irritation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15–20% of patients complain of an unpleasant taste from nedocromil.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Safety is the primary advantage of these.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>One dose of cromolyn before exercise or allergen exposure provides effective prophylaxis for 1–2 hours. Not as effective as inhaled beta_2-agonists for EIB as SABA.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4- to 6-week trial of cromolyn or nedocromil may be needed to determine maximum benefit.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose by MDI may be inadequate to affect hyperresponsiveness</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Once control is achieved, the frequency of dosing may be reduced.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not administer more than 150 mg per injection site.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monitor patients following injections; be prepared and equipped to identify and treat anaphylaxis that may occur.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whether patients will develop significant antibody titers to the drug with long-term administration is unknown.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Chart continued on next page)
53. Asthma in Adults

### Usual Dosages for Long-Term Control Medications (continued)

<table>
<thead>
<tr>
<th>Medication</th>
<th>≥ 12 Years of Age and Adults</th>
<th>Potential Adverse Effects</th>
<th>Comments (not all inclusive)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leukotriene Modifiers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukotriene Receptor Antagonists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montelukast</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mg or 5 mg chewable tablet</td>
<td>10 mg qhs</td>
<td>No specific adverse effects have been identified.</td>
<td>Montelukast exhibits a flat dose-response curve. Doses &gt;10 mg will not produce a greater response in adults.</td>
</tr>
<tr>
<td>4 mg granule packets</td>
<td></td>
<td>Rare cases of Churg-Strauss have occurred, but the association is unclear.</td>
<td>No more efficacious than placebo in infants ages 6–24 months.</td>
</tr>
<tr>
<td>10 mg tablet</td>
<td></td>
<td></td>
<td>As long-term therapy may attenuate exercise-induced bronchoconstriction in some patients, but less effective than ICS therapy.</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td></td>
<td>Postmarketing surveillance has reported cases of reversible hepatitis and, rarely, irreversible hepatic failure resulting in death and liver transplantation.</td>
<td>For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals.</td>
</tr>
<tr>
<td>10 mg tablet</td>
<td>40 mg daily</td>
<td></td>
<td>For zafirlukast is a microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin. Doses of these drugs should be monitored accordingly.</td>
</tr>
<tr>
<td></td>
<td>(20 mg tablet b.i.d.)</td>
<td></td>
<td>Zafirlukast is a microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin. Doses of these drugs should be monitored accordingly.</td>
</tr>
<tr>
<td>5-Lipoxygenase inhibitor</td>
<td></td>
<td></td>
<td>Zafirlukast is a microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin. Doses of these drugs should be monitored accordingly.</td>
</tr>
<tr>
<td>Zileuton 600 mg tablet</td>
<td>2,400 mg daily</td>
<td>Elevation of liver enzymes has been reported. Limited case reports of reversible hepatitis and hyperbilirubinemia.</td>
<td>For zileuton, monitor hepatic enzymes (ALT). Zileuton is a microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin and theophylline. Doses of these drugs should be monitored accordingly.</td>
</tr>
<tr>
<td></td>
<td>(give tablets q.i.d.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Methylxanthines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline Liquids, sustained-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>release tablets, and capsules</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg/kg/day up to 300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>maximum; usual maximum:</td>
<td>Dose-related acute toxicities include tachycardia, nausea and vomiting, tachyarrhythmias (SVT), central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia, and hypokalemia.</td>
<td>Adjust dosage to achieve serum concentration of 5–15 mcg/mL at steady state (at least 48 hours on same dosage).</td>
</tr>
<tr>
<td></td>
<td>600 mg/day</td>
<td></td>
<td>Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is essential.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adverse effects at usual therapeutic doses include insomnia, gastric upset, aggravation of ulcer or reflux, increase in hyperactivity in some children, difficulty in urination in elderly males who have prostatism.</td>
<td>Patients should be told to discontinue if they experience toxicity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Various factors (diet, food, febrile illness, age, smoking, and other medications) can affect serum concentrations. See EPR—3 Full Report 2007 and package inserts for details.</td>
<td></td>
</tr>
</tbody>
</table>


C. Estimated comparative daily dosages for inhaled steroids: home treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose Adult*</th>
<th>Medium Daily Dose Adult*</th>
<th>High Daily Dose Adult*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide HFA 40 or 80 mcg/puff</td>
<td>96–200 mcg</td>
<td>192–400 mcg</td>
<td>488 mcg</td>
</tr>
<tr>
<td>Budesonide DPI 90, 185 or 200 mcg/puff</td>
<td>185–400 mcg</td>
<td>600–1,200 mcg</td>
<td>1,200 mcg</td>
</tr>
<tr>
<td>Flunisolide 255 mcg/puff</td>
<td>500–1,000 mcg</td>
<td>1,000–2,000 mcg</td>
<td>2,000 mcg</td>
</tr>
<tr>
<td>Flunisolide HFA 85 mcg/puff</td>
<td>320 mcg</td>
<td>320–640 mcg</td>
<td>640 mcg</td>
</tr>
<tr>
<td>Fluticasone HFA 44, 110, or 220 mcg/puff DPI 50, 100, or 250 mcg/puff</td>
<td>88–264 mcg</td>
<td>264–440 mcg</td>
<td>440 mcg</td>
</tr>
<tr>
<td></td>
<td>100–300 mcg</td>
<td>300–500 mcg</td>
<td>500 mcg</td>
</tr>
<tr>
<td>Fluticasone HFA 50 mcg/puff</td>
<td>300 mcg</td>
<td>400 mcg</td>
<td>600 mcg</td>
</tr>
<tr>
<td>Fluticasone DPI 200 mcg/puff</td>
<td>300–700 mcg</td>
<td>700–1,500 mcg</td>
<td>1,500 mcg</td>
</tr>
</tbody>
</table>

*Including children ≥ 12 years of age
D. Management of asthma exacerbations: home treatment

**Assess Symptoms/Peak Flow**

**Mild-to-Moderate Exacerbation**
- PEF 50-80% predicted or personal best
- Signs and Symptoms:
  - Cough, breathlessness, wheeze, or chest tightness (correlate imperfectly with severity of exacerbation), or
  - Waking at night due to asthma, or
  - Decreased ability to perform usual activities

**Severe Exacerbation**
- PEF <50% predicted or personal best
- Signs and Symptoms:
  - Marked wheezing and shortness of breath
  - Cyanosis
  - Trouble walking or talking due to asthma
  - Accessory muscle use
  - Suprasternal retractions

**Instructions to Patient**
- Inhaled short-acting beta₂-agonist:
  - Up to three treatments of 2-4 puffs by MDI at 20-minute intervals, or
  - Single nebulizer treatment
  - Assess symptoms and/or peak flow after 1 hour

**Good Response (Mild Exacerbation)**
- PEF >80% predicted or personal best
- Signs and Symptoms:
  - No wheezing, shortness of breath, cough, or chest tightness, and
  - Response to beta₂-agonist sustained for 4 hours

**Incomplete Response (Moderate Exacerbation)**
- PEF 50-80% predicted or personal best
- Signs and Symptoms:
  - Persistent wheezing, shortness of breath, cough, or chest tightness

**Poor Response (Severe Exacerbation)**
- PEF <50% predicted or personal best
- Signs and Symptoms:
  - Marked wheezing, shortness of breath, cough, or chest tightness
  - Distress is severe and nonresponsive
  - Response to beta₂-agonist lasts <2 hours

**Instructions to Patient**
- Take 2-4 puffs beta₂-agonist for 24-48 hours prn
- Contact clinician urgently (same day) every 2-4 hours

**Instructions to Patient**
- May continue 2-4 puffs beta₂-agonist 3-4 hours for 24-48 hours prn
- For patients on inhaled steroids, double dose for 7-10 days
- Contact clinician within 48 hours for instructions

**Instructions to Patient**
- Take 2-4 puffs beta₂-agonist every 2-4 hours for 24-48 hours pm
- Add oral steroid**
- Contact clinician urgently (same day) for instructions

**Instructions to Patient**
- IMMEDIATELY:
  - Take up to 3 treatments of 2-4 puffs beta₂-agonist every 20 minutes pm
  - Start oral steroid**
  - Contact clinician
  - Proceed to emergency department, or call ambulance or 9-1-1

**Instructions to Patient**
- Add oral steroid**
- Contact clinician within 48 hours for instructions

**Instructions to Patient**
- Double dose for 7-10 days
- Contact clinician within 48 hours for instructions

**Instructions to Patient**
- Start oral steroid**
- Contact clinician
- Proceed to emergency department, or call ambulance or 9-1-1

* Patients at high risk for asthma-related death should receive immediate clinical attention after initial treatment. More intensive therapy may be required.

** Oral steroid dosages:
- Adult: 40-60 mg, single or 2 divided doses for 3-10 days.
- Child: 1-2 mg/kg/day, maximum 60 mg/day, for 3-10 days.


**CLINICAL PEARLS**
- During a severe exacerbation, wheezing may not be present
- Exercise-induced asthma usually begins within 3 minutes of the completion of the
exercise and peaks in 10–15 minutes

• Most effective meds for controlling long term outcomes in children are inhaled corticosteroids. Potentially small risk of delayed growth (but benefit seems to outweigh risk)
• No benefit to adding ATBs for acute asthma exacerbations (unless infectious etiology suspected)
• With severe asthma exacerbation, the PaCO₂ returns to normal and is a marker for possible impending respiratory failure
• Duration of symptoms prior to presentation predicts duration of symptoms from institution of treatment to resolution

References

Michael B. Weinstock, MD
Miriam Chan PharmD
David P. Buck, MD

54. CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

I. GENERAL
A. COPD classically encompasses several diffuse pulmonary diseases including chronic asthma, bronchiectasis, chronic bronchitis, cystic fibrosis, and emphysema. This section focuses on chronic bronchitis and emphysema

B. Definitions
1. Chronic obstructive pulmonary disease (COPD) is defined as the progressive development of airflow limitation that is not fully reversible (American Thoracic Society). Most patients will have components of chronic bronchitis and emphysema
2. Chronic bronchitis: A recurrent and productive cough on most days for 3 months or more in 2 consecutive years without another explanation. Caused by obstruction of small airways
3. Emphysema: The destruction of interalveolar septa characterized as having abnormal, permanent enlargement or air spaces distal to the terminal bronchiole without obvious fibrosis. Caused by enlargement of air spaces and destruction of lung parenchyma, loss of lung elasticity, and closure of small airways

C. COPD affects 30 million Americans and is the 4th leading cause of death in the US. Airway obstruction is present in 14% of white, male smokers compared to 3% of non-smokers

D. Classification of severity of airflow limitation in COPD (based on post-bronchodilator FEV₁)
1. GOLD 1: Mild—FEV₁ ≥ 80% predicted
2. GOLD 2: Moderate—50% ≤ FEV₁ < 80% predicted
3. GOLD 3: Severe—30% ≤ FEV₁ < 50% predicted
4. GOLD 4: Very Severe—FEV₁ < 30% predicted
(Adapted From the Global Strategy for Diagnosis, Management and Prevention of COPD, 2014, ©Global Initiative for Chronic Obstructive Lung Disease (GOLD), all rights reserved. Table 3. Available from http://www.goldcopd.org)
## Combined Assessment of COPD

When assessing risk, choose the **highest risk** according to GOLD grade or exacerbation history.

(One or more hospitalizations for COPD exacerbations should be considered high risk.)

<table>
<thead>
<tr>
<th>Risk (Gold Classification of Airflow Limitation)</th>
<th>CAT &lt; 10</th>
<th>CAT ≥ 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>mMRC 0-1</td>
<td>mMRC ≥ 2</td>
</tr>
<tr>
<td>Breathlessness</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient</th>
<th>Characteristic</th>
<th>Spirometric Classification</th>
<th>Exacerbations per year</th>
<th>CAT</th>
<th>mMRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low Risk Less Symptoms</td>
<td>GOLD 1-2</td>
<td>≤ 1</td>
<td>&lt; 10</td>
<td>0-1</td>
</tr>
<tr>
<td>B</td>
<td>Low Risk More Symptoms</td>
<td>GOLD 1-2</td>
<td>≤ 1</td>
<td>≥ 10</td>
<td>≥ 2</td>
</tr>
<tr>
<td>C</td>
<td>High Risk Less Symptoms</td>
<td>GOLD 3-4</td>
<td>≥ 2</td>
<td>&lt; 10</td>
<td>0-1</td>
</tr>
<tr>
<td>D</td>
<td>High Risk More Symptoms</td>
<td>GOLD 3-4</td>
<td>≥ 2</td>
<td>≥ 10</td>
<td>≥ 2</td>
</tr>
</tbody>
</table>


### II. HISTORY
Inquire about fever, cough, dyspnea, exercise tolerance (current and baseline), chest pain, peripheral edema, history of environmental exposures, and cigarette smoking.

### III. PHYSICAL EXAMINATION
Increased A-P diameter, decreased lung sounds, prolonged expiration, dyspnea at rest, wheezing, pursed lip breathing, peri orbital cyanosis, use of accessory muscles to breathe, rales and rhonchi, pedal edema, ascites, pink puffer (emphysema) vs. blue bloater (chronic bronchitis).

### IV. COPD EXACERBATING FACTORS (in order of frequency)
- BIRCHES—Bronchospasm, Infection (respiratory), Retained secretions, CHF, Hypoventilation ( meds, neuromuscular), Emboli, Systemic illness (fever, MI, non-pulmonary infection)

### V. DIAGNOSTIC PROCEDURES
- **Chest x-ray:** In later stages may show flattening of the diaphragms, increased lung volumes, bullae and blebs, small heart (secondary to vertical orientation), increased retrosternal clear space. May see increased bronchovascular markings with chronic bronchitis.
B. Laboratory
1. ABG: Useful for patients suspected of having moderate to severe lung disease
2. α-1 antitrypsin levels: Obtain if patient presents with emphysema at < age 50, if there is a family history of early onset emphysema, or if < 20 pack/yr smoking history

C. Pulmonary function testing: Perform spirometry pre- and post-bronchodilator and/or DLCO and lung volumes in selected patients. The presence of a post-bronchodilator FEV1/FVC < 0.70 confirms the presence of persistent airflow limitation and thus of COPD. For a table of Interpretation of PFTs, see Chapter 51, Shortness of Breath

VI. DIFFERENTIAL DIAGNOSIS
Acute bronchitis, acute viral infection, asthma, bronchiectasis, bronchogenic carcinoma, chronic pulmonary embolism, sleep apnea, primary alveolar hypoventilation, and chronic sinusitis

VII. MANAGEMENT OF COPD
A. Smoking cessation (see Chapter 39, Smoking Cessation)
B. Bronchodilators
1. Central to the symptomatic management of COPD
2. Inhaled therapy is preferred
3. Can be given “as needed” for acute symptom relief, and on a regular basis to prevent or reduce persistent symptoms
4. 3 groups of bronchodilators:
   a. Anticholinergics (Inhaled)
      i. Ipratropium (Atrovent) is a short-acting agent with an onset of action 15 minutes and a duration of action up to 6 hours. It has limited systemic absorption
      ii. Tiotropium (Spiriva) is a long-acting agent with a long duration of action that allows once-daily dosing. Results of some studies have suggested that it is more effective than a long-acting β2-agonist
   b. β2-agonists (Inhaled)
      i. Short-acting β2-agonists have a rapid onset (<5 minutes) and a duration of ≤4 hours. Commonly used β2-agonists include Albuterol, Levalbuterol, and Pirbuterol
      ii. Long-acting β2-agonists are Salmeterol, Formoterol, Arformoterol and Indacaterol. All of them have a black box warning about an increased risk of asthma-related deaths; but patients with COPD are not at risk
   c. Methylxanthines (oral)
      i. Use slow-release Theophylline (e.g., Theodur)
      ii. Has a narrow therapeutic index; monitoring is warranted to maintain a serum level of 5–12mcg/mL
      iii. Interacts with many drugs including Cimetidine, Ciprofloxacin, and Erythromycin
      iv. Adjust dose in older patients, patients with cor pulmonale or CHF
5. The choice of bronchodilators depends on the availability of medication and each patient's individual response in terms of both symptom relief and side effects
6. Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators
7. Bronchodilators can be used alone or in combination
8. Combining bronchodilators (Ipratropium/Albuterol) has been more effective than either drug alone
C. Corticosteroids
1. Use of an inhaled corticosteroid is recommended in patients with severe COPD (FEV1<50%) who experience frequent exacerbation while receiving ≤1 long-acting bronchodilators
2. The dose-response relationships and long-term safety of inhaled corticosteroids in COPD are not known
3. Treatment of inhaled steroids (especially in high doses) increases the likelihood of pneumonia and does not reduce overall mortality
4. The combination of an inhaled steroid and a long-acting α2-agonist is more effective than the individual drug alone in reducing exacerbations and improving lung function
5. Long-term treatment with oral corticosteroids is not recommended
### COMMONLY USED DRUGS FOR COPD

**DRUG (BRAND NAME)** | **DOSAGE** | **COMMON SIDE EFFECTS**
---|---|---
**ANTICHOLINERGICS (INHALED)**

**Short-acting Anticholinergics**
- Ipratropium (Atrovent 17 mcg) MDI: 2 puffs QID, may increase dose as needed, but not >12 puffs/day. Nebulizer: 500 mcg (0.02%) q6-8 hrs
  - Dry mouth, constipation, blurred vision, increased heart rate, urinary retention

**Long-acting Anticholinergics**
- Tiotropium (Spiriva HandiHaler) Powder: one capsule (18 mcg) once daily
  - Similar to ipratropium

**ß₂-AGONISTS (INHALED)**

**Short-acting ß₂-agonists**
- Albuterol (Proventil, Ventolin, ProAir 90 mcg) MDI: 2 puffs q 4-6 hrs prn. Nebulizer: 0.63 mg q 4-6 hrs or 1.25 mg TID
  - Tachycardia, tremors, palpitations, QTc prolongation, insomnia, hypokalemia, hyperglycemia
- Levalbuterol (Xopenex HFA 45 mcg) MDI: 2 puffs q 4-6 hrs prn. Nebulizer: 0.63 mg q 6-8 hrs or 1.25 mg TID
  - R isomer of albuterol (responsible for bronchodilation effect) may have side effects = than albuterol
- Pirbuterol (Maxair 200 mcg) MDI: 2 puffs q 4-6 hrs prn
  - Similar to albuterol

**Long-acting ß₂-agonists**
- Formoterol (Foradil Aerolizer, Perforomist) Powder: one capsule (12 mcg) q12h. Nebulizer: 20 mcg/2 mL BID
  - Similar to albuterol
- Salmeterol (Severent Diskus) Powder: one inhalation (50 mcg) q12h. Nebulizer: 15 mcg/2 mL BID
  - R-R enantiomer: 2× more potent than racemic formoterol
- Indacaterol (Arcapta, Neohaler) Powder: one capsule (75 mcg once daily)
  - Similar to albuterol

**INHALED CORTICOSTEROIDS**
- Beclomethasone (QVAR 40, 80 mcg) MDI: 1-2 puffs bid; max 320 mg BID
  - Cough, pharyngitis, dry mouth/throat, localized Candida infection - minimize risk by rinsing mouth after use
- Budesonide (Pulmicort Flexhaler 90, 180 mcg) Powder: 360-720 mcg BID. Nebulizer: 0.25-0.5 mg 1x/d or BID
  - Similar to corticosteroids and albuterol
- Fluticasone (Flovent HFA 44, 110, 220 mcg, Diskus 50, 100, 250 mcg)
  - Powder: 220-440 mcg QD or BID (Max 880 mcg/d)
  - Similar to corticosteroids and albuterol
- Mometasone (Asmanex 220 mcg)
  - Powder: 220-440 mcg QD or BID (Max 880 mcg/d)
  - Similar to corticosteroids and albuterol
  - Triamcinolone (Azmacort 72 mcg) MDI: 2 puffs TID-QID or 4 puffs BID
  - Similar to corticosteroids and albuterol

**INHALED SHORT-ACTING ß₂—AGONISTS/ANTICHOLINERGICS COMBINATION**
- Albuterol/ipratropium (Combivent 90 mcg/18 mcg): MDI: 2 puffs QID pm, max 12 puffs/day. Nebulizer: 2.6 mg 0.025 mcg QID pm, max 6 doses (DuoNeb)
  - Similar to albuterol and ipratropium

**INHALED CORTICOSTEROID/LONG-ACTING ß₂—AGONISTS COMBINATION**
- Fluticasone/Salmeterol (Advair Diskus 100, 250, 500 mcg/25 mcg. HFA 44, 110, 220 mcg/4.5 mcg)
  - Powder: one inhalation BID. MDI: 2 puffs BID
  - Similar to corticosteroids and albuterol
- Budesonide/Formoterol (Symbicort HFA 80, 160 mcg/4.5 mcg)
  - Powder: one inhalation BID. MDI: 2 puffs BID
  - Similar to corticosteroids and albuterol
- Fluticasone/Vilanterol (Breo 100 mcg/25 mcg)
  - Powder: one inhalation QD. MDI: 2 puffs BID
  - Similar to corticosteroids and albuterol
- Umeclidinium/Vilanterol (Anoro 62.5 mcg/24 mcg)
  - Powder: one inhalation QD. MDI: 2 puffs BID
  - Similar to corticosteroids and albuterol

**METHYLXANTHINES (ORAL)**
- Theophylline SR (Theodur, Theo-24) 200-600 mg/d
  - N/V, tachycardia, nervousness, insomnia, headache, restlessness

**ORAL CORTICOSTEROIDS**
- Prednisone 40-60 mg/d x 5-7 days
  - Insomnia, nervousness, increased appetite, fluid retention, increased BP, hyperglycemia, ulcers

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**D. Phosphodiesterase-4 inhibitors: Roflumilast (Daliresp)**
1. Action: Reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP. It is not a bronchodilator
2. Dose: 1 oral tab 500mcg QD
3. Side effects: Nausea, reduced appetite, abdominal pain, diarrhea, sleep disturbances and headache
4. Caution: **Roflumilast** should not be used in patients with depression. Do not use **Roflumilast** with **Theophylline**. It may be useful in advanced stage of COPD. Potential benefits should be weighed against the potential risks prior to initiating this drug.

5. **Roflumilast** is a preferred option over **Theophylline**. It may be useful in advanced stage of COPD. Potential benefits should be weighed against the potential risks prior to initiating this drug.

**E. Antibiotics**: Exacerbations may be due to bacterial, viral, or URI infections.

1. Antibiotics have been shown to have an effect on clinical recovery and outcome in acute infectious exacerbations of COPD.
2. Therapy should be directed at *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Consider *C. pneumoniae* and *Mycoplasma pneumoniae*.
3. **Doxycycline**, **Bactrim DS**, **Augmentin**, or a respiratory quinolone (**Levoﬂoxacin** or **Moxifloxacin**) are appropriate first line agents.
4. Prophylactic ATB have not been shown to be helpful.

**F. Adjunctive therapy**: Mucolytic-expectorant may be used in patients with thick or viscous sputum or difficulty with expectoration. Examples are **Iodinated Glycerol** 60mg PO QID and **Guaifenesin** (**Robitussin**, **Humibid LA**, **Mucinex**) 1–2 PO BID. The overall benefits seem to be very small.

**G. Nonpharmacologic management**

1. Pulmonary rehabilitation: Shown to decrease hospital mortality and increase quality of life. No change in mortality.
2. Nocturnal ventilation with **BiPAP**.
3. Lung volume reduction surgery: Most useful in patients with localized upper-lobe emphysema. Improvements include increased FEV₁, improved exercise capacity, and improved quality of life which persist for at least 1yr.
4. Lung transplantation.

**VIII. VACCINATIONS**

A. **Influenza vaccine**: Annually.
B. **Pneumococcal vaccine**: In COPD patients ≥ 65 years and for COPD patients <65 years with an FEV₁ <40% predicted.

**IX. INDICATIONS FOR SUPPLEMENTAL OXYGEN**

A. Resting PaO₂ < 55mm Hg or O₂ saturation < 88% at rest, with exercise or during sleep.
B. pO₂ 55–59mm Hg with concurrent cor pulmonale ≥ than 16hrs/day.
C. Goal: PaO₂ 60–80mm Hg.

**X. PULMONARY REHABILITATION**

A. Goals are to enhance standard medical therapy, maximize functional capacity, increase exercise tolerance, and improve quality of life.
B. No change in mortality.
C. Shown to decrease hospitalizations.

**CLINICAL PEARLS**

- For patients requiring chronic oral corticosteroids, remember to monitor for osteoporosis and DM.
- Genetic factors may determine which smokers will develop airflow limitation.

**References**


55. Acute Bronchitis

I. GENERAL
   A. Definition: A respiratory tract infection which causes inflammation of the trachea-bronchial tree
   B. Approximately 90–95% of cases are viral in origin
   C. The cough generally lasts for 1–3 weeks. May persist for weeks to months after infection has resolved due to inflammatory changes. Up to 25% of patients may have a cough which persists longer than 1 month
   D. Up to 60% of patients have decreased FEV\textsubscript{1} and peak flows to less than 80% of predicted
   E. Cigarette smokers are predisposed to the development of acute bronchitis secondary to direct injury to airway epithelium, less cilia present, and delayed mucociliary clearance. Smokers have infections that are more frequent, more severe, and last longer

II. ETIOLOGY
   A. Viral (most common): Influenza A & B, Parainfluenza, RSV, Adenovirus, and Rhinovirus
   B. Bacteria: Mycoplasma pneumonia, Chlamydia pneumonia, Moraxella catarrhalis, Bordetella pertussis, Legionella pneumophila, or Haemophilus influenzae (most common cause in smokers)

III. DIFFERENTIAL DIAGNOSIS
   A. Reactive airway disease, asthma, COPD, bronchiectasis
   B. Occupational exposures, inhalation injuries
   C. Upper respiratory infection, common cold, sinusitis, influenza, pneumonia
   D. Congestive heart failure
   E. Gastroesophageal reflux disease
   F. Lung cancer
   G. Foreign body

IV. CLINICAL FEATURES
   A. Symptoms may vary depending on the etiologic agent and host factors including age, smoking history, and comorbidities such as asthma and/or COPD
   B. Common signs and symptoms
      1. Cough, initially dry and non-productive, then productive of mucopurulent sputum
      2. Preceding URI with sore throat, myalgias, chills, malaise, coryza, etc.
      3. Fever
      4. Fatigue and malaise
      5. Occasional dyspnea, rales, rhonchi, wheezing

V. DIAGNOSIS: Usually based on symptoms and physical exam. Culture of the sputum is generally unhelpful. Exclude pneumonia and non-pulmonary causes

VI. TREATMENT: Symptomatic (see Chapter 124, Symptomatic Medications)
   A. $\beta_{2}$-agonist metered dose inhaler. Multiple studies suggest a benefit including decreased
duration of cough and earlier return to work

B. Cough suppression
C. Expectorants/Mucolytics: Widely prescribed but probably do not alter the course of the disease
D. Adequate hydration
E. Encourage smoking cessation if patient smokes
F. Antibiotics
   1. Most cases are viral but ATBs are very frequently prescribed, usually because of physicians’ perceptions of patients’ expectations. At least one study has shown that when physicians explain the diagnosis and rationale for treatment, patients who did not receive ATBs were as satisfied as those who did
   2. Studies of ATB use have found that there may be a slight improvement in duration of cough (0–1 day less cough) and feeling ill (0–1 day). There was no change in night cough, productive cough, or activity limitation. The patients treated with ATB had more adverse effects including nausea/vomiting, headache, skin rash, or vaginitis. Number needed to treat for benefit was 5–14 and the number needed to harm was 17. The CDC recommends against treating acute bronchitis with ATBs

CLINICAL PEARLS
• Antibiotics are prescribed at 70–90% of office visits for acute bronchitis despite the fact that about 90% are caused by viruses
• Purulent secretions or fever from the nares or throat neither predict bacterial infection nor benefit from ATB treatment
• Pulmonary function testing for asthma may yield false positive results in patients with acute bronchitis due to transient PFT obstructive abnormalities
• 10th most common diagnosis in the US
• Use of widespread ATBs has led to an increase in emergence of resistant bacteria

References
Knutson D, Braun C. Diagnosis and management of acute bronchitis. Am Fam Phys 2002;65:2039–44.
## VI. Management of Common Ambulatory Conditions

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56. MANAGEMENT OF TYPE 2 DIABETES MELLITUS

I. PREVALENCE (CDC 2014 National Diabetes Statistics Report)
A. Diabetes affects 29.1 million people, i.e., 9.3% of the US population. Of these, 8.1 million people have undiagnosed diabetes
B. In 2005–2008, 35% of adults aged over 20 years had prediabetes (50% of adults aged ≥65 years)

Section II through Section VIII summarize the guidelines in the 2014 ADA Standards of Medical Care in Diabetes (Reference 1). Following is a guide to using this chapter:

II. Classification; III. Diagnosis; IV Management of Prediabetes; V. Diabetes Care; VI. Management of Type 2 Diabetes; VII. Prevention and Management of Diabetes Complications; VIII. Assessment of Common Comorbid Conditions; IX. Medications Used in the Treatment of T2DM; X. Insulin Therapy

II. CLASSIFICATION
A. Type 1 diabetes (T1DM)
1. β-cell destruction, leading to absolute insulin deficiency
2. Immune mediated and idiopathic
3. 95% with genetic marker of human leukocyte antigen DR3 and/or DR4
B. Type 2 diabetes (T2DM)
1. Insulin resistance with progressive insulin secretory defect
2. 50% of patients with T2DM present with end-organ damage at the time of diagnosis
3. As obesity rates in children have climbed, so has the incidence of T2DM among adolescents and children
C. Gestational diabetes (GDM):
1. Diagnosed during pregnancy
2. About 200,000 cases annually
D. Diabetes due to other causes, e.g., genetic defects, cystic fibrosis, drug-induced (such as in the treatment of HIV/AIDS or after organ transplant)

III. DIAGNOSIS
A. The diagnostic criteria for diabetes mellitus have recently been modified to include the use of A1C ≥6.5%
1. The A1C test should be National Glycohemoglobin Standardization Program (NGSP) certified and standardized to DCCT reference assay
2. Use of point-of-care A1C is not recommended at this time as proficiency testing is not mandated for performing the test
B. The ADA criteria for the diagnosis of diabetes are shown in Table 1

<table>
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<td>A1C ≥6.5%</td>
<td>The A1C test should be certified by the NGSP and standardized to the DCCT assay</td>
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<tr>
<td>FPG ≥126mg/dL*</td>
<td>Fasting is defined as no caloric intake for at least 8 hr</td>
</tr>
<tr>
<td>2-h plasma glucose ≥200mg/dL during an OGTT (75-g)*</td>
<td>Use a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water</td>
</tr>
<tr>
<td>Symptoms of diabetes plus a random plasma glucose ≥200mg/dL</td>
<td>Classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.</td>
</tr>
</tbody>
</table>

In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing on a different day

C. Categories of increased risk for diabetes (prediabetes)
1. FPG 100–125mg/dL, or
2. 2-h plasma glucose in the 75-g OGTT 140–199mg/dL, or
3. A1C 5.7–6.4%
D. Criteria for testing for diabetes in asymptomatic adult patients

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m²) and have additional risk factors:
   - Physical inactivity
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - Women who delivered a baby >9 lb or were diagnosed with GDM
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - A1C ≥5.7%, IGT, or IFG on previous testing
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   - History of CVD

2. In the absence of the above criteria, testing for diabetes should begin at age 45 years

3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status


E. Testing for type 2 diabetes in asymptomatic children (age ≤18 y)

1. Screening for type 2 diabetes should be considered in children and adolescents who are overweight and have ≥2 additional risk factors for diabetes

2. Overweight is defined as BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height

3. Risk factors:
   - Family history of type 2 diabetes in first- or second-degree relative
   - Race/ethnicity: Native American, African American, Latino, Asian American, Pacific Islander
   - Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight)
   - Maternal history of diabetes or GDM during the child’s gestation

4. Initiate testing at age 10 yrs or at onset of puberty, if puberty occurs at a younger age

5. Test every 3 years

F. Diagnosis of Gestational Diabetes Mellitus (GDM)

1. Screen for undiagnosed T2DM at the first prenatal visit in those with risk factors, using standard diagnostic criteria

2. Screen for GDM using one of the two following strategies:
   a. One-step (International Association of Diabetes and Pregnancy Study Groups—IAADPSG consensus)
      - Screen at 24–28 weeks of gestation using a 75-g OGTT (oral glucose tolerance test)
      - The OGTT should be performed in the morning after an overnight fast of 8 h or more
      - Measure plasma glucose at fasting and at 1 and 2 h post OGTT
      - Use the diagnostic cut points listed below:
        - Fasting: ≥92 mg/dL
        - 1 h: ≥180 mg/dL
        - 2 h: ≥153 mg/dL
   b. Two-step (NIH consensus)
      - Step 1: At 24–28 weeks of gestation, perform a nonfasting 50-g GLT (glucose load test) and measure plasma glucose at 1 h after the load. If ≥140 mg/dL, go to step 2
      - Step 2: Perform a 100-g OGTT when the patient is fasting. The diagnosis is
made when the plasma glucose at 3 h after the test is ≥ 140 mg/dL
- The ACOG recommends a lower threshold of 135 mg/dL in high-risk ethnic minorities with higher prevalence of GDM

3. Glycemic goals in pregnant women with GDM:
   Preprandial: ≤ 95 mg/dL, and either:
   - 1 h postmeal: ≤ 140 mg/dL or
   - 2 h postmeal: ≤ 120 mg/dL

4. Screen women with GDM for persistent diabetes at 6–12 weeks postpartum, using OGTT and nonpregnancy diagnostic criteria

5. Women with a history of GDM should be screened at least every 3 years

IV. MANAGEMENT OF PREDIABETES
A. Effective ongoing support program targeting weight loss of 7% of body weight and increasing physical activity to ≥ 150 min/week of moderate activity (such as walking)
B. Metformin therapy especially for those with BMI ≥ 35 kg/m², age < 60 yr, and women with prior GDM
C. Assess and treat cardiovascular risk factors

V. DIABETES CARE
A. A complete medical evaluation will assist the health care team to ensure optimal management of the patient with diabetes.
B. Components of a comprehensive diabetes evaluation are listed in Table 2

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<th>Table 2: Components of the Comprehensive Diabetes Evaluation</th>
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<td>- Age and characteristics of onset of diabetes (e.g., DKA, asymptomatic laboratory finding)</td>
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<td>- Eating patterns, physical activity habits, nutritional status, and weight history; growth and development in children and adolescents</td>
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<td>- Diabetes education history</td>
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<td>- Review of previous treatment regimens and response to therapy (A1C records)</td>
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<td>- Current treatment of diabetes, including medications, medication adherence and barriers thereto, meal plan, physical activity patterns, and readiness for behavior change</td>
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<td>- Results of glucose monitoring and patient’s use of data</td>
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<td>- History of diabetes-related complications</td>
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<tr>
<td>- Microvascular: retinopathy, nephropathy, neuropathy (sensory, including history of foot lesions: autonomic, including sexual dysfunction and gastroparesis)</td>
</tr>
<tr>
<td>- Macrovascular: CHD, cerebrovascular disease, and PAD</td>
</tr>
<tr>
<td>- Other: psychosocial problems*, dental disease*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Height, weight, BMI</td>
</tr>
<tr>
<td>- Blood pressure determination, including orthostatic measurements when indicated</td>
</tr>
<tr>
<td>- Fundoscopic examination*</td>
</tr>
<tr>
<td>- Thyroid palpation</td>
</tr>
<tr>
<td>- Skin examination (for acanthosis nigricans and insulin injection sites)</td>
</tr>
<tr>
<td>- Comprehensive foot examination</td>
</tr>
<tr>
<td>- Inspection</td>
</tr>
<tr>
<td>- Palpation of dorsalis pedis and posterior tibial pulses</td>
</tr>
<tr>
<td>- Presence/absence of patellar and Achilles reflexes</td>
</tr>
<tr>
<td>- Determination of proprioception, vibration, and monofilament sensation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>- A1C, if results not available within past 2–3 months</td>
</tr>
<tr>
<td>If not performed/available within past year</td>
</tr>
<tr>
<td>- Fasting lipid profile, including total, LDL and HDL cholesterol and triglycerides</td>
</tr>
<tr>
<td>- Liver function tests</td>
</tr>
<tr>
<td>- Test for urine albumin excretion with spot urine albumin-to-creatinine ratio</td>
</tr>
<tr>
<td>- Serum creatinine and calculated GFR</td>
</tr>
<tr>
<td>- TSH in type 1 diabetes, dyslipidemia or women over age 50 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Referrals</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Eye care professional for annual dilated eye exam</td>
</tr>
<tr>
<td>- Family planning for women of reproductive age</td>
</tr>
<tr>
<td>- Registered dietitian for MNT</td>
</tr>
<tr>
<td>- DSME</td>
</tr>
<tr>
<td>- Dentist for comprehensive periodontal examination</td>
</tr>
<tr>
<td>- Mental health professional, if needed</td>
</tr>
</tbody>
</table>

*See appropriate referrals for these categories.

VI. MANAGEMENT OF TYPE 2 DIABETES INC. HBA1C GOAL

A. Glycemic control
1. Glycemic goals (A1C and capillary plasma glucose) should be individualized based on:
   - Duration of diabetes
   - Age/life expectancy
   - Comorbid conditions
   - Known CVD or advanced microvascular complications
   - Hypoglycemia unawareness
   - Individual patient considerations

2. A1C goal
   - A1C goal <7% for most adult patients: Lowering A1C to ≤7% has been shown to reduce microvascular complications of diabetes. Its effect on the risk of macrovascular disease especially in well-established diabetes is less certain
   - A1C <6.5% for selected patients if implemented safely, without significant hypoglycemia
   - A1C <8% for older patients with a history of severe hypoglycemia, or those with long-standing diabetes and cardiovascular disease

3. Frequency of A1C testing
   - Patients who are meeting treatment goals: at least 2 ×/yr
   - Patients whose therapy has changed or who are not meeting glycemic goals: every 3 months

4. Correlation of A1C with average glucose:

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>Mean Plasma Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>126</td>
</tr>
<tr>
<td>7</td>
<td>154</td>
</tr>
<tr>
<td>8</td>
<td>183</td>
</tr>
<tr>
<td>9</td>
<td>212</td>
</tr>
<tr>
<td>10</td>
<td>240</td>
</tr>
<tr>
<td>11</td>
<td>269</td>
</tr>
<tr>
<td>12</td>
<td>298</td>
</tr>
</tbody>
</table>

5. Capillary plasma glucose targets
   - Fasting or preprandial glucose: 70–130mg/dL
   - Peak postprandial (1–2 hr after the beginning of the meal) glucose level <180mg/dL
   - Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals

6. Self-monitoring of blood glucose (SMBG)
   - On multiple-dose insulin or insulin pump therapy: SMBG at least before meals and at bedtime; occasionally postprandially, prior to exercise, when low BG is suspected, after treating low BG until normoglycemic, prior to critical tasks such as driving
   - On less frequent insulin injections or noninsulin therapies: SMBG may be used to guide treatment decisions and/or patient self-management

7. Continuous glucose monitoring (CGM) may be used in T1DM, those with hypoglycemia unawareness, and/or those with frequent hypoglycemic episodes

B. Medical Nutrition Therapy (MNT)
1. Refer patients to a registered dietitian who should also be a certified diabetes educator (CDE). Goal is to educate on meal planning and healthy food choices
2. The ADA recommends a balanced diet that is rich in fiber, whole grains, and legumes. Monitor carbohydrate intake. Saturated fat intake should be <7% of total calories. Reduce intake of trans fat
3. Weight loss is recommended for all overweight or obese patients
4. Limit alcohol intake (≤1 drink/day for women, ≤2 drinks/day for men) and take precautions to prevent hypoglycemia

C. Physical activity
1. At least 150 min/wk of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over ≥3 days/wk with no more than 2 consecutive days without exercise
2. If no contraindication, perform resistance training ≥2 times/week
3. High-risk patients should be encouraged to start with short periods of low-intensity exercise and increase the intensity and duration slowly

4. Special populations
   • Patients with diabetic autonomic neuropathy should undergo cardiac evaluation before beginning physical activity that is more intense than what they are accustomed
   • Patients with proliferative diabetic retinopathy (PDR) or severe non-PDR should not do vigorous aerobic or resistance exercise because of the risk of triggering vitreous hemorrhage or retinal detachment
   • Patients with peripheral neuropathy should wear proper footwear and examine their feet daily to detect lesions early
   • Patients with a foot injury or open sore should be restricted to non-weight-bearing activities

D. Diabetes Self-Management Education (DSME)
   1. DSME should be provided to all patients when diabetes is diagnosed and as needed thereafter
   2. DSME should be provided according to the National Standards for Diabetes Self-Management Education and Support
   3. Effective self-management and quality of life are key outcomes of DSME
   4. Psychosocial issues should be addressed in DSME
   5. DSME also apply to the education and support of people with prediabetes

E. Psychosocial assessment and care
   1. Assessment of psychological and social situation should be an ongoing part of the medical management of diabetes
   2. Psychosocial screening and follow-up include attitudes about the illness, expectations for medical management and outcomes, affect/mood, general and diabetes-related quality of life, resources, and psychiatric history
   3. When self-management is poor, consider screen for depression, diabetes-related distress, anxiety, eating disorders, and cognitive impairment

F. Bariatric surgery
   1. Adults with T2DM and BMI ≥35kg/m², especially if the diabetes or associated comorbidities are difficult to control with lifestyle or drug therapy, may consider bariatric surgery as a weight loss treatment option
   2. Benefit of bariatric surgery in patients with T2DM and BMI 30–35 kg/m² has not been proven
   3. Patients with T2DM who have undergone bariatric surgery need life-long lifestyle support and medical monitoring

G. Immunizations
   1. Annual flu vaccination for all diabetic patients (≥6 mo of age)
   2. PPSV23 (Pneumovax) vaccination for all diabetic patients (≥2 yr of age)
   • A one-time revaccination at/after age 65 (use a minimum interval of 5 years between PPSV23 doses)
   • Repeat vaccination in those with nephritic syndrome, chronic renal disease, and other immunocompromised states (e.g., after transplantation). Use a minimum interval of 5 years between PPSV23 doses
   3. Hepatitis B vaccination for adults aged 19–59 years with diabetes
   • 3-dose series: 0, 1, 6 months
   • Diabetics aged ≥60 yrs may be vaccinated at the clinician’s discretion

VII. PREVENTION AND MANAGEMENT OF DIABETES COMPLICATIONS

A. Hypertension (HTN)
   1. General information
   • Affects 20–60% of patients with diabetes
   • In T1DM, HTN is often the result of underlying nephropathy
   • In T2DM, HTN usually coexists with other cardiometabolic risk factors
   2. Screening
   • Measure BP at every visit
   • Diagnose HTN when BP elevated in 2 separate days
3. Goals
   - <140/80 for most patients
   - <130/80 for younger patients and those without undue treatment burden
   - 110–129/65–79 for pregnant patients with diabetes and chronic HTN

4. Treatment
   - Patients with BP >120/80: lifestyle modification
   - Patients with BP >140/80: lifestyle and drug therapy
   - Lifestyle: weight loss if overweight; DASH (reduce sodium and increase potassium intake; alcohol in moderation; increase physical activity)
   - Drug therapy
     a. The regimen should include either an ACE inhibitor or ARB
     b. ≥2 drugs at maximal doses is generally required to achieve BP goals
     c. Administer ≥1 antihypertensive agents at bedtime
     d. Monitor serum creatinine or eGFR and serum potassium levels if ACE inhibitor, ARB, or diuretics are used
     e. Note: ACE inhibitors and ARBs are contraindicated during pregnancy
     f. Antihypertensive agents that are effective and safe in pregnancy: Methyldopa, Labetalol, Diltiazem, Clonidine, Prazosin

B. Dyslipidemia
1. Prevalence
   - Increased in patients with T2DM
   - Contributes to high CVD risk
2. Screening
   - Fasting lipid profile at least annually
   - Adults with low-risk lipid values (LDL<100, HDL >50, TG <150) may repeat lipid assessment every 2 years
3. Treatment
   - Lifestyle modification recommended for patients with diabetes
     a. Reduce saturated fat, trans fat, and cholesterol intake
     b. Increase n-3 fatty acids, viscous fiber, and plant stanols/sterols
     c. Weight loss if overweight
     d. Increase physical activity
   - Statin therapy regardless of baseline lipid levels in diabetes patients:
     a. With overt CVD
     b. Without CVD who are ≥age 40 and have ≥1 other CVD risk factors (family history of CVD, HTN, smoking, dyslipidemia, or albuminuria)
   - Statin therapy for lower-risk patients (e.g., without overt CVD and <40 y/o) with LDL>100mg/dL or in those with multiple CVD risk factors
4. Primary target: LDL
   - In individuals with overt CVD, LDL goal <70mg/dL, using a high dose of a statin, is an option
   - In individuals without overt CVD, LDL goal <100mg/dL
   - If drug-treated patients do not reach the above targets on maximal tolerated statin therapy, a reduction in LDL of ~30–40% from baseline is an alternative therapeutic goal
5. Triglycerides goal: <150mg/dL
6. HDL goal: Men >40mg/dL; Women >50mg/dL
7. Combination therapy is not generally recommended due to the lack of additional CV benefit above statin therapy alone
8. Note: Statin therapy is contraindicated in pregnancy

C. Antiplatelet agents
1. Aspirin: 75–162mg/day
   - Primary prevention
     a. Consider Aspirin therapy in those with T1DM or T2DM who are at increased CV risk (10-year risk >10%). This includes most men aged >50 or women aged >60 who have at least one additional major risk factor (family history of CVD, HTN, smoking, dyslipidemia, or albuminuria)
     b. Use clinical judgment to determine the need for Aspirin therapy in patients
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with moderate CVD risk (10-year 5–10%)  
c. Aspirin is not recommended in diabetic adults at low CVD risk (10-year risk <5%)  
  • Secondary prevention: Use Aspirin in those with diabetes with a history of CVD  
2. Clopidogrel: 75mg/day should be used in patients with CVD and documented Aspirin allergy  
3. Aspirin (75–162mg/day) and Clopidogrel (75mg/day) as dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome  

D. Smoking cessation (See Chapter 39, Smoking Cessation)  
1. Advise all patients not to smoke  
2. Management: Smoking cessation counseling and other forms of treatment  

E. CHD screening and treatment  
1. Screening: in asymptomatic patients, routine screening is not recommended  
2. Treatment  
  • In patients with known CVD, consider ACE inhibitor, Aspirin and Statin therapy  
  • In patients with prior MI, continue β-blockers for at least 2 years after the event  
  • Avoid Thiazolidinedione (Pioglitazone [Actos]) in patients with symptomatic heart failure  
  • Metformin may be used in patients with stable CHF if renal function is normal; should be avoided in unstable or hospitalized patients with CHF  

F. Nephropathy  
1. General information  
  • Diabetic nephropathy occurs in 20–40% of patients with diabetes and is the leading cause of ESRD  
  • Optimize glucose and BP control to reduce the risk or slow the progression of nephropathy  
2. Definitions of abnormalities in albumin excretion  
  • Screen for increased urinary albumin excretion with the albumin to creatinine ratio in a random spot collection  
  • Normal: <30µg/mg creatinine  
  • Increased urinary albumin excretion: ≥30µg/mg creatinine  
  • Historically, ratios between 30 and 299 have been called microalbuminuria and ≥300 have been called macroalbuminuria (clinical albuminuria)  
  • Exercise within 24 h, infection, CHF, marked hyperglycemia, and marked hypertension may elevate urinary albumin excretion over baseline values  
  • 2 of 3 specimens collected within a 3- to 6-month period should be abnormal before considering a patient to have developed increased urinary albumin excretion or had a progression in albuminuria  
3. Screening  
  • Annual assessment of urine albumin excretion in:  
    a. T1DM with diabetes duration ≥5 years  
    b. All T2DM starting at diagnosis  
      • Assess serum creatinine at least annually in all adults with diabetes regardless of the degree of urine albumin excretion. Use serum creatinine to estimate GFR and stage the level of chronic kidney disease (CKD), if present  
4. Treatment  
  • In nonpregnant patients with modestly elevated (30–299mg/day) or higher levels (≥300mg/day) of urinary albumin excretion, an ACE inhibitor or ARB (but not both in combination) is recommended  
    a. In hypertensive T1DM with any degree of albuminuria, ACE inhibitors have shown to delay the progression of nephropathy  
    b. In hypertensive T2DM with microalbuminuria, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria  
    c. In T2DM with hypertension, macroalbuminuria, and renal insufficiency (serum creatinine>1.5), ARBs have been shown to delay the progression of nephropathy  
    d. Monitor serum creatinine and serum potassium when using ACE inhibitors,
ARBs, or diuretics
- Reduction of protein intake:
  a. 0.8–1.0g/kg/day for patients with diabetes and earlier stages of CKD
  b. 0.8g/kg/day in later stages of CKD
- Continue to monitor urine albumin excretion to assess both response to therapy and progression of disease
- Evaluate and manage potential complications of CKD when eGFR <60mL/min/1.73m²
- Referral to nephrology in patients with advanced kidney disease

G. Retinopathy
1. General information
   - Prevalence is strongly related to the duration of diabetes
   - The most frequent cause of new cases of blindness among adults aged 20–74 years
   - Glaucoma, cataracts and other eye disorders occur earlier and more frequently in diabetic patients
   - Optimize glucose and BP control to reduce the risk or slow the progression of retinopathy
2. Screening
   - T1DM: adults and children aged ≥10 years should have an initial dilated and comprehensive eye exam within 5 years after the onset of diabetes
   - T2DM: initial dilated and comprehensive eye exam shortly after the diagnosis of diabetes
   - Frequency of exam: annually for T1DM and T2DM patients.
     a. Less frequent exams (every 2 yr) may be considered if no retinopathy is present for one or more eye exams
     b. More frequently if retinopathy is progressing
   - High-quality fundus photographs can detect most clinically significant diabetic retinopathy. A trained eye care provider should interpret the images
     a. Retinal photography may be used as a screening tool
     b. It is not a substitute for a comprehensive eye exam
   - Women with pre-existing diabetes who are planning pregnancy or who have become pregnant should have:
     a. A comprehensive eye examination and be educated on diabetic retinopathy
     b. Eye exam should occur in the first trimester with close follow-up throughout pregnancy and for 1 year postpartum
3. Treatment
   - Prompt referral to ophthalmology specialists
   - Laser photocoagulation therapy is indicated to reduce vision loss in high-risk PDR, clinically significant macular edema, and in some cases of severe NPDR
   - Anti-vascular endothelial growth factor (VEG) therapy is indicated for diabetic macular edema
   - Aspirin therapy for cardioprotection does not increase the risk of retinal hemorrhage. Aspirin is not contraindicated in patients with retinopathy

H. Neuropathy
1. Screening for distal symmetric polyneuropathy (DPN)
   - All T2DM at diagnosis and at least annually thereafter
   - All D1DM 5 years after the diagnosis and at least annually thereafter
2. Screening for signs and symptoms of cardiovascular autonomic neuropathy (CAN)
   - T2DM: at diagnosis
   - T1DM: 5 years after diagnosis
3. Medications are recommended for the relief of specific symptoms related to painful DPN and autonomic neuropathy. Drugs approved for the treatment of pain related to DPN:
   - Duloxetine (Cymbalta): 60mg QD
   - Pregabalin (Lyrica): 50mg TID

I. Foot care
1. All patients with diabetes should have an annual comprehensive foot exam to identify risk factors predictive of ulcers and amputations. Foot exam should include:
• Inspection
• Assessment of foot pulse
• Testing for loss of protective sensation (LOPS): 10-g monofilament plus testing any one of the following:
  a. Vibration using tuning fork
  b. Pinprick sensation
  c. Ankle reflexes
  d. Vibration perception threshold

2. All patients with diabetes should receive general foot self-care education
3. A multidisciplinary approach is recommended for patients with foot ulcers and high-risk feet
4. Refer patients who smoke, have LOPS and structural abnormalities, or have history of prior lower-extremity complications to foot care specialists for ongoing monitoring and lifelong surveillance
5. Initial screening for peripheral arterial disease (PAD) should include a history for claudication and an assessment of the pedal pulses. Consider obtaining an ankle-brachial index (ABI)
6. Refer patients with significant claudication or a positive ABI for further assessment and treatment

VIII. ASSESSMENT OF COMMON COMORBID CONDITIONS

A. Hearing impairment
  1. High frequency loss is associated with history of CHD and with peripheral neuropathy
  2. Low/mid frequency loss is associated with low HDL and with poor reported health status

B. Obstructive sleep apnea
  1. A risk factor for CVD
  2. Age-adjusted rates are 4- to 10-fold higher with obesity
  3. Prevalence in general population with T2DM may be up to 23% and in obese patients with T2DM exceeding 80%
  4. Treatment significantly improves quality of life and BP control

C. Fatty liver disease
  1. Unexplained elevation of LFTs is associated with higher BMI, waist circumference, TG, and fasting insulin, and with lower HDL
  2. T2DM and HTN are independent risk factors in women
  3. Interventions: improve metabolic abnormalities

D. Low testosterone in men
  1. Obesity is a major cofounder
  2. Screening and treatment of men without symptoms are not recommended

E. Periodontal disease
  1. More severe in patients with diabetes than those without diabetes
  2. Evidence that periodontal disease treatment improves glycemic control is mixed

F. Cancer: Recommend age- and sex-appropriate cancer screenings and reduce modifiable cancer risk factors

G. Fracture: Avoid Thiazolidinediones in patients with T2DM and fracture risk factors

H. Cognitive impairment

I. Depression

IX. MEDICATIONS USED IN THE TREATMENT OF T2DM

A. Criteria for selecting a drug to achieve glycemic targets:
  1. A1C reduction needed
  2. Effect on weight
  3. Risk for hypoglycemia
  4. Comorbidities
  5. Tolerability
  6. Side effect profile
  7. Ease of use
  8. Cost
B. Pharmacologic treatment

1. Oral therapies (Table 3)
   - Sulfonylurea
   - Meglitinides (Non-sulfonylurea)
   - Metformin
   - Thiazolidinediones (Glitazones)
   - Dipeptidyl peptidase-4 (DDP4) inhibitors
   - Alpha glucosidase inhibitors
   - Bile acid sequestrants (Colestipol, Cholestyramine)
   - Dopamine-2 agonists (Bromocriptine)

2. Oral combination products (Table 4)

3. Parenteral therapies
   - Amylin analog
   - GLP-1 receptor agonists (Exenatide, Liraglutide)
   - Insulin (Basal, Bolus, Mixed)—Table 5

C. Therapeutic strategies (Note: For a detailed outline in chart form of this topic, see Figure 2 in the second citation in the References at the end of this chapter, located online at http://care.diabetesjournals.org/content/35/6/1364/F2.expansion.html)

1. Initial drug therapy
   - Metformin, if no contraindication, is the preferred and most cost-effective first drug. To minimize GI side effects, Metformin should be started at a low dose with gradual titration.
   - If Metformin cannot be used, consider another oral drug such as Sulfonylurea/Glinide, Pioglitazone, or a DDP-4 inhibitor.
   - If A1C ≥9%, a combination of two noninsulin agents or with insulin itself may be necessary.
   - If patient presents with significant hyperglycemic symptoms and/or has plasma glucose >300–350 mg/dL or A1C ≥10–12%, insulin should be considered at the outset.

2. Advancing to dual combination therapy
   - If A1C is not at target after ~3 months of monotherapy, add a second oral agent, a sulfonylurea, TZD, DDP-4 inhibitor, GLP-1 receptor agonist or basal insulin.
   - The higher the A1C, the more likely insulin will be required.
   - Choice is based on patient and drug characteristics, with the goal to improve glycemic control while minimizing side effects.

3. Advancing to triple combination therapy
   - If A1C is not at target after ~3 months of dual therapy, proceed to 3-drug combination.
   - Use agents with complementary mechanisms.
   - Insulin usually provides the most robust response at this juncture where many patients would have progressive beta-cell loss.

4. Transitions to and titrations of insulin
   - Basal insulin (long-acting insulin or NPH) alone is usually the optimal initial insulin regimen in conjunction with 1 or 2 oral agents.
   - Start at a low dose 0.1–0.2 units/kg/day. Depending on the degree of hyperglycemia, larger doses (0.3–0.4 units/kg/day) may be used.
   - Titrate by 1–2 units (or increments of 5–10%) to the daily dose once or twice weekly if FBG > preagreed target.
   - Give long-acting insulin (Lantus or Lepramine) once daily or NPH at hs.
   - As the target is neared, dosage adjustments should be more modest and occur less frequently.
   - Downward titration is needed if any hypoglycemia occurs.
   - Prandial or mealtime insulin (typically the rapid insulin analogs)
     - If FBG is at target but A1C is >7%, add prandial insulin to on-going basal insulin (basal-bolus therapy).
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b. First step is to get more SMBG data to verify that postprandial hyperglycemia is occurring (e.g., >180mg/dL)

c. Two approaches

i. Gradual approach over several weeks: Add the first prandial insulin before the biggest meal, often the evening meal. Then, a second prandial insulin can be added before the meal with the next glucose excursion, often breakfast. Finally, a third prandial insulin is added before the smallest meal, often lunch

ii. Progression from basal insulin to a twice-daily premixed insulin (before breakfast and evening meals)

Table 3: Oral Drugs For Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dosage</th>
<th>Efficacy</th>
<th>Adverse Events</th>
<th>Cost/ mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas- 2nd generation (↑ insulin secretion)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride (Amaryl, generic) 1, 2, 4 mg tabs</td>
<td>1-4 mg qd</td>
<td>↓ HbA1c: 1.5-2 %</td>
<td>Hypoglycemia, weight gain</td>
<td>$13-30</td>
</tr>
<tr>
<td>Glipizide (Glucomet, generic 5, 10 mg tabs) (Glucomet XL, generic 2.5, 5, 10 mg tabs)</td>
<td>5-20 mg qd or 5-30 mg fl qd</td>
<td>↓ HbA1c: 1.5-2 % (Prandin); 0.7-1.4</td>
<td>↓ FPG: 50-70 mg/dL, No effect on lipids</td>
<td>$17-38</td>
</tr>
<tr>
<td>Glyburide (Micronase, generic 2.5, 5 mg tabs)</td>
<td>2-20 mg qd or 1.5-12 mg qd (micronized)</td>
<td>↓ HbA1c: 1.5-2 %</td>
<td>Hypoglycemia if a meal is missed, weight gain</td>
<td>$14-150</td>
</tr>
<tr>
<td>Non-sulfonylurea Secretagogues (↑ insulin secretion)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nateglinide (Starlix, generic) 60, 120 mg tabs</td>
<td>60-120 mg tid before meals</td>
<td>↓ HbA1c: 1.5-2 % (Prandin); 0.7-1.4</td>
<td>↓ FPG: 50-70 mg/dL</td>
<td>$249-480</td>
</tr>
<tr>
<td>Repaglinide (Prandin) 0.5, 1, 2 mg tabs</td>
<td>1-4 mg tid before meals</td>
<td>↓ HbA1c: 1.5-2 % (Starlix)</td>
<td>↓ FPG: 50-70 mg/dL</td>
<td>$249-480</td>
</tr>
<tr>
<td>Biguanides (↓ hepatic glucose output, ↑ peripheral glucose uptake, ↑ intestinal glucose use)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin (Glumetza, Fortamet, Glumetza) 500, 1000 mg tabs</td>
<td>500-1000 mg qd</td>
<td>↓ HbA1c: 1.5-2 %</td>
<td>↓ FPG: 50-70 mg/dL, ↓ LDL, ↓ HDL, ↓ weight</td>
<td>$13-36</td>
</tr>
<tr>
<td>Metformin ER-24h</td>
<td>500 -2000 mg qd or 1000 mg bid with meals</td>
<td>↓ HbA1c: 1.5-2 %</td>
<td>↓ FPG: 50-70 mg/dL, ↓ LDL, ↓ HDL, ↓ weight</td>
<td>$35-140</td>
</tr>
<tr>
<td>Thiazolidinediones (&quot;Glitazones&quot;) (improve peripheral insulin sensitivity)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>15-45 mg qd</td>
<td>↓ HbA1c: 1.2-1.5 %</td>
<td>↓ FPG: 35-40 mg/dL</td>
<td>$194-234</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>4-8 mg qd</td>
<td>↓ HbA1c: 1.2-1.5 %</td>
<td>↓ FPG: 35-40 mg/dL</td>
<td>$182-250</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors (delay carbohydrate absorption)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose (Precose, generic) 25, 50, 100 mg tabs</td>
<td>50-100 mg tid with meals</td>
<td>↓ HbA1c: 0.5-1 %</td>
<td>GI disturbances, ↑ LFTs</td>
<td>$86-110</td>
</tr>
<tr>
<td>Miglitol (Glyset) 25, 50, 100 mg tabs</td>
<td>50-100 mg tid with meals</td>
<td>↓ HbA1c: 0.5-1 %</td>
<td>GI disturbances, ↑ LFTs</td>
<td>$118</td>
</tr>
<tr>
<td>DPP-4 Inhibitors (↑ insulin secretion and ↓ glucagons secretion)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alogliptin (Nesina) 6.25, 12.5, 25 mg</td>
<td>25 mg qd</td>
<td>↓ HbA1c: 0.5-0.8 %</td>
<td>GI disturbances, ↑ LFTs</td>
<td>$270</td>
</tr>
<tr>
<td>Linagliptin (Tradjenta) 5 mg tabs</td>
<td>5 mg qd</td>
<td>↓ HbA1c: 0.5-0.8 %</td>
<td>GI disturbances, ↑ LFTs</td>
<td>$270</td>
</tr>
<tr>
<td>Saxagliptin (Onglyza) 2.5, 5 mg tabs</td>
<td>2.5-5 mg qd</td>
<td>↓ HbA1c: 0.5-0.8 %</td>
<td>GI disturbances, ↑ LFTs</td>
<td>$270</td>
</tr>
<tr>
<td>Sitagliptin (Januvia) 25, 50, 100 mg tabs</td>
<td>100 mg qd</td>
<td>↓ HbA1c: 0.5-0.8 %</td>
<td>GI disturbances, ↑ LFTs</td>
<td>$270</td>
</tr>
<tr>
<td>GLP-1 Agonists (injections) (↑ insulin secretion, ↓ glucagons secretion; slows gastric emptying; ↑ satiety)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide (Byetta) 250 mcg/mL in 1.2 and 2.4 mL pre-filled pens</td>
<td>5-10 mcg SQ bid before breakfast and dinner</td>
<td>↓ HbA1c: 0.5-1 %</td>
<td>N/V, diarrhea, acute pancreatitis, thyroid tumor</td>
<td>$282-385</td>
</tr>
<tr>
<td>Liraglutide (Victoza) 6 mg/mL in 3 mL pre-filled pens</td>
<td>1.2-1.8 mg SQ qd</td>
<td>↓ HbA1c: 0.5-1 %</td>
<td>N/V, diarrhea, acute pancreatitis, thyroid tumor</td>
<td>$340/2 pens</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin (Invokana)</td>
<td>100-300 mg qd</td>
<td>↓ HbA1c: 0.5-1 %</td>
<td>Myotic genital infections, ↑ risk of bladder infection (Dapagliflozin)</td>
<td>$300</td>
</tr>
<tr>
<td>Dapagliflozin (Farxiga)</td>
<td>100-300 mg qd</td>
<td>↓ HbA1c: 0.5-1 %</td>
<td>Myotic genital infections, ↑ risk of bladder infection (Dapagliflozin)</td>
<td>$270</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colesevelam (Welchol) 625 mg tabs</td>
<td>3.8 g (tabs) qd or divided bid</td>
<td>↓ HbA1c: 0.5-1 %</td>
<td>Constipation, dyspepsia, ↑ T0L drug interaction</td>
<td>$245</td>
</tr>
<tr>
<td>Pramlintide (Symryn) 1000 mcg/mL in 1.5 and 2.7 mL pre-filled pens</td>
<td>60-120 mcg SQ bid immediately prior to meals</td>
<td>↓ HbA1c: 0.3-0.6 %</td>
<td>N/V, anorexia, headache</td>
<td>$462/ pen</td>
</tr>
</tbody>
</table>
### Table 4: Oral Combination Products

<table>
<thead>
<tr>
<th>Drug (Formulations)</th>
<th>Usual Dosage</th>
<th>Cost/month*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actoplus Met (pioglitazone/metformin generic)</td>
<td>15/500 mg bid or 15/1000 mg XR qd</td>
<td>$143-429, $156-458 XR</td>
</tr>
<tr>
<td>Avandam® (glibenclamide/pioglitazone)</td>
<td>1 tab qd</td>
<td>$85-200</td>
</tr>
<tr>
<td>Avandaryl® (rosiglitazone/metformin)</td>
<td>2/500, 4/500, 4/1000, 4/10000 labs</td>
<td>$130-280</td>
</tr>
<tr>
<td>Duetact (glimepiride/pioglitazone, generic)</td>
<td>4/30 mg qd</td>
<td>$130-297</td>
</tr>
<tr>
<td>Glucovance (glyburide/metformin, generic)</td>
<td>1 tab bid with meals</td>
<td>$23-101</td>
</tr>
<tr>
<td>Jentadueto (linagliptin/metformin)</td>
<td>1 tab bid</td>
<td>$135</td>
</tr>
<tr>
<td>Kazarol (glibenclamide/metformin)</td>
<td>1 tab bid</td>
<td>$140</td>
</tr>
<tr>
<td>Kombiglyze XR (saaxiglitazone/metformin)</td>
<td>5/1000 mg to 5/2000 mg qd</td>
<td>$230-240</td>
</tr>
<tr>
<td>Metaglu (glipizide/metformin, generic)</td>
<td>2.5/500 mg bid</td>
<td>$130-280</td>
</tr>
<tr>
<td>Oseni (alogliptin/pioglitazone)</td>
<td>1 tab qd</td>
<td>$274</td>
</tr>
<tr>
<td>Prandimet (repaglinide/metformin)</td>
<td>1/500-2/500 mg bid-tid</td>
<td>$96</td>
</tr>
<tr>
<td>Janumet (sitagliptin/metformin)</td>
<td>50/500 mg bid</td>
<td>$217</td>
</tr>
<tr>
<td>Juvisync (sitagliptin/simvastatin)</td>
<td>1 tab qd</td>
<td>$271</td>
</tr>
</tbody>
</table>

*The Avandia-Rosiglitazone Medicines Access Program (a REMs program) now restricts Avandia use to patients who have already been on Avandia, or Type 2 diabetics who have not achieved adequate glucose control with the other antidiabetic medications.

*Cost/month with usual dosage range starting with starting dose and going up to max dose, rounded to the nearest dollar, based on price listed at www.goodrx.com (assessed 3/17/2013). Generic prices are used if available.

### Table 5: Types Of Insulin

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Common Insulin Product (Brand Name)</th>
<th>Onset of Action</th>
<th>Time to Peak</th>
<th>Duration of Action</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting</td>
<td>Lispro (Humalog), aspart (Novolog), glulisine (Apidra)</td>
<td>15-30 min</td>
<td>0.5-1 h</td>
<td>4-6 h</td>
<td>$160/v, $300/5 pens</td>
</tr>
<tr>
<td>Short-acting</td>
<td>Human Regular (Humulin-R, Novolin-R, ReliOn/Novolin R)</td>
<td>0.5-1 h</td>
<td>2-3 h</td>
<td>6-8 h</td>
<td>$85/v, $25 (ReliOn)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Human NPH (Humulin N, Novolin N, ReliOn/Novolin N)</td>
<td>2-4 h</td>
<td>4-10 h</td>
<td>10-16 h</td>
<td>$86/v, $25 (ReliOn)</td>
</tr>
<tr>
<td>Long-acting</td>
<td>Detemir (Levemir)</td>
<td>2-4 h</td>
<td>Flat</td>
<td>17-23 h</td>
<td>$150/v, $250/5 pens</td>
</tr>
<tr>
<td>Glargine (Lantus)</td>
<td>2-4 h</td>
<td>Flat</td>
<td>24 h</td>
<td>$1500, $2425/5 pens</td>
<td></td>
</tr>
<tr>
<td>Premixed Combinations</td>
<td>70% NPH/30% Regular (Humulin 70/30, Novolin 70/30, ReliOn/Novolin 70/30)</td>
<td>0.5-1 h</td>
<td>Dual</td>
<td>10-16 h</td>
<td>$186/v, $25 (ReliOn)</td>
</tr>
<tr>
<td>70% NPA/30% Aspart (Novolog Mix 70/30)</td>
<td>&lt;0.25 h</td>
<td>Dual</td>
<td>10-16 h</td>
<td>$300/5 pens</td>
<td></td>
</tr>
<tr>
<td>75% NPL/25% Lispro (Humalog Mix 75/25)</td>
<td>&lt;0.25 h</td>
<td>Dual</td>
<td>10-16 h</td>
<td>$300/5 pens</td>
<td></td>
</tr>
<tr>
<td>50% NPL/50% Lispro (Humalog Mix 50/50)</td>
<td>&lt;0.25 h</td>
<td>Dual</td>
<td>10-16 h</td>
<td>$300/5 pens</td>
<td></td>
</tr>
</tbody>
</table>

*The time course may vary considerably in different individuals or at different times in the same individual. NPL = neutral protamine lispro, NPA = neutral protamine aspart.

*Cost rounded to the nearest dollar, based on price listed at www.goodrx.com (assessed 3/17/2013). Generic prices are used if available.

### Table 6: Which Insulin to Adjust

<table>
<thead>
<tr>
<th>Out of Range Blood Glucose Value</th>
<th>Insulin Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning fasting blood glucose</td>
<td>PM or bedtime NPH or glargine or detemir</td>
</tr>
<tr>
<td>Before lunch</td>
<td>Morning rapid/short-acting insulin</td>
</tr>
<tr>
<td>Before dinner</td>
<td>Morning NPH or lunchtime rapid/short-acting insulin</td>
</tr>
<tr>
<td>Before bedtime</td>
<td>Dinner rapid/short-acting</td>
</tr>
<tr>
<td>During the night (low)</td>
<td>Evening NPH or move dinner NPH to bedtime</td>
</tr>
</tbody>
</table>

---

56. Diabetes Mellitus
Management of Common Ambulatory Conditions
X. INSULIN THERAPY

A. Basal-bolus insulin regimens

1. Dosage calculations for multiple dose injection (MDI):
   - **First**, estimate the patient’s total daily dose of insulin (TDD)
     \[ \text{TDD} = 0.4-0.5 \text{ u/kg/d} \times \text{patient’s weight (kg)} \]
   - **Second**, calculate the basal insulin dose
     Glargine or Detemir or NPH dose = TDD \times 50%
   - **Third**, calculate the insulin coverage for each meal (Humalog, NovoLog, Regular)
     Pre-meal insulin dose = TDD \times 50% \div 3
   - **Fourth**, calculate the corrective insulin ratio (supplemental scale)
     \[ 1800 \div \text{TDD} = \text{fall in blood glucose per 1 unit of Humalog or NovoLog} \]
     \[ 1500 \div \text{TDD} = \text{fall in blood glucose per 1 unit of Regular insulin} \]
     Or use:
     An arbitrary carb: insulin ratio (CIR): 1 unit per 50mg/dL
     An arbitrary insulin: carb = 1:15g CHO

B. Twice-daily, mixed insulin regimen

1. Dosage calculations:
   - **First**, estimate the patient’s total daily dose of insulin (TDD)
     \[ \text{TDD} = 0.4–0.5 \text{ u/kg/d} \times \text{patient’s weight (kg)} \]
   - **Second**, calculate the dose before breakfast (AM dose)
     \[ \text{AM dose} = \text{TDD} \times \text{b} (\text{b} \text{as NPH and } \text{a} \text{as rapid- or short-acting insulin}) \]
   - **Third**, calculate the dose before dinner (PM dose)
     \[ \text{PM dose} = \text{TDD} \times \text{a} (\text{½ as NPH } \text{½ as rapid- or short-acting insulin}) \]

C. Other considerations

1. Use lower starting dosage in patients who have normal weight, physically active, or unusual eating, in elderly or those with severe renal impairment
2. SMBG: fasting, pre-meal or 2 h post-meal, and bedtime
3. Insulin dose adjustment (refer to Table 6)

D. Writing insulin prescriptions and ordering supplies

1. Write insulin name in full. Avoid abbreviation “U” for units
2. Insulin is available in 10mL vials of 100 units/ml concentration. Each vial contains 1000 units
3. Some insulin products are also available in disposable pens (300 U/3mL). They are useful for patients who have difficulty drawing up accurate doses
4. Insulin syringes package in boxes of 100 ($16–26). They are available in sizes of 0.3mL (30 U), 0.5mL (50 U), 1mL (100 U). Needle size: 29, 30, 31 gauge; needle length: 12, 8, 6mm (no pitch if use short needles)
5. Disposable pens require single-use needle tips in 100/box (29, 30, 31, 32 gauge) ($3–40), needle length: 8, 6, 5, 4mm
6. Alcohol wipes in boxes of 200 ($3)
7. Refer the patient for Diabetes Education

CLINICAL PEARLS

- Diabetes mellitus is a progressive disease which requires multidisciplinary treatment approach and ongoing patient self-management of the disease
- Comprehensive CV risk reduction must be a major focus of therapy. Care should be focused on treatment of blood pressure, glycemic control, dyslipidemia, and smoking cessation
- Select appropriate medication management to get to goals
- Glycemic targets and hypoglycemic therapies must be individualized to meet the patient’s needs
- Diet and lifestyle modifications are the cornerstone of T2DM treatment
- Metformin is recommended as the first-line drug. It is common to require 2–3 drug combinations to achieve glycemic control. Ultimately, many T2DM patients will require insulin therapy
57. Thyroid Disease & Testing

Management of Common Ambulatory Conditions

References

Michael B. Wenstock, MD

57. Thyroid Disease & Testing

Note: These recommendations are for nonpregnant patients

I. INTRODUCTION/BACKGROUND
A. Thyroid-stimulating hormone (TSH): Secreted by the pituitary. Stimulates the steps of thyroid hormone production
B. The thyroid gland: Secretes mostly T4 and a small amount of T3
C. The most active thyroid hormone is T3. About 90% of circulating T3 is derived from peripheral deiodination of T4
D. Over 99% of circulating thyroid hormones are bound to proteins, mostly thyroid-binding globulin (TBG)
E. Approximately 2% of the adult population has hypothyroidism and another 5–17% have mild/subclinical hypothyroidism (elevated TSH, normal serum free thyroxine)
F. Approximately 0.2% of the adult population has hyperthyroidism and 0.1–6.0% has mild/subclinical hyperthyroidism (decreased TSH, normal free thyroxine)
G. Screening: The American Thyroid Association recommends that adults be screened for thyroid dysfunction by measurement of the TSH beginning at age 35yrs and every 5yrs thereafter. Patients at high risk for thyroid disease should be screened more often

II. DIFFERENTIAL DIAGNOSIS
A. Hyperthyroidism
1. Toxic diffuse goiter (Graves’ disease)—most common cause
2. Iatrogenic illness: Excessive administration of Thyroxine or Triiodothyronine (second most common cause)
3. Autonomous toxic adenoma (toxic nodular goiter)
   a. Single adenoma (Plummer’s disease)
   b. Multiple adenomas (toxic multinodular goiter)
4. Thyroiditis: Inflammation induced release of thyroxine. May be subacute, silent (non-tender gland) or post-partum
5. Iodine-induced hyperthyroidism: Jod-Basedow disease may occur in patients with multinodular goiter who take large amounts of iodine; health food preparations; Amiodarone
6. Excessive pituitary TSH (TSH secreting pituitary adenoma) or trophoblastic disease
7. Excessive ingestion of thyroid hormone (Thyrotoxicosis factitia)
8. Rarely: Thyroid cancer, choriocarcinoma, hydatidiform mole, embryonal testicular carcinoma, struma ovarii
B. Hypothyroidism
1. Primary hypothyroidism
   a. Autoimmune thyroiditis (Hashimoto’s thyroiditis/Chronic lymphocytic thyroiditis): Most common cause in the US
b. Surgical removal of the thyroid gland
c. Radioactive iodine thyroid gland ablation
d. External irradiation
e. Thyroid gland iodine organification defect
f. Idiopathic
2. Secondary (central) hypothyroidism
   a. Pituitary disease
   b. Hypothalamic disease

III. SIGNS AND SYMPTOMS AND LAB ABNORMALITIES
A. Hyperthyroidism: Severity of symptoms may vary (age of patient, duration of illness, magnitude of hormone excess)
   1. General: Weight loss, poor sleep, alterations in appetite, fatigue, heat intolerance, increased sweating, mental disturbances
   2. Eye: Vision change, photophobia, diplopia, exophthalmos
   3. Neck: Possibly thyroid enlargement
   4. Cardio: Palpitations and tachycardia, exertional intolerance/dyspnea on exertion
   5. Neuro: Tremor, sudden paralysis
   6. GYN: Menstrual disturbance (decreased flow), impaired fertility
   7. Extremities: Pretibial myxedema (Graves’ disease)
B. Hypothyroidism
   1. General: Weight gain, poor sleep, alterations in appetite, fatigue, cold intolerance, hypothermia, dry or yellow skin, loss of hair, constipation
   2. ENT: Thick tongue
   3. Neck: Possibly thyroid enlargement (goiter)
   4. Cardio: Bradycardia, cardiomyopathy
   5. Neuro: Reflex delay, ataxia, memory and mental impairment, decreased concentration, depression, myalgias
   6. GYN: Menstrual disturbance (increased flow), impaired fertility
   7. Extremities: Myxedema
   8. Lab abnormalities: In addition to abnormal thyroid tests (see below), increased cholesterol, increased liver enzymes and CPK, increased prolactin, hyponatremia, hypoglycemia, anemia (normal or increased MCV)

IV. TECHNIQUE FOR PHYSICAL EXAMINATION OF THE THYROID GLAND
A. Inspection: Located below the cricoid cartilage, observe while patient is swallowing water
B. Palpation
   1. Examine from behind the patient
   2. Palpate with 3 fingers on either side of the lower trachea (index fingers just below the cricoid) for size, shape, consistency, tenderness or nodularity
C. Examination during swallowing: The thyroid gland moves upward with swallowing and may be more easily palpated

V. INTERPRETATION OF LAB TESTS
A. Introduction
   1. Primary screening test for thyroid abnormalities is TSH (third generation) (see below)
   2. Free T₄ can be measured directly
   3. FTI (free thyroxine index) is a calculation of the T₄ and T₃RU (see below) and is an estimation of the free T₄. Used because the T₄ level may not be a true indication of a patient’s thyroid status because it is affected by altered states of protein binding
   4. If the free T₄ is measured, FTI (which is an approximation of free T₄) does not need to be measured
B. Definition of commonly obtained thyroid tests
   1. TSH
      a. Third generation assays measure TSH as low as 0.01mU/L. Second generation
assays measure to 0.1mU/L.

b. TSH levels are decreased with:
   i. Primary hyperthyroidism (see II. A. Differential diagnosis of hyperthyroidism)
   ii. Thyroid hormone replacement
   iii. Severe nonthyroidal illness, pregnancy (1st trimester)
   iv. Dopamine, Dopamine agonists (Levodopa) and Glucocorticoids
   v. Mild/subclinical hyperthyroidism (decreased TSH and normal free level T4)

c. TSH levels are elevated with:
   i. Primary hypothyroidism (see II. B. Differential diagnosis of hyperthyroidism)
   ii. Hyperthyroidism secondary to pituitary neoplastic secretion of thyrotropin
   iii. Recovery from nonthyroidal illness
   iv. With dopamine antagonists (Metoclopramide), Phenothiazines, Lithium, Amiodarone, and some antipsychotics
   v. Mild/subclinical hypothyroidism (elevated TSH and normal free T4)

2. Free T4: Measures the actual free T4. May be falsely elevated in patients receiving Heparin (especially with dialysis), with depressed patients or with severe nonthyroidal illness

3. T3RU: Measures thyroxine by radioimmunoassay and is affected by states of altered thyroxine binding. It measures both circulating thyroxine bound to protein and active (unbound) thyroxine

4. T4RU: Measures the percentage of T4 not bound to protein. If normal, thyroid binding proteins are not significantly altering the T4 measurement, and T4 will usually be an accurate estimation of free T4. If T4RU is abnormal, then look at FTI

5. T3: For diagnosis of T3 thyrotoxicosis (thyrotoxicosis with normal T4 values). Like T4, only measures bound T3. Not useful in hypothyroidism. Obtain when suspect thyrotoxicosis in patients with low TSH and normal or low T4 (T3 toxicosis)

6. FTI: The FTI = T4 × T3RU/100. The FTI usually corrects for abnormalities of thyroxine binding and is a good approximation of the amount of active (unbound) thyroxine

7. Reverse T3 (RT3): RT3 is an inactive isomer of T3. Level is increased in hyperthyroidism, by drugs that block conversion of T4 to T3 (Amiodarone, Propranolol), and in nonthyroid illnesses that decrease the T3 concentration

8. Serum thyroglobulin: Storage site for thyroid hormones. Elevated in hyperthyroidism and thyroiditis. Reduced or undetectable in thyrotoxicosis factitia (exogenous thyroid hormone suppresses endogenous production)

9. Thyroid antibodies: Found in 5–10% of normal subjects and 20% of hospitalized patients
   a. Antimicrosomal antibodies: Elevated in Hashimoto’s thyroiditis or Graves’ disease
   b. Antithyroglobulin antibodies: Elevated in Hashimoto’s thyroiditis or Graves’ disease

VI. OTHER TESTS

A. Calcitonin assay: Useful serum marker in medullary thyroid carcinoma. May also be elevated in azotemia, hypercalcemia, pernicious anemia, thyroiditis, and pregnancy as well as other malignancies

B. Radioiodine (123I) Uptake and scan of thyroid gland: Provides a picture of thyroid uptake
   1. Elevated: Graves’ disease, toxic nodular goiter, toxic adenoma, dietary iodine deficiency, pregnancy, early Hashimoto’s thyroiditis, nephrotic syndrome, recovery from thyroid hormone suppression, recovery from subacute thyroiditis, some thyroid enzyme deficiencies
   2. Decreased: Administration of iodine (including drugs, contrast dyes, etc.), antithyroid drugs, subacute thyroiditis, thyroid hormone administration, severe (high turnover) Graves’ disease, thyroid gland damage (thyroiditis, surgery, radioiodine), ectopic functioning thyroid tissue

C. Ultrasound: To differentiate solid from cystic nodules. Purely cystic are usually not cancer
D. Fine-needle aspiration (FNA) thyroid biopsy: See X. D. below

VII. ALGORITHM FOR EVALUATION OF THYROID STATUS IN AMBULATORY PATIENTS

![Algorithm Diagram]

—Serum TSH may be in normal range in patients with hyperthyroidism secondary to hypothalamic or pituitary disease

Table adapted from: Pittman JG. Evaluation of patients with mildly abnormal thyroid function tests. Am Fam Phys 1996;54:962. Used with permission.

VIII. MANAGEMENT OF HYPERTHYROIDISM

A. Graves’ disease (Basedow’s disease): Guidelines below are for non-pregnant patients

1. Diagnosis
   a. Caused by thyroid stimulating antibodies which bind to and activate the thyroid stimulating hormone receptor on thyroid cells
   b. Symptoms of hyperthyroidism, low TSH, high free T₄, elevated antithyroglobulin and antimicrosomal antibodies, diffusely enlarged thyroid gland

2. Approach
   a. Drugs: If mild or moderate hyperthyroidism/small or moderately enlarged thyroid gland, then consider use of antithyroid drugs. If relapse while on drugs, then proceed to definitive radioiodine therapy
   b. Radioiodine therapy: If markedly elevated serum thyroxine, goiter > 4 times normal size or serum triiodothyronine:thyroxine ratio > 20:1, then proceed to definitive therapy with radioiodine

3. Antithyroid drugs: Perform follow-up thyroid testing in 4–6 weeks
   a. Methimazole (Tapazole): Preferred agent
      i. Less frequent dosing than Propylthiouracil and lower incidence of acute hepatic necrosis
      ii. Initially 15–30mg PO QD and then decrease dose as symptoms resolve and free T₄ returns to normal, maintenance 5–10mg/day
   b. Propylthiouracil (PTU)
      i. Drug of choice in breast-feeding or pregnancy (use lower doses)
      ii. Blocks peripheral conversion of T₄ to T₃
iii. Dose 300mg PO QD in 3 divided doses and then decrease dose as symptoms resolve and free T₄ returns to normal, maintenance: 100–200mg/day
c. Side effects: Minor skin rashes, rarely agranulocytosis, acute hepatic necrosis

4. Symptomatic relief: β-blockers (Propranolol)
a. Symptomatic relief until hyperthyroidism is resolved. It has no effect on thyroid hormone secretion
b. Dose: Begin with 10mg PO QID and increase. Usual dose is 20mg PO QID

5. Radioactive iodine
a. May be given in an ablative dose (with life-long thyroid replacement therapy necessary) or in a smaller dose to attempt to induce a euthyroid state
b. Elderly or patients with cardiac history may benefit from treatment with antithyroid drugs before radioactive iodine therapy (to deplete the gland of stored hormone)
c. Contraindicated in pregnancy
d. Patients usually become hypothyroid by 3 months. May require partial thyroid replacement 2 months after radioactive iodine treatment. Note: TSH may not be a good indicator of thyroid status for the first several months after treatment
e. Frequency of follow-up: 3 months, 6 months, 1yr, then, if thyroid status has normalized (with replacement therapy), every 1–2yrs

6. Surgery: Not commonly performed in the US, but may be appropriate with pregnant women intolerant of antithyroid drugs or pediatric patients

B. Toxic solitary thyroid nodules
1. Definition: A single hyperfunctioning thyroid nodule causing hyperthyroidism
2. Symptomatic: Propranolol with doses as above in Graves’ disease
3. Definitive treatment
   a. Radioactive iodine: Permanent hypothyroidism occurs in less than 10% of patients
   b. Surgery: If radioactive iodine is contraindicated or <40

C. Toxic multinodular goiter
1. General: Usually affects older patients
2. Symptomatic: Propranolol with dose as above in Graves’ disease
3. Antithyroid meds: 95% recurrence rate after thioureas are stopped
4. Definitive treatment
   a. Radioactive iodine: Thiourea treatment before iodine. Requires high doses of radioactive iodine. Recurrences are common—patients need close follow-up
   b. Surgery: Reserved for cosmetic purposes or pressure symptoms

D. Subacute thyroiditis
1. General: Painless inflammation of the thyroid gland lasting weeks to months causing transient hypo- or hyperthyroidism. Subsides spontaneously
2. Symptomatic hyperthyroidism: Propranolol 10–40mg PO QID
3. Treat transient hypothyroidism with Levothyroxine 0.05–0.1mg PO QD if symptomatic
4. Antithyroid medication and radioactive iodine are ineffective as thyroid hormone production is low

E. Suppurative (bacterial) thyroiditis
1. Often occurs during course of systemic infection
2. ATBs: Empiric
3. Surgical drainage if fluctuant

F. Thyrotoxicosis factitia
1. Occurs from exogenous ingestion of thyroid hormone
2. If it is suspected, then check serum thyroglobulin. The thyroglobulin level is reduced or undetectable in thyrotoxicosis factitia (exogenous thyroid hormone suppresses endogenous production)
3. Manage with patient education or psychiatric referral

G. Mild/subclinical hyperthyroidism (also called compensated hypothyroidism, decreased thyroid reserve, and prehypothyroidism)
1. Definition: Low TSH and normal free T₄
IX. MANAGEMENT OF HYPOTHYROIDISM

A. Autoimmune thyroiditis (Hashimoto’s thyroiditis):
   1. Most common thyroid disorder in the US. Thyroid gland is usually diffusely enlarged, firm and finely nodular.
   2. Thyroid autoantibodies (antithyroid peroxidase) are positive 95% of the time. Antithyroglobulin antibodies are increased 60% of the time.
   3. Management
      a. Elderly or patients with coronary disease: Start with Levothyroxine (Synthroid, Levothroid) 0.025mg PO QD (This dosage can be increased in the increments of 0.025–0.050 mg every 4–6 weeks until TSH level returns to normal).
      b. Young patients/healthy patient: Start with Levothyroxine (Synthroid) 0.05–0.1mg PO QD, with the dosage increased as indicated by TSH levels.
      c. Note: Older patients generally require 2/3 the amount as younger patients.
   4. Follow-up: Once TSH normalizes and patient is asymptomatic, then check TSH every 1–2yrs.
   5. Half-life of T4 is about 7 days. Check TSH level 6–8 weeks after a change in dosage of thyroid replacement. Early testing may lead to over-treatment.

B. Surgical removal of the thyroid gland
   1. Hypothyroidism develops in 25% at 8–12yrs post-op in patients with subtotal thyroidectomy.
   2. Management as above.

C. Radioactive iodine thyroid gland ablation
   1. Hypothyroidism develops at rate of 2–5%/yr (30–70% at 10–15yrs after treatment).
   2. Management as above.

D. Subclinical hypothyroidism
   1. Normal free T4 and high TSH.
   2. Longitudinal progression to hypothyroidism of 5–8%/yr in patients with high TSH and significant titer of antimicrosomal antibodies. Incidence of hypothyroidism in patients over age 65 is 80% over 4yrs.
   3. Indications for Levothroid replacement therapy
      a. All patients with elevated TSH and a significant titer of antimicrosomal antibodies.
      b. Elderly patients with TSH greater than 20 µU/mL (20mU/L) and a negative antimicrosomal antibody test.
      c. Patients with elevated TSH and goiter (+/- antimicrosomal antibodies).
      d. History of radioiodine treatment for thyrotoxicosis and elevated TSH.
      e. Consider in symptomatic patients with elevated TSH: Start at sub-therapeutic dose of 0.05–0.075mg PO QD.
   4. If treatment is not initiated, then follow closely.

X. DIAGNOSIS AND MANAGEMENT OF SOLITARY THYROID NODULES

A. Enlargement of the thyroid gland may be diffuse or nodular and is detectable in 4% of adults. Most thyroid nodules are benign, less than 5% are malignant. If an incidental nodule > 1 cm is found, then consider fine needle aspiration. Solitary nodules are associated with higher incidence of malignancy.

B. Risk factors for thyroid cancer
   1. History: Age < 20 or > 45, male, exposure to ionizing radiation (especially in childhood), family history.
   2. Physical exam: Cervical lymphadenopathy, vocal cord paralysis, very firm nodule, rapid tumor growth, fixation to adjacent structures.

C. Factors which do not differentiate benign from malignant nodules:
1. History and physical exam  
2. Thyroid function tests  
3. Antithyroglobulin and antithyroid microsomal antibodies  
4. Ultrasound: May differentiate solid from cystic, but either may be malignant  
5. Thyroid radioiodine uptake and scan: May differentiate between a “cold” (nonfunctioning) nodule which is more likely to be malignant, and a “hot” (functioning nodule) which is less likely to be malignant, but does not definitively distinguish between benign and malignant nodules  

D. Fine needle aspiration (FNA): Test of choice  
1. Safe, reliable, inexpensive and is performed as an outpatient  
2. Technique  
   a. No anesthesia necessary  
   b. Aspiration with 25 gauge needle. Success is increased by ultrasound guidance  

E. Results  
1. If positive (suspicious or malignant), then referral for definitive therapy (surgery)  
2. If indeterminate, then consider:  
   a. Repeat FNA—or—  
   b. Radionuclide scanning: If “hot” then follow and if “cold” then surgery—or—  
   c. Trial of suppression therapy with monthly follow-up over 6 months  
      i. If size increases, then surgery  
      ii. If size decreases, then follow  
      iii. If size does not change, then consider surgery or repeat FNA  
3. If inadequate, consider referral for surgical excision in patients with one or more risk factors  
4. If benign, then trial of suppression therapy with monthly follow-up over 6 months  

XI. GOITER  
A. Differential diagnosis  
1. Hashimoto’s thyroiditis  
2. Iodide deficiency  
3. Genetic thyroid hormone defects  
4. Drug goitrogens: Lithium, Iodide, PTU, Methimazole, Phenylbutazone, Sulfonamides, Amiodarone  
5. Infiltrating diseases: Cancer, sarcoidosis  

B. Evaluation  
1. History and physical exam as above  
2. Obtain TSH, Free T4  
3. Consider thyroid radioiodine uptake and scan  
4. Consider ultrasound and FNA if nodule(s) are present  
C. Management: Per specific diagnosis  

CLINICAL PEARLS  
• Approximately 5% of the world’s population have goiter, mostly from iodine deficiency  
• Free T4 represents about 0.025% of total T4 (bound and unbound)  
• Amiodarone causes clinically significant hypothyroidism in about 8% of patients and asymptomatic hypothyroidism in another 17% of patients due to the high iodine concentration (TSH high and T4 low or normal)  
• Use caution with diagnosis of hospitalized patients. Up to 70% of moderately ill hospitalized patients will have thyroid function abnormalities  
• Symptoms of thyrotoxicosis vary with age and may be atypical, especially in the elderly  

References  
Garber JR, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the
58. Headache: Diagnosis & Management

I. Epidemiology
Most common pain problem seen in the ambulatory setting (greater than 10 million office visits/yr). Over 4 billion dollars are spent annually on over-the-counter meds for headaches. This does not include time missed from work, prescription meds, or physician visits.

II. History: The cornerstone of diagnosis is to determine which headaches are more dangerous (secondary to medical problems) by classifying as a primary (migraine, tension, cluster, etc.) or secondary (CNS mass lesions, infections/meningitis, etc.) headache.

A. Headache characteristics: Age of headache onset, location, frequency, severity, quality, speed of onset, or triggers (foods, stress, hunger, menstrual cycle, cough/exertion, position changes, etc.)

B. Associated symptoms: Photophobia, phonophobia, nausea/vomiting, sinus symptoms, fever, stiff neck, focal neurologic complaints, visual changes.

C. Meds: Past and present meds and response to treatment. Consider both abortive and prophylactic therapies. OTC meds, caffeine use, and foods may be triggers (MSG, red wine). Chronic analgesic use/abuse may lead to rebound headaches. Meds which may cause headaches (nitrates, Reserpin, Indomethacin, Minoxidil, Apresoline, oral contraceptives, hormone replacement therapy).

D. Past medical and surgical history: Malignancy, stroke, head trauma, neurosurgery, psychosocial history, hypertension, hematologic abnormalities, polymyalgia rheumatica.

E. Family History: Migraines tend to be hereditary and begin in childhood or early adult life; other headaches less so.

III. Physical Exam
A. Vital signs: Fever (meningitis, sinusitis, viral syndromes), BP
B. Ophthalmologic: Pupils, funduscopic
C. HEENT: Typanic membrane, nares and sinus exams, TMJ exam, temporal artery swelling and tenderness (especially over age 50), scalp exam, neck exam (nuchal rigidity, paraspinal tenderness or spasm, range of motion).
D. Neurologic: Visual fields, cranial nerves, motor, sensory, coordination, gait, and mental status changes

IV. DIFFERENTIAL DIAGNOSIS
A. Primary headaches (benign)
1. Tension-type headache (related to physical, mental and/or emotional stress): 47%
2. Migraine headache (with or without aura): 31%
3. Cluster headache: 7%
4. Mixed headache (usually migraine/tension)
5. Rebound headache: Caffeine, Butalbital, and narcotics
6. Neuralgias (trigeminal, occipital) characterized by brief electrical/lanceting pains
7. Uncommon syndromes (chronic paroxysmal hemicrania, hemicrania continua, cough/exertional headache, coital headache)
8. Miscellaneous: TMJ dysfunction, chronic sinus/allergies

B. Secondary headaches (not so benign)
1. CNS mass lesions (tumor, abscess)
2. Vascular (cerebral/subarachnoid hemorrhage, arteriovenous malformations, stroke/TIA, carotid dissection)
3. Infectious (meningitis, sinusitis, encephalitis)
4. Traumatic (epidural/subdural hematoma, subarachnoid/intracranial hemorrhage, post-concussion syndrome)
5. Temporal arteritis: greater than age 50, increased sedimentation rate, jaw claudication, pain centered about one temple, visual symptoms
6. Pseudotumor cerebri: headache with papilledema, visual loss and elevated CSF pressure (typically occurs in young, overweight females), abrupt-onset HA with n/v, exacerbated by coughing, straining, position changes
7. Miscellaneous: Post lumbar puncture, sleep apnea (morning headaches), carbon monoxide poisoning, glaucoma, hypertensive

V. RED FLAGS: Worrisome features that indicate need for further workup
A. First severe headache over 50 (temporal arteritis, mass lesion, stroke)
B. Intense headache without prior history of headache (subarachnoid hemorrhage)
C. Fever, nuchal rigidity, Kernig’s/Brudzinski’s sign (meningitis)
D. Papilledema
E. Diplopia
F. New/persistent neurologic signs
G. Elevated BP (diastolic >110)
H. Unexplained vomiting
I. Exertional/cough headache (need MRI to rule out posterior fossa lesion)
J. Sudden change in headache pattern (Note: prior history of benign headache does not rule out development of new cause for headache)
K. History of head trauma, malignancy or coagulopathy

VI. TESTING: Consider testing as appropriate when any of the “red flags” above are present
A. Neuroimaging, including:
1. Computed tomography (CT) scan: Best for detection of acute bleed (non-contrast)
2. Magnetic resonance imaging (MRI): Best for detection of posterior fossa disease, more sensitive than CT for most conditions. More expensive
3. Magnetic resonance angiography (MRA): Aneurysm or other vascular lesion
B. Lumbar puncture: Evaluating meningitis or subarachnoid hemorrhage, increased intracranial pressure (assuming neuroimaging shows no mass lesion)
C. Electroencephalogram (EEG): Rarely helpful
D. Other diagnostic tests including CBC, sed. rate, thyroid panel, drug levels (Lithium).
Labs not generally helpful unless a specific diagnosis is suspected (e.g., hyperthyroidism, pseudotumor cerebri (sed. rate), etc.)
## Table 1. Diagnosis and Management of Primary Headaches

<table>
<thead>
<tr>
<th>Character</th>
<th>Tension-type headache</th>
<th>Migraine headache</th>
<th>Cluster Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Bilateral intense about the neck</td>
<td>Usually unilateral</td>
<td>Strictly unilateral, retroorbital</td>
</tr>
<tr>
<td>Quality</td>
<td>Pressure, “vise-like”</td>
<td>Throbbing, aching</td>
<td>Sharp, stabbing</td>
</tr>
<tr>
<td>Severity</td>
<td>Mild to moderate</td>
<td>Moderate to severe</td>
<td>Extremely severe</td>
</tr>
<tr>
<td>Frequency</td>
<td>Variable, may be constant or intermittent</td>
<td>Intermittent (&lt;15/month), not typically daily</td>
<td>Episodic, 1-4/day for weeks to months, same time each day, esp. night, repeats over days to weeks then may disappear for up to months</td>
</tr>
<tr>
<td>Duration</td>
<td>Several hours/days, fluctuating</td>
<td>4-72 hours, gradual build-up and decline</td>
<td>15-120 minutes, rapid onset and decline</td>
</tr>
<tr>
<td>Aura</td>
<td>None</td>
<td>15-20%, lasts 5-60 minutes, HA should follow within 1 hour, esp. visual (zig-zag scotoma, etc.)</td>
<td>None</td>
</tr>
<tr>
<td>Activity level</td>
<td>Variable</td>
<td>Passive, rest in dark room</td>
<td>Active, pacing</td>
</tr>
<tr>
<td>Precipitants</td>
<td>Stress</td>
<td>Numerous (foods, chocolate, menstrual cycle, etc.)</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Associated symptoms</td>
<td>Muscular tenderness, mild photo/phonophobia</td>
<td>Photo/phonophobia, nausea/vomiting, diarrhea</td>
<td>Horner's syndrome, rhinorrhea, lacrimation</td>
</tr>
<tr>
<td>Therapy: Abortive</td>
<td>First choice: Acetaminophen, Aspirin, NSAIDs</td>
<td>Use combination analgesics containing caffeine (be aware of overuse headache)</td>
<td>See tables below</td>
</tr>
<tr>
<td></td>
<td>Second choice: Combination analgesics containing caffeine (be aware of overuse headache)</td>
<td>Use combination analgesics/butalbital or opioid only in cases when analgesics/caffeine are ineffective or contraindicated</td>
<td>Sumatriptan 6mg SQ 100% O₂, NRB mask for 15 minutes DHE-45 1 mL IV/IM, may repeat x 1 in 1 hr</td>
</tr>
<tr>
<td>Therapy: Prophylactic</td>
<td>First choice: Amitriptyline 30-75 mg/day (start at 10-25 mg/day and titrate weekly)</td>
<td>Second choice: mirtazapine 30 mg/day, venlafaxine 150 mg/day Nonpharmacological: psycho-behavioral treatment - EMG biofeedback (A recommendation), cognitive-behavioral, relaxation, physical therapy, acupuncture</td>
<td>See tables below</td>
</tr>
<tr>
<td></td>
<td>Second choice:</td>
<td></td>
<td>Prednisone 60mg QD and taper over 2-3 weeks for new/recurrent cluster Add prophylactic to continue 2 wks after headache controlled</td>
</tr>
<tr>
<td></td>
<td>Nonpharmacological: psycho-behavioral treatment - EMG biofeedback (A recommendation), cognitive-behavioral, relaxation, physical therapy, acupuncture</td>
<td></td>
<td>Verapamil 180-240mg QD, Lithium 900mg QD Depakote 250mg BID</td>
</tr>
</tbody>
</table>
VIII. ACUTE TREATMENT OF MIGRAINE

A. NSAIDs: 1st line for mild to moderate migraine; effective for short-term relief

B. Combination analgesics

1. Combination analgesics containing Acetaminophen/caffeine/ASA (Excedrine migraine) are effective, inexpensive and available without prescription. Be aware of rebound headache
2. Barbiturate-containing compounds (Butalbital/ASA/caffeine-Fiorinal) have not demonstrated effectiveness

C. Triptans: 1st line for moderate to severe headache or mild to moderate headache not responsive to NSAIDs or combination analgesics

1. Triptans are effective in 65%–70% of migraine attacks
2. Available in many forms: PO, rapidly-dissolving tablets, SC injection, IV, nasal sprays. Oral triptan tablets are more effective if taken in the early phases of attack. If treatment is delayed, injection or nasal spray may be more beneficial
3. Avoid in patient with cardio- or cerebrovascular disease, uncontrolled HTN, hemiplegic migraine due to vasoconstrictive properties.
4. Caution in those taking MAOIs or SSRIs due to serotonin syndrome as triptans work by binding to serotonin receptor
5. All triptans have similar efficacy, tolerability, and cost
6. Triptans are different in their pharmacokinetic profile and route of administration. Select a triptan that matches the needs of the individual patient. E.g., a slow onset of action and longer-lasting triptan may be appropriate for slow-onset, longer-lasting migraine attacks
7. Non-responders of one triptan may respond to another of the class

D. Anti-emetics: Evidence supports role of IV, but not PO preparations in emergency setting. Reglan, Ondansetron (Zofran), Compazine and Phenergan also available

E. Dexamethasone: Used as adjunctive therapy only in emergency setting

F. Ergot alkaloids: Bind to serotonin receptor. 2nd line after triptans

1. Ergotamine has long half-life and duration of action (up to 3 days). Avoid frequent use due to rebound headache
2. Dihydroergotamine is available in IV, IM, SC, (DHE-45) and nasal spray (Migranal)
3. Use limited by poor absorption and adverse SEs (n/v, peripheral and central vasoconstriction)
4. Avoid in patients with cardiovascular history

Table 2 Some Drugs for the Treatment of Migraine (Table on next page)
### Table 2. Some Drugs for Treatment of Migraine*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Usual dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serotonin (5-HT1B/1D Receptor Agonists (&quot;Triptans&quot;)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almotriptan – Axert (Janssen)</td>
<td>6.25, 12.5 mg tabs</td>
<td>6.25-12.5 mg PO; can be repeated once after 2 hrs (max 25 mg/d)</td>
</tr>
<tr>
<td>Eletriptan – Relpax (Pfizer)</td>
<td>20, 40 mg tabs</td>
<td>20 or 40 mg PO; can be repeated after 2 hrs (max 80 mg/d)</td>
</tr>
<tr>
<td>Frovatriptan – Frova (Endo)</td>
<td>2.5 mg tabs</td>
<td>2.5 mg PO; can be repeated after 2 hrs (max 7.5 mg/d)</td>
</tr>
<tr>
<td>Naratriptan – generic Amerge (GSK)</td>
<td>1, 2.5 mg tabs</td>
<td>2.5 mg PO; can be repeated once after 4 hrs (max 5 mg/d)</td>
</tr>
<tr>
<td>Rizatriptan – generic</td>
<td>5, 10 mg tabs; 5, 10 mg orally disintegrating tabs</td>
<td>5 or 10 mg PO; can be repeated after 2 hrs (max 30 mg/d)^1</td>
</tr>
<tr>
<td>Maxalt (Merck)</td>
<td>5,10 mg tabs</td>
<td></td>
</tr>
<tr>
<td>Maxalt-MLT</td>
<td>5, 10 mg orally disintegrating tabs</td>
<td></td>
</tr>
<tr>
<td>Sumatriptan – generic</td>
<td>25, 50, 100 mg tabs</td>
<td>50 or 100 mg PO; can be repeated after 2 hrs (max 200 mg/d)</td>
</tr>
<tr>
<td>Alsuma (Pfizer)</td>
<td>4, 6 mg/0.5 mL auto-injector, vials</td>
<td>6 mg SC; can be repeated once after 1 hr (max 12 mg/d)</td>
</tr>
<tr>
<td>Imitrex (GSK)</td>
<td>5, 20 mg/0.1 mL nasal spray; 6 mg/0.5 mL vials</td>
<td>5, 10 or 20 mg intranasally; can be repeated once after 2 hrs (max 40 mg/d)</td>
</tr>
<tr>
<td>Sumavel DosePro (Zogenix)</td>
<td>6 mg/0.5 mL SC (needle-free)</td>
<td>6 mg SC; can be repeated once after 1 hr (max 12 mg/d)</td>
</tr>
<tr>
<td>Zecuity (NuPath®)</td>
<td>6.5 mg transdermal patch</td>
<td>6.5 mg transdermally; a second patch can be applied after 2 hrs (max 2 patches/d)</td>
</tr>
<tr>
<td>Zolmitriptan – generic</td>
<td>2.5, 5 mg tabs; 2.5, 5 mg orally disintegrating tabs</td>
<td>2.5 or 5 mg PO; can be repeated after 2 hrs (max 10 mg/d)</td>
</tr>
<tr>
<td>Zomig (AstraZeneca/Impax)</td>
<td>2.5, 5 mg tabs</td>
<td></td>
</tr>
<tr>
<td>Zomig-ZMT</td>
<td>2.5, 5 mg orally disintegrating tabs</td>
<td></td>
</tr>
<tr>
<td>Zomig nasal spray</td>
<td>2.5, 5 mg/0.1 mL nasal spray</td>
<td>2.5 or 5 mg intranasally; can be repeated once after 2 hrs (max 10 mg/d)</td>
</tr>
<tr>
<td><strong>Triptan Combination Product</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumatriptan/naproxen – Treximet (GSK)</td>
<td>85 mg/500 mg tabs</td>
<td>85 mg/500 mg PO; can be repeated once after 2 hrs (max 170 mg/1000 mg/d)</td>
</tr>
<tr>
<td><strong>Ergots</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydroergotamine mesylate – generic DHE 45 (Valeant)</td>
<td>1 mg/mL ampules</td>
<td>1 mg IM or SC; can be repeated at 1 hr intervals (max 3 mg/d, 6 mg/wk)</td>
</tr>
<tr>
<td>Migranal Nasal Spray (Valeant)</td>
<td>4 mg/mL nasal spray</td>
<td>1 spray (0.5 mg) into each nostril, repeated 15 min later (2 mg/dose; max 3 mg/d)</td>
</tr>
<tr>
<td>Ergotamine tartrate – Ergomar (Rosedale)</td>
<td>2 mg sublingual tabs</td>
<td>2 mg sublingually; can be repeated q 30 min PRN (max 6 mg/d, 10 mg/wk)</td>
</tr>
<tr>
<td>Ergotamine/caffeine – generic Caregol (Sandoz)</td>
<td>1 mg/100 mg tabs</td>
<td>2 tabs PO; can be repeated q 30 min x 4 PRN (max 6 tabs/attack)</td>
</tr>
</tbody>
</table>

* Cost information from original chart omitted.
1. Patients also taking propranolol should only use a 5-mg dose (max 15 mg/d).


### IX. MIGRAINE PROPHYLAXIS

#### A. When to consider prophylaxis
1. ≥2 migraines/month with disability lasting ≥3 days/month
2. Failure of, contraindication to, or adverse events from acute treatments
3. Use of abortive medication ≥2 × per week
4. Uncommon migraine conditions (e.g., hemiplegic migraine, basilar migraine, migraine with aura, migrainous infarction)

#### B. When to stop therapy:
After successful therapy (migraine frequency reduction by ≥50%) has been maintained for 6–12 months
### Table 3. Evaluation of Drugs for Migraine Prophylaxis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Recommended Level</th>
<th>Disadvantages/side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td></td>
<td></td>
<td>Fatigue, sexual dysfunction, bradycardia, hypotension, exercise intolerance</td>
<td>Low drop-out rate (&lt;5%) *Probably no significant difference between individual meds *Contraindicated in asthma, hypoglycemia associated with diabetes treatment, heart block, and hypotension</td>
</tr>
<tr>
<td>Propranolol</td>
<td>80-240 mg QD</td>
<td>A</td>
<td>*Demonstrated effect in children</td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td>40-80 mg QD</td>
<td>A/B</td>
<td>*Demonstrated effect in children</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>200 mg QD</td>
<td>A</td>
<td>*Demonstrated effect in children</td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td>10-15 mg BID</td>
<td>A</td>
<td>*Demonstrated effect in children</td>
<td></td>
</tr>
<tr>
<td>Anti-epileptics:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>100 mg QD</td>
<td>A</td>
<td>Paresthesias, sleepiness, fatigue, and gastrointestinal intolerance</td>
<td>*Good for coexisting epilepsy</td>
</tr>
<tr>
<td>Divalproex sodium/Sodium valproate</td>
<td>500-1,000 mg QD</td>
<td>A</td>
<td>Nausea, somnolence, tremor, dizziness, weight gain, hepatotoxicity, teratogenicity</td>
<td>*Give with folic acid in women of child-bearing age but avoid using in this population, potential for teratogenicity *monitor drug levels for toxicity, for pancreatitis, liver failure or compliance *GI effects usually decrease with continued use</td>
</tr>
<tr>
<td>Anti-depressants:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>10-100 mg QHS</td>
<td>B</td>
<td>Dry mouth, weight gain, drowsiness</td>
<td>*Reduces sleep latency, good for insomnia</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>150 mg QD</td>
<td>B</td>
<td>Nausea/emesis, drowsiness</td>
<td></td>
</tr>
<tr>
<td>Other Anti-hypertensives:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>20 mg QD</td>
<td>C</td>
<td>Cough, dizziness, angioedema, teratogenic</td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>16 mg QD</td>
<td>C</td>
<td>Dizziness, MSK symptoms, fatigue, teratogenic</td>
<td></td>
</tr>
<tr>
<td>Herbs, Minerals, Supplements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium citrate</td>
<td>600 mg QD</td>
<td>C</td>
<td>Diarrhea</td>
<td>*Only agent category A in pregnancy</td>
</tr>
<tr>
<td>Riboflavin (B2)</td>
<td>400 mg QD</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>100 mg TID</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butterbur</td>
<td>50 mg BID</td>
<td>C</td>
<td>Burping</td>
<td></td>
</tr>
<tr>
<td>Feverfew</td>
<td>50-82 mg QD</td>
<td>C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Evidence is conflicting or inadequate to support or refute the use of the following medications for migraine prevention:**
- SSRIs, calcium-channel blockers, acetazolamide, gabapentin, Botulinum toxin type A

## Clinical Pearls

- Myofascial pain, difficulty in concentration, emotional lability, divorce and job loss frequently accompany post-traumatic headache
- Headaches typically worse in the morning are: pseudotumor cerebri, sleep apnea, and carbon monoxide poisoning
- Frequent use of Ergotamine, caffeine/Butalbital containing products, NSAIDs, and Excedrin can cause rebound headaches
- Migraines are frequently misdiagnosed as sinus headaches (many migraines hurt over sinus region, have congestion and are triggered by weather changes)
- Use abortive therapies as early as possible
- Avoid opiates and barbiturates in migraine abortive therapy due to potential for abuse and rebound headache, use only in recalcitrant migraines
59. Evaluation & Management of Dizziness

I. INTRODUCTION
A. About 5% of outpatient visits are for dizziness
B. The 4 main categories are:
   1. Vertigo
   2. Presyncope/syncope
   3. Imbalance and ataxia (disequilibrium)
   4. Psychogenic
C. The history and physical exam are the cornerstone of diagnosis
D. Medications are frequent causes of dizziness

II. HISTORY
A. Define the type of dizziness—vertigo v. lightheadedness v. imbalance/ataxia
B. Provoking factors: Positional changes, changes in head positions
C. Acuity of onset
D. Aural symptoms: Hearing loss, tinnitus
E. Focal neuro symptoms
F. Visual symptoms: Diplopia, decreased acuity
G. Cardiac symptoms: Palpitations, chest pain, shortness of breath
H. Infectious symptoms
I. Past medical history: Diabetes, alcohol, syphilis, migraine headaches, cardiac disease
J. Meds
K. Trauma
L. Recent travel history (cruises and long plane flights can induce dizziness)

III. PHYSICAL EXAM
A. Neuro exam: Cranial nerves, finger to nose, dysdiadochokinesia and Romberg—distinguish central from peripheral lesions
B. Eye: Visual acuity, extra-ocular muscles, fundi and discs
C. Ear: Tympanic membrane, external ear. Hearing test
D. Neck: Nuchal rigidity or pain with movement. Reproduction of symptoms with movement. Carotid bruits
E. Cardiac: Murmurs, signs of ischemia
F. Gait
59. Dizziness

Management of Common Ambulatory Conditions

G. Hallpike maneuver: Patient sits on bed while clinician supports head. Patient rapidly assumes supine position first with head straight, then turned 45° left then 45° right. With reproduction of symptoms, vertigo and nystagmus, benign positional vertigo is suggested. Also vertigo duration less than 1 minute, latency 2–20 seconds, unidirectional nystagmus, fatigability. Note: This test is neither sensitive nor specific and should be used in context of complete evaluation to make a diagnosis.

IV. OTHER TESTS—As indicated by history and physical

A. Brain MRI or CT: MRI is much more sensitive than CT for dizziness since the region of the brain to be evaluated is usually the posterior fossa. Usually performed with contrast to help pick up acoustic neuromas.

B. Audiography: Low frequency loss in Ménière’s disease.

C. Electronystagmography (ENG): Most helpful in Ménière’s disease and benign positional vertigo. Helpful in cases with medicolegal implications and psychogenic vertigo.

D. Lumbar puncture: Helpful when suspect multiple sclerosis, meningitis, or subarachnoid bleed.

E. Cardiac evaluation if presyncope: Consider ECG, ECHO, EPS depending on symptoms.

EVALUATION AND MANAGEMENT OF VERTIGINOUS DIZZINESS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Vertiginous symptoms</th>
<th>Nystagmus</th>
<th>Comments</th>
<th>Associated symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign positional vertigo</td>
<td>Vertigo: Positional, provoked by certain head positions.</td>
<td>Positional with latency, brief duration and fatigability. Horizontal.</td>
<td>Usually idiopathic, may result from head trauma, ear surgery, or sequelae of vestibular neuronitis.</td>
<td>None.</td>
<td>Positioning maneuvers to rid the posterior semicircular canal of debris.</td>
</tr>
<tr>
<td>Vestibular neuronitis</td>
<td>Vertigo accompanied by nausea and vomiting lasting days to weeks. Acute onset.</td>
<td>Increases when gaze is directed away from affected ear and is suppressed with visual fixation.</td>
<td>Auditory function not affected. BPV may develop as sequelae.</td>
<td>Antecedent or concomitant acute viral illness.</td>
<td>Does not recur.</td>
</tr>
<tr>
<td>Labyrinthitis</td>
<td>Acute onset of vertigo and hearing loss which lasts 3–5 days. Rapid head movements may bring on vertigo.</td>
<td>Same as vestibular neuronitis.</td>
<td>Hearing loss may be total and permanent. Need to differentiate viral (serous) from bacterial (suppurative) labyrinthitis.</td>
<td>Antecedent or concomitant acute viral illness.</td>
<td>Does not recur.</td>
</tr>
<tr>
<td>CNS vertigo</td>
<td>Vertigo: Nearly always positional — provoked by certain head positions.</td>
<td>Usually accompanies the vertigo.</td>
<td>Usually accompanies the vertigo.</td>
<td>1. Usually in the elderly. 2. Symptoms associated with arteriosclerosis, brainstem ischemia (visual symptoms), or cervical arthritis.</td>
<td>Directed to specific etiology.</td>
</tr>
</tbody>
</table>
V. SYMPTOMATIC MANAGEMENT OF TRUE VERTIGO

A. Acute vertigo: First few days
1. Vestibular suppressants
   a. Meclizine: 12.5–25mg PO Q6hrs PRN
   b. Valium: 2–5mg PO Q6hrs PRN
2. Antiemetics: Compazine, Phenergan, Ondansetron (Zofran)
3. Hospitalize if dehydrated or for other medical reasons

B. Subacute vertigo
1. Stop vestibular suppressants
2. Vestibular exercises

C. Benign paroxysmal positional vertigo (BPPV): Perform Epley maneuver. Maneuver is 80+% effective for this condition and has been demonstrated effective in the primary care setting. Don’t use with known severe cervical spine disease or high grade carotid/vertebrobasilar disease
1. Step A: Perform the Dix-Hallpike test with the patient’s head rotated 45° toward the affected (right) ear, the neck slightly extended, and the chin pointed slightly upward
2. Step B: When the vertigo and nystagmus provoked by the Dix-Hallpike test stop, rotate the patient’s head about the rostral-caudal body axis until the unaffected ear is downward
3. Step C: Further rotate the head and body until the patient is face down, and maintain this position for 10 to 15 seconds
4. Step D: Keeping the head facing toward the shoulder on the unaffected side, bring the patient to a seated position and keep the head tilted so that the chin points slightly downward
5. Have patient sleep at 45–90° angle for next 1–2 nights

CLINICAL PEARLS

- Patients with BPPV (especially those who respond favorably to maneuvers) do not generally need further testing. BPPV recurs about 30% of the time over the next 30 months
- Gait disturbance can be seen in central and peripheral vertigo
- In patients with multiple sclerosis, vertigo is the initial complaint in 5% and ultimately occurs in 50% of patients
- Symptoms of Ménière’s disease may be mimicked in secondary and tertiary syphilis. Consider screening all patients with Ménière’s disease with VDRL or RPR
- The average time from onset of symptoms to diagnosis of acoustic neuroma is 4yrs with an incidence of 1 case in 100,000 persons

References
60. CV As
Management of Common Ambulatory Conditions

John A. Vaughn, MD

60. PREVENTION & MANAGEMENT OF CVAs

I. INTRODUCTION
A. Approximately 750,000 strokes occur/yr in the US
B. Cost of all strokes is $40 billion annually
C. Stroke is the third leading cause of death

II. TYPES OF STROKE
A. Ischemic infarct (80%): Results from decrease in bloodflow to a specific area of brain. In transient ischemic attack (TIA), symptoms last < 24 hrs
B. Intracranial hemorrhage (15%): Results from rupture of a blood vessel into specific area of brain
C. Subarachnoid hemorrhage (5%): Results from rupture of a blood vessel into subarachnoid space

III. ETIOLOGY OF ISCHEMIC STROKE
A. Embolic (20%): Cardiac (atrial fibrillation, MI, valvular disease), aortic
B. Large vessel (20%): Carotid, vertebrobasilar
C. Small vessel (lacunar) (25%)
D. Cryptogenic/unusual (35%): Vasculitis, hypercoagulability, HIV, etc.

IV. RISK FACTORS
A. Non-modifiable: Age, gender, race/ethnicity, family history
B. Modifiable: Hypertension is strongest risk factor for stroke; others include diabetes mellitus, hyperlipidemia, smoking, excessive ETOH intake, cardiac disease (especially atrial fibrillation), oral contraceptives, hormone replacement therapy
C. Risk factor management is the cornerstone of prevention

V. HISTORY
A. Prior TIAS (amaurosis fugax, etc.) often are harbingers of future stroke
B. Severe headache or decreased level of consciousness suggests hemorrhage
C. Type of symptoms (and exam) should help localize lesion
1. Anterior circulation (carotid circulation and branches)—contralateral numbness, weakness, visual field defect. Left sided cortical lesions often have language difficulties (aphasia), while right side lesions often have neglect
2. Posterior circulation (vertebrobasilar circulation)—often times have “crossed signs” (e.g., right sided weakness, left sided numbness). Diplopia, dizziness, dysarthria, dysphagia (the “four D’s”) and gait ataxia are also seen

VI. EXAMINATION: Complete neuro exam, cardiac exam (rhythm, murmurs), vascular exam (especially carotid bruits), ophthalmologic (retinal emboli), and vital signs

VII. DIFFERENTIAL DIAGNOSIS OF STROKE MIMICS: Todd’s paralysis (postepileptic paralysis), hypoglycemia, complicated migraine, conversion disorder or malingering, brain tumor, drug overdose, Bell’s palsy

VIII. EVALUATION: To evaluate stroke and rule out stroke “mimics” (migraine, seizure, mass lesions, multiple sclerosis, hypoglycemia, etc.)
A. Neuroimaging
   1. CT head: Usually first step
      a. Quick, rules out hemorrhage easily
b. Not sensitive for posterior fossa strokes or early infarcts. Note: within the first several hours the head CT will be negative

2. MRI head
   a. Routine MRI more sensitive for acute stroke than for CT
   b. Visualization of posterior fossa stroke
   c. Use restricted in patients with pacemakers, aneurysm clips, etc.
   d. Diffusion techniques extremely sensitive for acute stroke and can localize areas of poor perfusion

B. Laboratory
   1. Routine: CBC with platelets, glucose, PT/PTT, lipid profile, electrolytes, BUN/Cr, liver enzymes can help establish other medical illnesses/issues
   2. Vasculitis or hypercoagulable state (especially in young patients without risk factors):
      ESR, ANA, protein C & S, antiphospholipid antibodies, RPR, antithrombin III, Factor V and II

C. Cardiac
   1. Rhythm: EKG and Holter monitor
   2. Structural: ECHO to evaluate for structural heart disease. A TEE most sensitive, especially for unexplained stroke, stroke in the young

D. Vascular
   1. Carotid Doppler/ultrasound: Safe/non-invasive, though operator dependent and difficulty with total vs. subtotal carotid occlusion. It only measures narrowing in the cervical carotid artery
   2. MRA: Can evaluate cervical carotid, vertebrobasilar and intracranial circulation
   3. CT angiography: Useful especially for those who cannot have MRA, can be done in the acute setting
   4. Cerebral angiography
      a. Gold standard
      b. Invasive, with 0.5 to 3% complication rate (groin hematoma, dye reaction, stroke)

IX. PREVENTION
A. Cardiac source: Anticoagulation is often recommended for prevention of stroke in atrial fibrillation. See Chapter 48, Atrial Fibrillation, VII. C.

B. Carotid disease: All patients should have risk factor modification and antiplatelet therapy
   1. Symptomatic (unilateral amaurosis fugax or hemispheric TIA referable to the stenosed carotid artery)
      a. 70–99% stenosis: Clear benefit over medical therapy
      b. 50–69% stenosis: Less clear benefit, especially if surgical complication rate is not low
      c. < 50% stenosis, no benefit
   2. Asymptomatic
      a. Slight reduction in risk of stroke with > 60% stenosis
      b. Benefit not realized if surgical complications > 3%

C. Antiplatelet therapy
   1. Aspirin: 50–325mg PO QD
   2. Clopidogrel (Plavix): 75mg QD—superior to Aspirin in preventing vascular events (peripheral, cardiac, or stroke) in patients that had a vascular event. MATCH trial showed no advantage in stroke prevention by adding Aspirin to Plavix (use monotherapy for stroke)
   3. Aggrenox (Aspirin 25mg and Extended-Release Dipyridamole 200mg): 1 PO BID. PROFESS trial showed Aggrenox and Plavix are equivalent in stroke prevention
   4. Ticlopidine (Ticlid): 250 mg BID—demonstrated > 20% reduction in recurrent stroke vs. aspirin. Use limited by risk of hematologic abnormalities and need to monitor CBC (Q 2 weeks for 3 months and periodically thereafter)
   5. Warfarin (Coumadin): Found to be equivalent to Aspirin for recurrent stroke (after eliminating cardiac sources and significant carotid disease). Will likely be used less for routine stroke prophylaxis given safety issues and monitoring hassles
D. Hypertension: See Chapter 45, Hypertension
E. Hyperlipidemia: See Chapter 44, Hyperlipidemia
F. Risk factor modification

X. REHABILITATION
A. Physical, occupational, and speech therapy as indicated
B. Transition to either inpatient (rehabilitation facility, nursing facility) or outpatient rehabilitation (therapists, social services can help guide appropriate choices)
C. Continued vigilance for medical complications, while maximizing functional improvements
D. Bowel/bladder programs
E. Need to involve caregivers from outset
F. DVT prevention
G. Swallowing study/speech therapy

CLINICAL PEARLS
• Acute stroke treatments are still being investigated (intra-arterial thrombolysis, neuroprotective agents). Angioplasty and stenting of carotid and other arteries are actively being studied, but still investigational
• While 10% of stroke patients are candidates for t-PA, only 1% receive treatment presently
• Lipid lowering agents (particularly HMGs) help prevent stroke, even in patients with normal lipid profiles (possibly by a different mechanism than lipid management)
• Non-US studies have suggested antihypertensive treatments (ACE inhibitors and diuretics) decrease the risk of recurrent stroke, even in normotensive individuals
• Isolated dizziness, confusion, or syncope is unlikely indicator of TIA/stroke

References
61. **Seizure Disorders**

I. **Definitions**

A. **Seizure**: A brief, sudden, excessive discharge of electrical activity in the brain that alters behavior

B. **Epilepsy**: Recurrent seizures without clear precipitating factors (such as alcohol withdrawal, hypoglycemia)

II. **Epidemiology**

A. 1 in 11 will have at least 1 seizure
B. US 1.5 million with active epilepsy
C. 7 million with epilepsy at some time
D. Peaks in infancy and again later in life

III. **Seizure Classification**

A. **Reactive**: Abnormal reaction of an otherwise normal brain (febrile, hypoglycemia)
B. **Symptomatic**: Secondary to underlying structural or biochemical abnormality
C. **Idiopathic**: No known cause, except for possibly genetic

IV. **Principal Types of Seizures**

A. **Generalized**
   1. Absence seizures (petit mal)
      a. Seizure starts rapidly, averaging 10 seconds of unresponsiveness with rapid recovery
      b. Hyperventilation may precipitate seizure
      c. Muscle tone may be increased or decreased, with automatisms or mild clonic movement
      d. First seizure between ages of 3–20 years
   2. Primarily generalized tonic-clonic seizures (grand mal)
      a. Loss of consciousness without warning or preceded by myoclonic jerks
      b. Clinical features similar to those of a secondarily generalized partial seizure

B. **Partial**
   1. Simple partial seizures (focal)
      a. Signs and symptoms may be motor, sensory, autonomic, or psychic, depending on the electrical discharge location
      b. Consciousness not impaired
   2. Complex partial seizures (temporal lobe or psychomotor)
      a. May begin without warning or with motor, sensory, autonomic, or psychic signs or symptoms
      b. Consciousness impaired
      c. Automatisms may occur
      d. Period of confusion often follows seizure
   3. Secondarily generalized partial seizures (tonic-clonic, or grand mal)
      a. May begin with motor, sensory, autonomic or psychic signs or symptoms
      b. Loss of consciousness, with tonic increase in muscle tone
      c. Subsequent rhythmic (clonic) jerks subside slowly
      d. Patient comatose after seizure with slow recovery
      e. Tongue biting and/or incontinence may occur


V. **Etiology**

A. **Infection**: Meningitis, encephalitis, intracranial abscess
B. **Trauma**: Concussion, subdural/epidural hematoma, subarachnoid hemorrhage
C. **Intoxication**: Amphetamine, cocaine, PCP, Propoxyphene, Tricyclics, Phenothiazines,
Wellbutrin, Theophylline, alcohol (withdrawal), Aspirin, Romazicon, Organophosphates, carbon monoxide, Lithium

D. Metabolic: Hyper/hypoglycemia, hyper/hyponatremia, hypocalcemia, hypomagnesemia, kernicterus, hypoxia, uremia, inborn errors of metabolism, pyridoxine deficiency

E. Degenerative: Alzheimer’s, Huntington’s, Tay-Sachs, leukodystrophies

F. Congenital: Abnormal brain development, cerebral palsy, neuronal migrational defects, tuberous sclerosis, etc.

G. Neoplasms: Primary or metastatic

H. Vascular: Ischemic or hemorrhagic stroke, hypertensive encephalopathy, eclampsia, global cerebral hypoperfusion

I. Idiopathic: Mesial temporal sclerosis, genetic, etc.

J. Febrile seizures: See VII. I. below

VI. EVALUATION

A. History: Provoking factors, meds, premonitory symptoms, eyewitness accounts. Focal features, tongue biting/blood in the mouth, incontinence, post-ictal state

B. Physical examination: Complete neurologic exam, skin lesions (rash, neurocutaneous stigmata), fever, infection in ears or sinuses, trauma, congenital anomalies

C. Laboratory (as indicated for initial seizure)
   1. CBC/blood cultures (for febrile patients), glucose, electrolytes (including calcium/magnesium)
   2. Drug tests (look for intoxications, antiepileptic levels, ETOH)
   3. Lumbar puncture (in selected patients)

D. Neuroimaging
   1. CT head: For emergent evaluation/new onset seizures (trauma, vascular)
   2. MR head: Provides more detail, for more in depth evaluation of etiology
   3. PET/SPECT scans: Primarily for presurgical evaluation

E. Electrodiagnostics
   1. Routine EEG (yield for single EEG approximately 50% in patients with epilepsy)
   2. Sleep deprived EEG (more sensitive, combined with routine EEG, 80% sensitive)
   3. EEG monitoring (for refractory epilepsy or evaluation of pseudoseizures)

F. Differential diagnosis: Panic attacks, syncope, breath holding spell, pseudoseizures, sleep disorders (narcolepsy), migraine, TIA, episodic dyscontrol syndrome (rage attacks), Ménière’s disease, movement disorders

VII. MANAGEMENT

A. Indications for meds
   1. Two or more unprovoked seizures
   2. Single seizure with risk factors (abnormal EEG, certain neuroimaging abnormalities, certain hereditary epilepsies including family history of seizures)

B. Usual starting meds (see table below for dosing and cost)
   1. Generalized tonic-clonic seizures
      a. Divalproex Sodium (Depakote)
      b. Phenytoin (Dilantin)
   2. Absence
      a. Ethosuximide (Zarontin)
      b. Divalproex Sodium (Depakote)
   3. Partial seizures
      a. Carbamazepine (Tegretol)
      b. Divalproex Sodium (Depakote)
      c. Oxcarbazepine (Trileptal)
      d. Phenytoin (Dilantin)
      e. Pregabalin (Lyrica)
      f. Topiramate (Topamax)
      g. Levetiracetam (Keppra)

C. Common side effects with all meds are sedation, dizziness, ataxia, headache, nausea, and rash
D. Usual doses of antiepileptic drugs in patients ≥ age 16

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Initial Daily Dose</th>
<th>Daily Dosing Interval</th>
<th>Average Daily Maintenance Dose</th>
<th>Titration Schedule^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>400mg</td>
<td>3x</td>
<td>1200mg</td>
<td>Slow</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>900mg</td>
<td>3x</td>
<td>2400mg</td>
<td>Rapid</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>50mg</td>
<td>2x</td>
<td>400mg</td>
<td>Slow</td>
</tr>
<tr>
<td>Added to Valproate</td>
<td>25mg QOD</td>
<td>2x</td>
<td>100–200mg</td>
<td>Slow</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1000mg</td>
<td>2x</td>
<td>1500mg</td>
<td>Rapid</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>600mg</td>
<td>2x</td>
<td>1200mg</td>
<td>Slow</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>300mg</td>
<td>1x</td>
<td>300mg</td>
<td>Rapid</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>4mg</td>
<td>2–4x</td>
<td>48mg</td>
<td>Slow</td>
</tr>
<tr>
<td>Topiramate</td>
<td>25–50mg</td>
<td>2x</td>
<td>400mg</td>
<td>Slow</td>
</tr>
<tr>
<td>Valproate</td>
<td>750–1000mg</td>
<td>3x</td>
<td>2000mg</td>
<td>Rapid</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>100mg</td>
<td>1x</td>
<td>200mg</td>
<td>Slow</td>
</tr>
</tbody>
</table>

*Per manufacturer’s recommendation

^Rapid titration, maintenance dose obtained in < 2 weeks; slow titration, maintenance dose obtained within an average of 2–12 weeks


E. Women’s issues
1. Many seizure meds can increase failure rate for oral contraceptives (consider additional barrier method)
2. Many seizure meds increase the risk of birth defects (especially Valproic Acid and Carbamazepine which increase risk of neural tube defects)
3. Many seizure meds increase risk for bone loss. Increased use of bone density scanning and calcium and vitamin D supplements are recommended

F. Discontinuing therapy
1. Continue meds for 2yrs after starting (even if patient is seizure free during this time)
2. Risk of recurrent seizures is 25% for patients without risk factors, 50% for patients with risk factors

G. Surgery
1. Refractory seizures with identifiable seizure focus—may benefit from surgical resection (especially mesial temporal epilepsy)
2. Vagal nerve stimulator—refractory patients

H. Driving: Laws vary state to state, but most range from 3–12 months seizure free—it is usually the physician’s responsibility to report patient to BMV or inform patient of obligations

I. Febrile Seizures
1. The most common seizure of childhood
2. Diagnosis: Tonic-clonic movements associated with temperature > 100.4° F (38.0° C)
   a. Generally in children between 6 months and 5yrs
   b. Duration of seizure activity < 15 minutes
   c. Seizure activity within 24hrs of onset of fever
   d. Normal development and neurologic exam
   e. No family history of epilepsy
   f. Diagnosis of febrile seizure is a diagnosis of exclusion
3. Appropriate laboratory tests, including lumbar puncture, should be considered in any child with a seizure, especially if < 18 months old
4. If child with febrile seizure meets all of the criteria listed above (Section VII. I. 2) and child appears fine, an antipyretic may be given and no further studies or treatment are necessary. Risk of recurrence is 25–30% with simple febrile seizures
CLINICAL PEARLS

- Epilepsy peaks in childhood (75% begin in childhood) and again in later adulthood
- Most common reason for seizure recurrence (and status epilepticus) is med noncompliance
- After meds are discontinued, 80% of recurrences will occur during first 4 months and
  90% within first year
- Recurrence rate for a single, unprovoked seizure is 30 to 70% (higher for abnormal
tests or exam)
- In 50% of children with seizures, the etiology will be undetermined despite an appro-
  priate work-up
- Breath-holding spells, benign paroxysmal vertigo, and syncope are often confused
  with seizures and should be considered in differential diagnosis

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1348.
DEFINITION: A concussion is a transient post-traumatic alteration in mental status that may or may not involve loss of consciousness

I. GENERAL
   A. Multiple concussions may result in cumulative neurophysiologic deficits
   B. Concussion sustained while patient is still symptomatic from an earlier concussion may result in progressive cerebral edema.
   C. Since there is often pressure to continue sports participation, concussion may be unrecognized or ignored by coaches

II. PATHOPHYSIOLOGY: Possible causes of altered level of consciousness
   A. Axonal shear injury – often not evident on CT or MRI
   B. Cortical contusion – may result in cerebral edema, ischemia or mass effect
   C. Intracranial hemorrhage

III. HISTORY—SIGNS/SYMPTOMS
   A. Confusion and/or disorientation currently or at the time of event
   B. Amnesia to event and length of time of amnesia
   C. Headache; including duration, frequency, exacerbating factors, etc.
   D. Nausea/vomiting
   E. Dizziness/vertigo
   F. Balance problems
   G. Vision disturbances (blurred, double, photophobia)
   H. Sensitivity to noise or tinnitus
   I. Fatigue or sleep disturbances
   J. Memory dysfunction/poor attention and concentration
   K. Mood changes (anxiety, depression, irritability)
   L. Exacerbation of symptoms with exertion

IV. PHYSICAL EXAM
   A. General—Altered level of consciousness, dazed appearance, inappropriate behavior, slurred or incoherent speech
   B. Eyes—Pupillary concordance/accommodation, papilledema or retinal hemorrhages, extraocular movements
   C. Neurologic assessment should involve at least the following aspects:
      1. Cranial nerve exam
      2. Strength
      3. Sensation
      4. Memory/cognitive evaluation (orientation questions, immediate and delayed 3 item recall, serial 7’s/months in reverse)—poor concentration is common
      5. Coordination (finger-to-nose)—poor coordination is common
      6. Gait/Balance testing (modified Balance Error Scoring System (BESS)—see reference below) – Difficulty with testing is common. Hold each position for 20 seconds with eyes closed and hands on hips:
         a. Feet together
         b. Single leg
         c. Tandem stance with one foot in front of the other
   D. Serial monitoring for deterioration over the initial few hours after the injury

V. CLASSIFICATION—Historically, concussions have been described using several different grading or classification systems. Concussion grading systems are not clinically relevant, and this terminology should be avoided
VI. IMAGING/TESTING
A. Acute—CT scan is the imaging modality of choice to evaluate for intracranial hemorrhage or hematoma. Indications include: continued altered level of consciousness, focal neurological changes, weakness or paresthesias, incontinence or seizure
B. Chronic symptoms—MRI is the imaging modality of choice. Indications for MRI include: persistent headaches, difficulty concentrating or other signs of post-concussive syndrome or any of the symptoms/signs listed above for acute imaging. Note: Post-concussive symptoms which do not persist do not need neuroimaging
C. Neuropsychological testing—Formal neuropsychological testing should be considered in patients with chronic symptoms that are not resolving

VII. CONCUSSION MANAGEMENT
A. Physical and cognitive rest is the mainstay of treatment. Temporary school or work accommodations are often needed to aid in the recovery process
B. OTC analgesics as needed for headaches

VIII. RETURN TO PLAY
A. A graduated, step-wise return to play can be initiated after the patient has been symptom free for 24 hours
B. Note: There should be 24 hours between each step listed below. If any concussive symptoms return, the patient should drop back to the previous asymptomatic level

<table>
<thead>
<tr>
<th>Rehabilitation Stage</th>
<th>Functional exercise at each stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No activity</td>
<td>Complete physical and cognitive rest</td>
</tr>
<tr>
<td>2. Light aerobic exercise</td>
<td>Walking, stationary bike. No resistance training.</td>
</tr>
<tr>
<td>3. Sport-specific exercise</td>
<td>Running drills in soccer; skating drills in hockey. No head impact activities</td>
</tr>
<tr>
<td>4. Non-contact training drills</td>
<td>Progression to more complex training drills (passing drills in football, etc). May start progressive resistance training</td>
</tr>
<tr>
<td>5. Full contact practice</td>
<td>Following medical clearance, participate in normal training activities</td>
</tr>
<tr>
<td>6. Return to play</td>
<td>Normal game play</td>
</tr>
</tbody>
</table>


IX. ASSOCIATED CONDITIONS
A. Second-impact Syndrome: Return to play prior to full resolution of concussion symptoms and occurrence of second (even mild) head trauma. Pathophysiology involves loss of vascular autoregulation, vascular engorgement and subsequent brain herniation. Syndrome may be fatal
B. Postconcussive Syndrome
   1. Physical, cognitive, and emotional/behavioral symptoms following a concussion
   2. May persist weeks to months or permanently
   3. Symptoms may include headache, dizziness, fatigue, irritability, depression/anxiety, sensitivity to noise, memory problems or impaired concentration. May persist for weeks to months following the injury
   4. Patient should be evaluated with an MRI and neuropsychiatric testing with persistent symptoms
   5. Treatment aimed at symptom management
      i. Acetaminophen for headaches
      ii. Speech pathology for cognitive impairments
      iii. Psychotherapy or medications for depression/anxiety

CLINICAL PEARLS
- 20–50% of patients with epidural hemorrhage will have a “lucid interval” before the onset of neurologic deterioration
- Epidural hemorrhage usually results from tearing of middle meningeal artery; subdural hemorrhage results from tearing of bridging veins
CT is more sensitive than MRI for showing an acute bleed. MRI is more sensitive at showing small areas of axonal shear injury and cerebral contusion.

An athlete should not return to play until symptom free and completed a graduated return to play program.

References
Karlin A. Concussion in the pediatric and adolescent population: different population, different concerns. PM R 2011;3:S369-S79.

63. Liver Function Tests

I. INTRODUCTION
A. LFTs typically include ALT, AST, alkaline phosphatase, bilirubin, and GGT. They are indirect measures of liver function. Protime/INR and albumin are a more accurate (but still indirect) measurement of the liver’s function.
B. First step in evaluation of abnormal test result in asymptomatic patient is to repeat the test.
C. Ultrasound is the most useful initial radiographic study of the liver, especially for cholestasis.

II. HISTORY
A. Abdominal pain/discomfort
B. Nausea/vomiting/diarrhea, color of stools and urine
C. Weight loss, fever, fatigue, anorexia, amenorrhea
D. Jaundice
E. Arthralgias (autoimmune hepatitis, hemochromatosis), pruritus (primary sclerosing cholangitis, primary biliary cirrhosis)
F. Meds
G. Past medical history: History of hepatitis, COPD (α-1 anti-trypsin deficiency), transfusions
H. Social history: Alcohol and drugs, sexual history, travel history
I. Family history

III. PHYSICAL EXAM
A. General: Fever
B. Eyes: Scleral icterus or Kayser-Fleischer rings (Wilson’s disease)
C. Abdomen: Tenderness, enlargement of liver or spleen, ascites, palpable gall bladder (Courvoisier’s sign)
D. Skin: Spider angiomia or palmar erythema, jaundice and Dupuytren’s contracture
E. Other: Signs of hypo/hyperthyroidism, gynecomastia, fetor hepatica, asterixis

IV. LIVER ENZYMES
A. Aminotransferases (ALT/AST)
1. Useful in diagnosing acute hepatocellular disease. There is poor correlation between liver damage and levels of aminotransferases.
2. ALT is present in high concentrations in the liver whereas AST is found in liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes.
3. Increases in both ALT and AST indicate hepatocellular necrosis or inflammation.
4. Etiology
   a. Hepatic causes of elevated aminotransferases: Alcohol-related liver injury, chronic hepatitis B and C, autoimmune hepatitis, meds (see below), hepatic steatosis (fatty infiltration of liver), nonalcoholic steatohepatitis, hemochromatosis, Wilson’s disease, α-1-antitrypsin deficiency
   b. Non-hepatic causes of elevated aminotransferases: celiac sprue, inherited and acquired muscle diseases, exercise

5. In liver disease secondary to alcohol, the transaminase values rarely exceed 300 U/L. Levels that are markedly increased in an alcoholic patient suggest another etiology. AST/ALT > 2 is suggestive of alcohol-induced liver disease

6. Initial evaluation
   a. Obtain other LFTs if not done yet. If Alk Phos and GGT are elevated, consider obstructive etiology
   b. Consider meds as etiology, see V. below
   c. Evaluate for alcohol use and if AST/ALT are minimally increased or AST:ALT > 2:1, consider trial of abstinence and recheck in 4 weeks
   d. Testing for acute viral hepatitis including HAAb IgG, HAAb IgM, HBsAB, HBsAg, HBe IgG, HBe IgM, and possibly HC Ab or HC PCR. Viral hepatitis may show an increase in ALT and AST about 1 week preceding the onset of jaundice
   e. Consider other tests including:
      i. Ferritin and possibly iron saturation (hemochromatosis)
      ii. Serum ceruloplasmin (decreased levels in Wilson’s disease)
      iii. Serum protein electrophoresis (autoimmune hepatitis, α-1 antitrypsin deficiency)
      iv. Serum antidiomysial and antigliadin antibodies (celiac sprue)
      v. Creatine kinase and aldolase (disorders of striated muscle)
   f. Ultrasound evaluation for obstructive picture of hepatic steatosis or nonalcoholic steatohepatitis
   g. If etiologies are not evident after history, physical, and further testing, consider liver biopsy
   h. If aminotransferases are elevated but less than 2 × upper limit of normal, then observation alone may be sufficient (as opposed to liver biopsy)

B. Alkaline Phosphatase (Alk Phos)
   1. Elevation usually indicates cholestatic liver disease (defined as intra- or extrahepatic biliary obstruction)
   2. Primarily found in liver, bone, intestines, kidney, WBCs, and placenta
   3. Hepatic causes of elevated Alk Phos include:
      a. Cholestatic diseases or conditions include partial obstruction of bile ducts—primary biliary cirrhosis, primary sclerosing cholangitis, adult bile ductopenia, and cholestasis induced by the use of drugs such as anabolic steroids
      b. Infiltrative diseases include sarcoidosis, other types of granulomatous diseases, and less often, unsuspected metastasis of cancer to the liver
   4. Is normally elevated in 3rd trimester of pregnancy
   5. Initial evaluation
      a. If the Alk Phos is elevated, order a GGT to help differentiate liver vs. bone. If the GGT is normal, the elevation is most likely due to non-hepatic causes
      b. Initial tests include RUQ ultrasound (to assess for obstruction and to assess hepatic parenchyma) and antimitochondrial antibodies (to assess for primary biliary cirrhosis)
      c. If above tests are negative and Alk Phos is < 50% of upper limit of normal, may observe and follow
      d. If above tests are negative and Alk Phos is > 50% of upper limit of normal, consider liver biopsy and either endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography

C. Gamma-glutamyl Transpeptidase (GGT)
   1. Elevated often seen in cholestatic liver disease (along with concurrent increased Alk Phos). Test is sensitive for liver disease or alcohol use, but not specific
2. Found in hepatocytes and biliary epithelial cells
3. Elevated in pancreatic disease, myocardial infarction, renal failure, chronic obstructive pulmonary disease, diabetes, alcoholism, and with drugs such as Phenytin (Dilantin), and barbiturates
4. A GGT level which is disproportionately higher than the AST, ALT, or Alk Phos in a patient not taking Dilantin or barbiturates is likely secondary to alcohol
5. GGT may be increased in thyrotoxicosis, renal failure, status post myocardial infarction, pancreatitis, diabetes, and prostate CA

D. Bilirubin (Bili)
1. Bilirubin is an end-product of destruction of red blood cells. Unconjugated bili is bound to albumin in serum. When it gets to the liver, it is conjugated, becomes water-soluble, and is excreted in the bile. Bilirubin may be elevated from increased production, decreased uptake by the liver, decreased conjugation, decreased secretion from the liver, or blockage of the bile ducts
2. Direct (conjugated) hyperbilirubinemia is almost always due to hepatobiliary disease, whereas indirect (unconjugated) hyperbilirubinemia has many causes
3. Etiology
   a. Elevated indirect (unconjugated) hyperbilirubinemia
      i. Increased bilirubin production: Hemolytic anemias, hemolytic reactions, hematoma, pulmonary infarction
      ii. Impaired bilirubin uptake and storage: Posthepatitis hyperbilirubinemia, Gilbert's disease, Crigler-Najjar syndrome, drug reactions
   b. Elevated direct (conjugated) hyperbilirubinemia
      i. Hereditary cholestatic syndromes: Faulty excretion of bilirubin conjugates such as Dubin-Johnson syndrome, Rotor's syndrome
      ii. Hepatocellular dysfunction: Biliary epithelial damage (hepatitis, hepatic cirrhosis), intrahepatic cholestasis (drugs, biliary cirrhosis, sepsis, postoperative jaundice), miscellaneous (spirochetal infections, mononucleosis, cholangitis, sarcoidosis, lymphomas, toxins)
      iii. Biliary obstruction: Choledocholithiasis, biliary atresia, carcinoma of bile duct, sclerosing cholangitis, pancreatitis, and pancreatic neoplasms
4. Evaluation: Assess whether bilirubin elevation is direct or indirect and whether other LFTs are elevated. Determine if elevation is secondary to hepatocellular cause vs. obstructive vs. benign cause (Gilbert's disease or recurrent jaundice of pregnancy)
5. Gilbert's disease: Benign, asymptomatic elevation of indirect bilirubin. Bili level is usually < 3mg/dL. Patients with Gilbert's disease have no evidence of hemolysis and other LFTs are normal. May be present in 7–10% of the population

E. Albumin
1. Is synthesized in liver and excreted in blood. Good indicator (along with the Protime) of the liver's ability to function properly and make protein
2. Is decreased with cirrhosis and with significant liver damage in addition to malnutrition, certain kidney diseases, and other rarer causes
3. Trauma, sepsis, or severe burns may rapidly lower the albumin level secondary to fluid shifts

F. Prothrombin Time (Protime)/INR
1. The liver makes all of the clotting factors, except factor VIII. With severe liver disease, the ability of the blood to clot may be compromised
2. Elevated PT/INR may also be caused by hepatocellular disease or Vitamin K deficiency
3. To determine the etiology of increased PT in patients with cholestasis, give Vitamin K 10mg IM and recheck PT/INR in 24hrs. If hepatocellular function is satisfactory, PT will improve by at least 30%

V. MEDICATIONS WHICH MAY CAUSE ELEVATIONS IN LIVER ENZYME LEVELS
A. Antibiotics: Synthetic Penicillins, Ciprofloxacin, Nitrofurantoin, Ketoconazole, Fluconazole, Isoniazid
B. Antiepileptic drugs: Phenytin, Carbamazepine
C. HMG CoA reductase inhibitors: Simvastatin, Pravastatin, Lovastatin, Atorvastatin
D. NSAIDS/Acetaminophen
63. Liver Function Tests

E. Sulfonylureas: Glipizide
F. Herbal/homeopathic: Chaparral, Chinese herbs (Jin Bu Huan and Ephedra), gentian, germander, Alchemilla, senna, shark cartilage, Scutellaria, Kava Kava
G. Drugs: Anabolic steroids, cocaine, MMDMA (Ecstasy), phencyclidine (angel dust), glues and solvents, Amiodarone, Allopurinol, Acarbose

<table>
<thead>
<tr>
<th>Test</th>
<th>Hepatocellular Necrosis</th>
<th>Biliary Obstruction</th>
<th>Hepatic Infiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Toxic/ischemic</td>
<td>Viral</td>
<td>Alcoholic</td>
</tr>
<tr>
<td>Acetaminophen or shock liver</td>
<td>50-100x</td>
<td>5-50x</td>
<td>2-5x</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>1-3x</td>
<td>1-5x</td>
<td>1-10x</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1-5x</td>
<td>1-30x</td>
<td>1-30x</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Prolonged and unresponsive to vitamin K in severe disease</td>
<td>Often prolonged and responsive to parenteral vitamin K</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Albumin</td>
<td>Decreased in chronic disease</td>
<td>Usually normal; decreased in advanced disease (i.e., cirrhosis)</td>
<td>Usually normal</td>
</tr>
</tbody>
</table>

*Table includes illustrative disorders for each category


CLINICAL PEARLS

- Jaundice is usually not clinically evident until bilirubin level is > 3
- In patients with AST>ALT by 2:1, 90% was from alcoholic liver disease. If the ratio is > 3:1, then 90% is from alcoholic liver disease. An alcohol user/abuser with elevated transaminases who stops drinking for 2–4 weeks should significantly lower those levels
- In patients who consume > 50g alcohol (about 4 drinks per day), incidence of alcoholic cirrhosis is 8–15% over 10yrs
- Abnormalities associated with drug-induced liver injury should resolve once drug has been stopped
- Most common causes of asymptomatic liver enzyme elevation are obesity and alcohol
- In an asymptomatic middle aged female with elevated liver enzymes, consider primary biliary cirrhosis and obtain a serum AMA
- In evaluating cholestasis, consider ultrasound early in the work-up to rule out bile duct enlargement
- Consider nonalcoholic steatohepatitis (NASH) in older, obese diabetics

References

64. DIAGNOSIS & MANAGEMENT OF HEPATITIS B

I. BACKGROUND
A. One of the major vaccine-preventable diseases. The hepatitis vaccine represents the first true vaccine to prevent cancer
B. Hepatitis B virus (HBV) infects more than 500 million people worldwide. An estimated 800,000-1.4 million people in the United States have chronic HBV infection, causing an estimated 2,000-4,000 deaths annually. Once chronic infection is established, the spectrum of illnesses ranges from the healthy carrier state to all of the sequelae of chronic hepatitis, including cirrhosis and hepatocellular carcinoma. Symptoms in infected individuals with HBV infection can range from asymptomatic to severe and fulminant hepatitis
C. Transmitted by blood or blood products (injection drug use, sexual activity, occupational exposure, vertical transmission)
D. Incubation period is 60-150 days. HBV can survive outside of the body for 7 days and still be capable of causing an infection. Symptoms begin at an average of 90 days after exposure to HBV
E. Of adult patients infected with hepatitis B:
   1. 95% recover completely
   2. 5% develop chronic hepatitis or chronic carrier state
F. Of those with chronic HBV, 20% develop cirrhosis within 20 years
G. Fulminant hepatitis occurs in < 1%. The mortality rate is about 60%

II. INTERPRETATION OF LAB TESTS
A. Overview: First look at HBsAg and HBsAb (see table below)
   1. If the HBsAg is positive, patient usually has either acute hepatitis B or chronic infection
   2. If the HBsAb is positive, patient usually has either past infection (and is noninfectious and protected from hepatitis B) or has received the HBV vaccine
   3. If both are negative (rare), patient may be in the “window phase” (see below)
   4. If both are positive (rare), see below
B. Tests
   1. HBsAg: First manifestation of HBV infection and persists throughout clinical illness. Persistence associated with chronic hepatitis and implies infectivity
   2. HBsAb: Occurs in most patients after clearance of HBsAg and implies noninfectivity and protection from recurrent HBV infection. (Occasionally, the appearance of HBsAb is delayed until clearance of HBsAg and during this “window phase,” both HBsAb and HBsAg may be negative—see below)
   3. HBeAb IgM: Appears during acute hepatitis B and indicates a diagnosis of acute hepatitis B
   4. HBeAb IgG: Appears during acute hepatitis B and persists indefinitely
   5. HBeAg: Indicates viral replication and infectivity
   6. HBcAb: Follows HBeAg and signifies diminished viral replication
   7. HBV DNA: Usually parallels the presence of HBeAg, but is a more precise marker of viral replication and infectivity

(Illustration and Chart on next page)
Interpretation of the Hepatitis B Panel

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td>Immune due to natural factors</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td>Immune due to hepatitis B vaccination</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Positive</td>
<td>Acutely infected</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>IgM anti-HBc</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Positive</td>
<td>Chronically infected</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>IgM anti-HBc</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

a (1) May be recovering from acute HBV infection. (2) May be distantly immune and the test is not sensitive enough to detect very low levels of anti-HBs in serum. (3) May be susceptible with a false-positive anti-HBc. (4) May be an undetectable level of HBsAg present in the serum and the person is actually a carrier.

III. EVALUATION

A. Acute hepatitis B

1. Acute illness usually subsides over 2–3 weeks and lab values are normalized within 16 weeks unless patient develops chronic hepatitis
2. Clinical picture is variable, with symptoms ranging from asymptomatic (30%) to general malaise, myalgia, arthralgia, easy fatigability, anorexia, nausea/vomiting, diarrhea, fever/chills, jaundice
3. Physical exam: Hepatomegaly (> 50%), splenomegaly (15%), lymphadenopathy
4. Lab: Low WBC, elevated ALT or AST (100–2000 units, ALT usually > AST), elevated bilirubin and alkaline phosphatase, elevated prothrombin time (in severe hepatitis), mild proteinuria, and bilirubinuria
5. Management
   a. Acute disease: Symptomatic: rest, good diet, avoidance of hepatotoxins (alcohol, acetaminophen) and behaviors that transmit hepatitis B
   b. Long-term management: Follow LFTs and HBsAg every month until disappearance of HBsAg. When this occurs, check for appearance of HBsAb. If HBsAg is still positive after 6 months, patient has chronic hepatitis
6. Indications for hospital admission
   a. Encephalopathy
   b. Prothrombin time prolonged > 3 seconds
   c. Intractable vomiting
   d. Hypoglycemia
   e. Age > 45yrs
   f. Immunosuppression

7. Consider anti-viral treatment if fulminant hepatitis or severe protracted course of acute infection. Entecavir (Baraclude) preferred; can use Lamivudine (Epivir) or Telbivudine (Tyzeka) if short term duration. Continue until there is documented clearance of HbsAg or indefinitely if liver transplant needed. Interferon-alpha is contraindicated. See IV. below for doses

B. Chronic hepatitis B
1. After the acute infection, chronic hepatitis develops in:
   a. 90% of infants
   b. 25–50% of children 1–5 years old
   c. 5% of adults

2. Definition: Persistent HBsAg > 6 months, chronic liver inflammation and characteristic histologic findings
   a. Chronic active hepatitis (replicative phase)
      i. Persistent HBsAg > 6 months
      ii. Persistent presence of HBV DNA or HBeAg
      iii. Liver injury (persistent elevation of LFTs > 6 months)

b. Chronic persistent hepatitis (nonreplicative phase)
   i. Persistent HBsAg > 6 months
   ii. Absence of HBV DNA
   iii. Minimal liver injury (modest LFT elevation)

Note: Remissions are characterized by the disappearance of HBV DNA and HBeAg (HBsAg persists). This means that the virus is in a nonreplicative phase, and patient is classified as having chronic persistent hepatitis—an important distinction from chronic active hepatitis, which is characterized by higher infectivity and greater risk from progression to cirrhosis. Likelihood of converting from replicative to nonreplicative disease is approximately 10–15% /yr

3. Symptoms and signs
   a. Chronic active hepatitis: Asymptomatic to severe symptoms, especially fatigue. Possibly jaundice, arthralgias, anorexia. End-stage includes ascites, edema, bleeding varices, hepatic encephalopathy, coagulopathy
   b. Chronic persistent hepatitis: Range from asymptomatic to mild symptoms; fatigue, anorexia, nausea, hepatomegaly

4. Labs: Aminotransferase elevations (usually 100–1000 units), minimally elevated alkaline phosphatase, hyperbilirubinemia, hypoalbuminemia, prolongation of prothrombin time

5. Work-up should include:
   a. History and physical (identifying risk factors for co-infection with HCV/HIV, EtOH use, family history)
   b. Labs: CBC with diff, LFTs, PT/INR, hepatitis B serologies, HAV IgG antibody to document immunity, HIV screening
   c. Evaluation of other causes of chronic liver disease: hepatitis C/D, iron & TIBV levels (hemochromatosis)
   d. Hepatocellular carcinoma (HCC) screening with AFP and ultrasound if high risk
   e. Consider liver biopsy for patients who meet criteria for chronic hepatitis (HbsAg positive for > 6 months, serum HBV DNA > 10 (5) copies/mL, persistent or intermittent elevation in ALT/AST levels)

6. Co-infections
   a. Hepatitis C (HCV): 10–15% of patients with chronic hepatitis B will have an HCV infection. More common among drug abusers. Co-infection with hepatitis C confers an increased risk of severe hepatitis, fulminant hepatitis as well as a higher rate of cirrhosis and hepatocellular carcinoma (HCC)
b. Hepatitis D (HDV): ONLY found in patients who are also infected with HBV. More common in Mediterranean and parts of South America
   i. Can occur in 2 forms:
      • Co-infection of HBV and HDV: more severe acute hepatitis and higher mortality but rarely develops into a chronic infection
      • Superinfection of HDV in a HBV carrier: almost always becomes chronic infection
   ii. There is a higher incidence of cirrhosis and HCC in chronic HBC/HDV co-infection than those with chronic HBV infection alone

c. HIV: 6–13% of HIV patients also have chronic HBV infection
   i. Patients with HIV have higher levels of HBV DNA and more severe liver disease
   ii. If non-immune, should receive hepatitis B vaccine when CD4 counts >200

7. Hepatocellular Carcinoma (HCC)
   a. The longer the duration of disease in HBsAg positive patients, the greater the risk for HCC
   b. High risk groups for the development of hepatocellular carcinoma include men older than 45 years, patients with cirrhosis, and patients with a positive family history
   c. Screening: Ultrasound every 6–12 months and α-fetoprotein (AFP) alone if ultrasound not available or cost is a concern. May use both AFP and ultrasound together

8. Cirrhosis
   a. Risk factors include older age, high levels of HBV DNA, habitual alcohol consumption, HCV/HDV/HIV infections, smoking and exposure to carcinogens
   b. Also address alcohol use, sexual practices, and smoking history for risk factor modifications to decrease risk of progression to cirrhosis

IV. MEDICATIONS: Indicated for patients with active viral replication (positive HBeAg and HBV DNA) and chronic hepatitis (elevated aminotransferases)
A. Interferon-alpha: Has anti-viral, anti-proliferative and immunomodulator activity
   1. Standard interferon (Intron A): 5MU SC daily or 10MU 3 times weekly for 16–24 weeks in HBeAg positive patients and 12–24 months in HBeAg negative patients
   2. Peginterferon-alpha (Pegasys): More convenient administration and more sustained viral suppression than standard Interferon-alpha
      • 180mcg SC weekly for 48 weeks
      • Could consider lower dose, shorter duration (90mcg SC weekly for 24 weeks) in HBeAg positive patients
      • Strongest predicting factor is pre-treatment ALT level
   3. Common side effects are flu-like symptoms, including fever, headache, chills, myalgia and fatigue. Can lead to flare up in ALT levels which can indicate a favorable response but can also lead to hepatic decompensation, especially in patients with underlying cirrhosis. Potential life threatening side effects neuropsychiatric (depression, suicidal ideation), autoimmune, ischemic and infectious disorders
B. Lamivudine (Epivir HBV), nucleotide analogue:
   1. 100mg PO daily (if there is no underlying HIV infection) for 1–2 years; adjust for CrCl < 50mL/min
   2. Well tolerated, can be used in patients with decompensated cirrhosis
   3. Highest rate of resistance development: 14–32% were shown to develop genotypic resistance after 1 year of treatment
C. Adefovir Dipivoxil (Hepsera), nucleotide analogue:
   1. 10mg PO daily, adjust dose when CrCl is < 50mL/min
   2. Rate of genotypic resistance exceeds 20% after 2 years of treatment
   3. Few side effects; monitor for nephrotoxicity
D. Entecavir (Baraclude), nucleotide analogue:
   1. Nucleoside-treatment naïve patients: 0.5mg PO daily
2. With Lamivudine or Lamivudine-resistant patients: 1mg PO daily
3. Adjust for CrCl < 50mL/min
4. Resistance in nucleoside-naive patients: 1.2% after up to 5 years of treatment; resistance in Lamivudine-resistant patients is significantly higher
5. Similar safety profile as Lamivudine; well tolerated

E. Telbivudine (Tyzeka), Thymidine nucleoside analogue:
   1. 600mg PO daily, adjust dose when CrCl < 50mL/min
   2. Well tolerated; few cases of myopathy and peripheral neuropathy (more common in combination therapy with Interferon)
   3. More potent than Lamivudine but has high rate of resistance and cross-resistance with Lamivudine
   4. Limited use for monotherapy

F. Tenofovir (Viread), nucleotide analogue
   1. 300mg PO daily, adjust for CrCl < 50mL/min
   2. Structurally similar to Adefovir but has higher potency
   3. Limited data on resistance beyond 72 weeks for therapy
   4. Side effects: Fanconi syndrome, nephrotoxicity, osteomalacia, decrease in bone density

V. HEPATITIS B IMMUNE GLOBULIN (HBIG)

A. Indications
   1. Newborn infants of HBsAg-positive mother
      a. Dose: 0.5mL IM within 12 hrs of birth
      b. Give 1st dose of Hep B vaccine concurrently at a separate site. 2nd and 3rd Hep B vaccine should be 1 mo and 6 mo after the 1st dose
   2. Acute exposure to blood containing HBsAg via parenteral (needle stick, sharps, bite), direct mucous membrane contact (accidental splash) or oral ingestion
   3. Sexual exposure to HBsAg-positive person
   4. Household exposure to person with acute HBV
      a. Dose for acute, sexual, and household exposure—0.06mL/kg IM ASAP or within 7 days of exposure
      b. Give Hep B vaccine series if unvaccinated

VI. VACCINATIONS

A. Hepatitis B vaccine (HBV vaccine)
   1. Indications:
      a. Routine childhood vaccination
      b. Selected patients and patient contacts (hemodialysis, hemophilia, hepatitis C, etc.), persons at increased risk due to sexual practices or IV drug use, traveler (> 6 months old) to hyperendemic regions, and natives of Alaska/Asia/Pacific Islands
      c. Advisory Committee for Immunization Practice (ACIP) recommends HBV vaccine also be given to all unvaccinated adults with diabetes mellitus ages 19–59 years old
      d. Health care workers/trainees: ACIP recommendations include pre-vaccination serologic testing for previous infection regardless of vaccination status, post-vaccination testing for higher risk practitioners. Should get another 3-dose series of vaccine if anti-HBs concentration is < 10 mIU/mL with repeat serologic testing 1–2 months after 3rd dose.
      e. Post-vaccination testing should also be performed in chronic hemodialysis patients and in infants of carrier mothers at 9–15 months of age
   2. Dose: Give as IM injection

   (Chart on next page)
### HBV Vaccine

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dose/Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19 y/o</td>
<td>10 mcg (Infant: birth, 1-4, 6-18mo; older children: 0, 1, 2, 4 mo)</td>
</tr>
<tr>
<td>&gt;19 y/o</td>
<td>20 mcg at 0, 1, 6 mo</td>
</tr>
<tr>
<td>Dialysis patients</td>
<td>40 mcg at 0, 1, 2, 6 mo*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dose/Schedule</th>
</tr>
</thead>
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<tr>
<td>0-19 y/o</td>
<td>5 mcg (Infant: birth, 1-4, 6-18mo; older children: 0, 1, 2, 4 mo)</td>
</tr>
<tr>
<td>11-15 y/o</td>
<td>10 mcg at 0, 4-6 mo</td>
</tr>
<tr>
<td>≥20 y/o</td>
<td>10 mcg at 0, 1, 6 mo</td>
</tr>
<tr>
<td>Dialysis patients</td>
<td>40 mcg at 0, 1, 6 mo*</td>
</tr>
</tbody>
</table>

### HBV-containing vaccine

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age Group</th>
<th>Formulation</th>
<th>Doses/Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comvax (Hib+HepB)</td>
<td>6 wks-4 yrs</td>
<td>0.5 mL at age 2, 4, 12-15 mo</td>
<td></td>
</tr>
<tr>
<td>Pediarix (DTaP+HepB+IPV)</td>
<td>6 wks-6 yrs</td>
<td>0.5 mL at age 2, 4, 6 mo</td>
<td></td>
</tr>
<tr>
<td>Twinrix (HepA+HepB)</td>
<td>≥18 yrs</td>
<td>3 doses at 0, 1, 6 mo; or 4 doses at 0, 7, 21-30 days, 12 mo</td>
<td></td>
</tr>
</tbody>
</table>

* 1 booster dose if anti-HBs level <10 mIU/mL 1-2 mo after 3rd dose or annual antibody testing decline to <10 mIU/mL

### B. Hepatitis A vaccine (HAV vaccine)

1. Indications:
   a. Routine childhood vaccination
   b. Current recommendation by the ACIP is that all persons with chronic liver disease in the US be vaccinated against hepatitis A

2. Dose: give as IM injection

<table>
<thead>
<tr>
<th>HAV Vaccine</th>
<th>Age Group</th>
<th>Formulation</th>
<th>Doses/Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Havrix</td>
<td>1-18 yrs</td>
<td>720 ELISA units 1440 ELISA units</td>
<td>2 doses at 0, 6-12 mo</td>
</tr>
<tr>
<td>Vaqta</td>
<td>≥18 yrs</td>
<td>25 units 50 units</td>
<td>2 doses at 0, 6-18 mo</td>
</tr>
</tbody>
</table>

### VII. SCREENING

A. Testing with HBsAg and HBsAb should be performed on the following patients:

1. Persons born in endemic areas: Asia, Africa, Pacific islands, etc.
2. Unvaccinated children whose parents are from endemic regions
3. Patients with chronically elevated aminotransferases
4. Patients on immunosuppressive therapy or on dialysis
5. Men who have sex with men, multiple sexual partners, history of sexually transmitted infections
6. Inmates of correctional facilities
7. IV drug abusers
8. History of HIV or Hepatitis C
9. All pregnant women
10. Family members, household and sexual contacts of infected individuals

(Chart on next page)
<table>
<thead>
<tr>
<th>HBeAg</th>
<th>HBV DNA (PCR)</th>
<th>ALT</th>
<th>Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>&gt; 20,000 IU/mL</td>
<td>&lt; 2 x ULN</td>
<td>Observe; consider treatment if ALT becomes elevated.</td>
</tr>
<tr>
<td>+</td>
<td>&gt; 20,000 IU/mL</td>
<td>&gt; 2 x ULN</td>
<td>Treatment with IFN; if contraindicated, consider TDF/ETV. LAM and LdT not preferred due to high rate of drug resistance. ADV not preferred due to weak anti-viral activity.</td>
</tr>
<tr>
<td>-</td>
<td>&gt; 2,000 IU/mL</td>
<td>&gt; 2 x ULN</td>
<td>Long term treatment. Treatment with IFN; if contraindicated, consider TDF/ETV. LAM and LdT not preferred due to high rate of drug resistance. ADV not preferred due to weak anti-viral activity.</td>
</tr>
<tr>
<td>-</td>
<td>&lt; 2,000 IU/mL</td>
<td>1-2x ULN</td>
<td>Consider liver biopsy and treat if it shows moderate/severe inflammation or significant fibrosis.</td>
</tr>
<tr>
<td>-</td>
<td>&lt; 2,000 IU/mL</td>
<td>&lt; ULN</td>
<td>Observe, consider treatment if ALT becomes elevated.</td>
</tr>
<tr>
<td>+/-</td>
<td>Detectable</td>
<td>Cirrhosis</td>
<td>Compensation: treat if HBV DNA &gt; 2,000 IU/mL; consider treatment if HBV DNA &lt; 2,000 IU/mL and ALT elevated. Decompensation: refer for liver transplant; treat with LAM or ADV + LAM, ADV, TDF or ETV preferred.</td>
</tr>
<tr>
<td>+/-</td>
<td>Undetectable</td>
<td>Cirrhosis</td>
<td>Compensation: observe. Decompensation: refer for liver transplant.</td>
</tr>
</tbody>
</table>

*Abbreviations: ALT (alanine aminotransferase); ULN (upper limit of normal); IFN (interferon); LAM (lamivudine); ADV (adefovir); ETV (entecavir); LdT (telbivudine); TDF (tenofovir disoproxil fumarate).*

**CLINICAL PEARLS**

- Mortality rate with acute hepatitis B is 0.1–1%. It is higher with superimposed hepatitis D.
- Risk of chronic infection in a neonate is 90% (when transmitted at the time of delivery by HBsAg positive mothers). They must receive the HB immune globulin, followed by the vaccine series.
- HDV is a defective virus that only causes hepatitis in the presence of HBV infection. In US, infection is primarily with IV drug users.
- There has been a 60% reduction in occupationally acquired hepatitis B infection due to immunization programs.
- Hepatitis B vaccine series induces protective antibodies in 95% of healthy volunteers ages 20–39.
- Incidence of hepatocellular carcinoma increases 200–300 fold in patients with chronic hepatitis B.

**References**

CDC, Hepatitis B Information for Health Professionals. Available at: http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#overview


65. GASTROESOPHAGEAL REFLUX DISEASE
& PEPTIC ULCER DISEASE

— PART ONE: GASTROESOPHAGEAL REFLUX DISEASE (GERD) —

I. SYMPTOMS
A. Classically, a burning feeling, rising from the stomach or lower chest and radiating toward the neck, throat, and occasionally the back. Other symptoms include dysphagia, water brash, odynophagia, burping, hiccups, nausea, and vomiting. Other patients may be totally asymptomatic
B. Extra-esophageal symptoms include chest pain, wheezing, cough, laryngitis, vocal cord ulceration, leukoplakia, and dental erosion (especially in bulimics)

II. ETIOLOGY
A. Incompetent lower esophageal sphincter (LES): Exacerbating factors include foods such as onion, fats, mint, ETOH, chocolate, caffeine as well as meds such as anticholinergics, β-blockers, progesterone containing oral contraceptives, NSAIDs, Prednisone
B. Impaired esophageal peristalsis: Associated diseases include CREST, scleroderma, Raynaud’s, reflux-induced injury
C. Decreased salivation: Associated conditions include Sjögren’s, cigarette use, and anti-cholinergic meds
D. Delayed gastric emptying: Associated conditions include gastroparesis, gastric outlet obstruction
E. Increased secretion of gastric acid: Associated conditions include gastrinoma, Zollinger-Ellison syndrome
F. Direct irritants: Citrus, tomato, cola, coffee (caffeine will decrease LESP)
G. Hiatal Hernia: Impairs LES function through several mechanisms, as well as impairing esophageal acid clearance. Reflux is worse in patients having a “nonreducible” hiatal hernia (where the gastric rugal folds remain above the diaphragm between swallows)

III. EVALUATION
A. Empiric treatment may be attempted in patients with typical “uncomplicated” symptoms (see V. Table 1)
B. Further evaluation, as below, is required in patients with:
   1. Atypical symptoms (early satiety, anorexia, dysphagia, odynophagia, cough, chest pain, asthma, laryngitis)
   2. Patients > 50 with new onset symptoms
   3. Patients whose symptoms persist after 8 weeks of treatment
   4. Patients presenting with complications (anemia, guaiac positive stool, weight loss, stricture)
C. Patients treated empirically who do not respond in 2 weeks or whose symptoms recur after 6 weeks of treatment should undergo further evaluation
D. Evaluations include:
   1. Upper endoscopy with biopsy: Best assessment of extent of mucosal damage, Barrett’s esophagus, stricture
   2. Esophageal pH monitoring: For diagnosing reflux and especially useful in patients with atypical symptoms of chronic cough, chest pain, asthma, laryngitis
   3. Upper GI: May identify ulcers or stricture, but is insensitive for reflux
   4. Esophageal motility: Useful assessment of motor function of the esophagus, especially preoperatively
   5. Gastroesophageal scintigraphy: Noninvasive evaluation of esophageal emptying, especially useful in pediatric population
   6. Although slightly controversial, there is currently no indication for H. pylori testing in uncomplicated GERD
E. Differential diagnosis: Achalasia, Zenker’s diverticulum, gastroparesis, gallstones, peptic ulcer disease, functional dyspepsia, and angina pectoris

Algorithm for Initial Evaluation and Treatment of Patients with Gastroesophageal Reflux Disease Symptoms

Classic Reflux Symptoms (Heartburn, Regurgitation, Water Brash)

Alarm Symptoms (Dysphagia, Odynophagia, Anemia, Weight Loss, Hematemesis) Present?

NO

YES

Begin Conservative Antireflux Measures
Discuss Use of Over-the-Counter Preparations
Provide Patient Education

Persistent Symptoms?

NO

YES

Begin Empiric Trial of Proton Pump Inhibitors

Persistent Symptoms?

NO

YES

Perform Upper Endoscopy

Continue Conservative Antireflux Measures

NO

YES

Continue Therapy, Decreasing to Least Potent Acid Suppression Necessary to Keep Patient Symptom-Free

Ulcration

Consider Causes of Ulceration, eg, Acid Peptic Disease, Viral or Fungal Infection, Neoplasia

Erosive Esophagitis

Intensify Proton Pump Inhibitor Therapy

Barrett Esophagus

Discuss Utility of Enrollment in Endoscopic Surveillance Program

Cancer

Referral to Appropriate Oncological Services

Normal

Consider 24-h pH Probe to Identify Nonerosive Reflux

Consider Other Causes of Symptoms


IV. MANAGEMENT

A. Behavior modification

1. Avoid foods that are direct irritants or decrease LES pressure (see above)
2. Stop smoking and avoid alcohol
3. Avoidance, if possible, of drugs that may injure the esophageal mucosa (tetracy-
cline, quinidine, potassium chloride tablets, NSAIDs, bisphosphonates) or
decrease sphincter tone (Theophylline, calcium channel blockers, anticholin-
ergics)
4. Avoidance of large evening meals near bedtime or before exercise
5. Weight loss
6. Avoid tight fitting clothes
7. Remain upright for 3hrs after eating
8. 4–8 inch blocks under head of bed
B. Antacids provide symptom relief but do not heal esophagitis
C. H₂ blockers: See V. Table 1
D. Proton pump inhibitors: See V. Table 1
E. Prokinetic agents aid in the competence of LES. They are approximately equivalent to
H₂ blockers for mild GERD and maintenance: Metoclopramide (Reglan): 10mg PO
QID, significant side effects. Long term use (>12 wks) or high doses (30–40mg QID) is
associated with increased risk of developing tardive dyskinesia
F. Mucosal protective agents: See Part Two of this chapter, PUD, III. A. 3.
G. Combinations: PPIs plus Reglan are more effective than PPIs alone
H. Surgery: Nissen fundoplication is the therapy of choice for patients with strictures
requiring repeated dilation or for patients who fail medical therapy. Surgery has a
90% efficacy and is especially effective in patients with atypical symptoms such as
chronic cough, asthma, etc. Laparoscopic methods have lower morbidity than the
standard open technique
I. Device to treat GERD
a. LINX Reflux Management System was approved by the FDA in 2012
b. Consists of a series of titanium beads, each with a magnetic core, connected together
with titanium wires to form a ring shape
c. The LINX device is implanted around the lower esophageal sphincter (LES) to
strengthen a weak LES muscle
d. Useful in patients who continue to have symptoms of GERD despite maximum
medical therapy
V. COMPLICATIONS
A. Degree of injury is poorly correlated with degree of symptoms
B. Specific complications include:
1. Esophagitis/ulceration: Seen in <5% of patients with heartburn. Treatment with PPI
for 4–12 weeks results in healing in most cases. Recurrence rates high after stopping
PPI, requiring continuation of acid suppression
2. Barrett’s Esophagus: In 10% of patients with chronic reflux, esophageal squa-
mo us cells may undergo metaplasia to columnar cells. Esophageal adenocar-
cinoma may develop in up to 10% of patients with metaplasia. If multiple foci
of high grade dysplasia are found on EGD, elective esophagectomy versus Q6
month EGDs with biopsy must be considered. For Barrett’s esophagus meta-
plasia without dysplasia, EGD with biopsy must be performed Q1–2yrs
3. Stricture: EGD in those with dysphagia should confirm the stricture (usually at
the GE junction) and dilation may be performed at the same time. Long term
proton pump therapy should follow dilation
4. Extra-esophageal complications include asthma (aspiration versus vagal),
 laryngitis, chronic cough, sleep apnea
C. Prolonged use of PPIs
1. Long-term PPI use may reduce the absorption of important nutrients including
Magnesium, Calcium and Vitamin B₁₂, and might reduce the effectiveness of other
medications
2. FDA warns that taking PPIs together with the anticoagulant agent Clopidogrel (Plavix)
can weaken the protective effect of Clopidogrel for heart patients
3. Long-term use of PPIs has been linked to Clostridium difficile-associated diarrhea,
fracture risk, and hypomagnesemia
Table 1—Common Medications Used in GERD/PUD

<table>
<thead>
<tr>
<th>common medications</th>
<th>acute duodenal ulcer</th>
<th>maintenance duodenal ulcer</th>
<th>acute gastric ulcer</th>
<th>GERD symptoms</th>
<th>esophageal lesions</th>
<th>maintenance esophageal ulcers/severe GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Famotidine (Pepcid)</td>
<td>20mg BID or 40mg hs x 6-8 wks</td>
<td>20mg hs 40mg hs x 6-8 wks</td>
<td>20mg BID</td>
<td>40mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine (Zantac)</td>
<td>150mg BID or 300mg hs x 6-8 wks</td>
<td>150mg hs 300mg hs x 6-8 wks</td>
<td>150mg BID</td>
<td>150mg BID 150mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimetidine (Tagamet)</td>
<td>800mg hs x 6-8 wks or 400mg BID</td>
<td>800mg hs 800mg hs x 6-8 wks</td>
<td>800mg BID</td>
<td>800mg BID or 400mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nizatidine (Axid)</td>
<td>150mg BID or 300mg hs x 6-8 wks</td>
<td>150mg hs 300mg hs x 6-8 wks</td>
<td>150mg BID</td>
<td>200mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazole (Prilosec)</td>
<td>20mg QD x 4-8 wks</td>
<td>20mg QD 40mg QD x 4-8 wks</td>
<td>20mg QD</td>
<td>20mg QD 20mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lansoprazole (Prevacid)</td>
<td>15mg QD x 4-8 wks</td>
<td>15mg QD 30mg QD x 4-8 wks</td>
<td>15mg QD</td>
<td>15mg QD 15mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabeprazole (AcipHex)</td>
<td>20mg QD x 4 wks</td>
<td>20mg QD 20mg QD x 4-8 wks</td>
<td>20mg QD</td>
<td>20mg QD 20mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esomeprazole (Nexium)</td>
<td>20mg QD</td>
<td>20mg QD 20-40mg QD x 40 wks</td>
<td>20mg QD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pantoprazole (Protonix)</td>
<td>40mg QD</td>
<td>20-40mg QD x 4 wks</td>
<td>40mg QD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexlansoprazole (Dexilant)</td>
<td>30mg QD x 4 wks (may use daily prn if symptoms persist)</td>
<td>60mg QD x 8 wks</td>
<td>30 mg QD for up to 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zegerid (Prilosec plus Sodium Bicarbonate)</td>
<td>20mg QD x 4-8 wks</td>
<td>20mg QD 40mg QD x 4-8 wks</td>
<td>20mg daily x 4-8 wks</td>
<td>20mg QD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Doses listed are for FDA approved indications

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### PART TWO: PEPTIC ULCER DISEASE (PUD)

#### I. SYMPTOMS
A. Duodenal ulcers frequently present with burning epigastric pain relieved by antacids. Symptoms may awaken the patient; may be asymptomatic
B. Gastric ulcers often present with nausea, vomiting, pain made worse by food, early satiety
C. Nonspecific symptoms include dyspepsia, bloating, gas; may be symptomatic
D. Alarm symptoms for underlying malignancy or complicated ulcer disease include: age > 45yrs, rectal bleeding or melena, weight loss, anemia, dysphagia, abdominal mass, jaundice, family history of gastric cancer, previous history of PUD and anorexia/early satiety
E. Diagnosis usually made by endoscopy (preferred) or upper GI

#### II. ETIOLOGY
A. *Helicobacter pylori*: See below
B. NSAID use: Clinical ulcers (usually gastric) develop in 1% of patients per year of NSAID use. Risks of complications include increased age, prior GI disease, concomitant steroid or anticoagulant use, female sex, and increased dose of NSAIDs. Nonselective NSAIDS cause inhibition of both Cox-1 and Cox-2, resulting in GI toxicity. Selective Cox-2 inhibitor, Celecoxib (Celebrex), or Meloxicam (Mobiz) inhibit Cox-2 to a greater extent than Cox-1, leading to better GI safety profile. However, recent reports of CV complications attributed to Cox-2 inhibitors have limited their use
C. Hypersecretory state: Zollinger Ellisson Syndrome, gastrinoma (diagnosed by fasting serum gastrin level)
D. Exacerbating factors
1. Tobacco: One study showed that the risk of duodenal ulcer, failure to heal, and recurrence was directly proportional to number of cigarettes
2. Alcohol is a strong stimulant of acid secretion
3. Corticosteroids
4. Diet (controversial)

III. TREATMENT
A. Acute ulcers
1. Testing and treatment for *H. pylori* (see IV), consider stopping NSAIDs
2. Antisecretory meds (PPIs and \( H_2 \) blockers) per Table 1; take PPIs on empty stomach in the morning
3. Mucosal protective agents (not as effective as \( H_2 \) blockers)
   a. Sucralfate (Carafate)
      i. Forms a barrier at the ulcer base and stimulates production of mucous, \( HCO_3 \), and prostaglandins
      ii. Comparable to \( H_2 \) blockers in healing duodenal ulcers and in GERD
      iii. Dose: 1g PO QID × 6–8 weeks
   b. Antacids
      i. Help relieve symptoms and are comparable to \( H_2 \) blockers in healing duodenal ulcers and in GERD
      ii. Example: Mylanta
   c. Bismuth (Pepto-Bismol) stimulates production of \( HCO_3 \) and prostaglandins
B. Maintenance therapy for 2–5 years if frequent symptom recurrence or failure to clear *H. pylori* infection
1. Duodenal ulcers: \( H_2 \) blockers (or Proton pump inhibitors) given at HS at half treatment dose (full dose in smokers or complicated disease)—or—Carafate 1g PO BID
2. Gastric ulcers: No approved maintenance therapy
3. NSAID ulcers: If discontinuing NSAIDs is not possible, a PPI (*Nexium, Prevacid*) should be given concurrently. Misoprostol (*Cytotec*) provides some protection. It acts as a prostaglandin analog and stimulates \( HCO_3 \) and mucous production. It is dosed at 200mcg PO QID with meals. Diarrhea and miscarriage induction limit its use
4. Patients successfully treated for *H. pylori* may attempt discontinuation of antisecretory therapy

IV. HELICOBACTER PYLORI
A. General
1. Approximately 30–40% of US population is infected with *H. pylori*. This bacteria is a cofactor in 75% of ulcers
2. Infection causes histological gastritis in almost 100% of patients, PUD, and is a risk factor in the development of gastric adenocarcinoma (risk increased 9 fold) and lymphoma
3. Patients infected have lifetime risk for PUD of approximately 15%
4. Cure is associated with a reduction of ulcer recurrence and ability to stop antisecretory therapy
5. Duodenal ulcers recurred in 6% of those cured of *H. pylori* and in 67% of those who remained positive for *H. pylori*
6. *H. pylori* produces large amounts of urease, an enzyme that catalyzes the breakdown of urea to alkaline ammonia and carbon dioxide. Through this reaction, the bacterium may protect itself from acid injury by surrounding itself with alkaline material
7. More than half of the world’s population is infected with *H. pylori*. It is likely spread fecal-oral
B. Indications for testing
1. Patients newly diagnosed (endoscopically or radiographically) with ulcer disease
2. Patients with history of ulcer disease on antisecretory therapy
3. Patients with ulcer-like dyspepsia
4. Patients with mucosa-associated lymphoid tissue lymphoma
5. Screening to prevent gastric cancer if risk factors present
C. Methods of *H. pylori* detection
1. Histological examination (after EGD)
2. Blood antibody tests
Management of Common Ambulatory Conditions

65. GERD/PUD

a. Tests for IgG antibodies to \( H. pylori \)
b. Most convenient but are less accurate
c. Not able to distinguish active infection (cannot use to monitor efficacy of therapy) as it may stay positive for years after successful treatment

3. Urea breath tests (UBTs)
a. A measure of current infection with a sensitivity of 80-100%
b. May be falsely negative in patients receiving PPIs or \( H. pylori \) therapy. Prior to testing, stop PPIs for 2 weeks and ATBs/bismuth for 4 weeks

4. Stool antigen: Highly sensitive and specific, comparable to UBT

D. Other
1. In patients with new onset PUD, if the initial test for \( H. pylori \) is negative, another test should be performed
2. Factors affecting cure rate include patient compliance, duration of therapy, and presence of resistance to the ATBs
3. Resistance to Metronidazole is 28–39% and to Clarithromycin is 11%. Amoxicillin and Tetracycline resistant strains are rare

E. Confirmation of eradication
1. May be helpful after course of therapy
2. Use nonendoscopic methods including UBT (antibody test may remain positive for years after eradication)
3. Wait 4–6 weeks after completion of therapy

F. There may be a genetic predisposition

V. EPIDEMIOLOGY
A. Approximately 500,000 new cases and 4 million recurrences of peptic ulcers occur in the US each year
B. 10% of individuals in Western countries will develop a peptic ulcer at some point during their lifetimes
C. Cigarette smoking is a risk factor for peptic ulcer disease, delays healing and may predispose to relapses
D. The prevalence of ulcer disease appears to be increased for patients with alcoholic cirrhosis but no such association has been established for drinkers without cirrhosis
E. A link between diet and peptic ulcer disease has not been established

VI. ERADICATION OF \( H. PYLORI \)

A. First-line therapies

<table>
<thead>
<tr>
<th>Patients who are not allergic to penicillin and have not previously received a macrolide</th>
<th>Standard dose PPI* twice daily (or esomeprazole 40 mg once daily) plus clarithromycin 500 mg twice daily, and amoxicillin 1000 mg twice daily for 10-14 days*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who are allergic to penicillin, and who have not previously received a macrolide or metronidazole or are unable to tolerate bismuth quadruple therapy</td>
<td>Standard dose PPI twice daily, clarithromycin 500 mg twice daily, metronidazole 500 mg twice daily for 10-14 days*</td>
</tr>
<tr>
<td>Patients who are allergic to penicillin or failed one course (above) of ( H. pylori ) treatment</td>
<td>Bismuth subsalicylate 525 mg four times daily, metronidazole 250 mg four times daily, tetracycline 500 mg four times daily*, standard dose PPI* twice daily for 10-14 days#</td>
</tr>
<tr>
<td></td>
<td>OR Bismuth subcitrate 420 mg four times daily, metronidazole 375 mg four times daily, tetracycline 375 mg four times daily*, standard dose PPI* twice daily for 10-14 days#</td>
</tr>
</tbody>
</table>

\( H. pylori \): Helicobacter pylori; PPI: proton pump inhibitor

* Lansoprazole 30 mg twice daily, omeprazole 20 mg twice daily, pantoprazole 40 mg twice daily, or rabeprazole 20 mg twice daily.

* Eradication rates of 70 to 85%.

# Eradication rates of 75 to 90%.

^ A combination preparation of bismuth subcitrate-metronidazole-tetracycline is available in the US (trade name Pylera).

B. Treatment failure can be due to compliance and antibiotic resistance. Clarithromycin resistance is an emerging problem.

VII. COMPLICATIONS OF PUD
A. Hemorrhage: Symptoms include coffee ground emesis, hematemesis, melena, or hematochezia. Up to 25% of patients with PUD may develop bleeding.
B. Perforation: Seen in up to 5% of ulcer patients. Usually occurs from ulcers on the anterior wall of the stomach or duodenum. Patients will usually have absent bowel sounds, rebound tenderness, and a very rigid abdomen. Upright or decubitus plain abdominal films will aid in diagnosis (free intraperitoneal air).
C. Gastric outlet obstruction: Occurs in up to 5% of ulcer patients due to edema or scarring of the pylorus or duodenal bulb. Upper endoscopy is necessary to define the extent of obstruction and to rule out carcinoma.
D. Gastric adenocarcinoma

— PART THREE: FUNCTIONAL/NONULCER DYSPEPSIA —

I. SYMPTOMS—Abdominal pain/discomfort, bloating/abdominal distention or fullness, nausea, early satiety

II. ETIOLOGY—Incompletely understood, prevalence around 25%
A. Increased visceral sensitivity
B. Abnormal gastric/duodenal motility
C. Psychosocial factors: anxiety, somatization, neuroticism, and depression are increased in this group
D. Possibly H. pylori infection
E. Medications: NSAIDs, antibiotics, estrogens, narcotics, Digoxin
F. Systemic illnesses: Post gastroenteritis, hyperthyroidism, hyperparathyroidism, collagen vascular diseases

III. DIAGNOSIS—Typically a diagnosis of exclusion (dyspeptic symptoms without evidence of structural disease)
A. Those who do not respond to empiric therapy should be referred to GI for EGD/evaluation (see below)
B. Those who exhibit alarm signs/symptoms should undergo early EGD: age >50, GI blood loss/anemia, weight loss, signs of obstruction (dysphagia, mass on exam, significant vomiting), severe/persistent pain

IV. TREATMENT
A. Empiric treatment with PPI or H2 blocker: if responds within 2 weeks, continue therapy for 6–8 weeks
B. If no response or if experience worse symptoms or relapse: test and treat for H. pylori; if no response, refer to GI for EGD/evaluation
C. Prokinetic agents may be beneficial
D. Low doses of Desipramine or Amitriptyline may be helpful
E. Avoidance of offending foods
F. Address psychological factors
G. Patient education/reassurance, minimizing use of invasive diagnostic tests: drug therapy not reliably effective (try switching medications rather than stacking therapy), symptoms often recur but are not life-threatening

CLINICAL PEARLS
• Long-term PPI use may increase fracture risk primarily in age >50, hypomagnesemia, clostridium difficile infections and community-acquired pneumonia
• Costs in US of treating H. pylori related diseases is $3–5.6 billion/yr
• Patient education regarding Aspirin and NSAID use is important. Patients should be made aware of common signs and symptoms of PUD (bleeding, etc.) and instructed to inform the physician if they should develop
• Smoking cessation is imperative in patients with PUD
If patients need to continue NSAIDs despite being diagnosed with PUD, consider cox-2 inhibitors (Celebrex) or shorter acting NSAIDs (so that dosage can be titrated) rather than the potent once-a-day NSAIDs. Consider Cytotec for prevention of PUD in chronic NSAID users. The 3 most common reasons for chronic cough are sinusitis, asthma, and GERD.

References

Daniel M. Neides, MD
Miriam Chan, PharmD
66. Diarrhea in Adults  

Management of Common Ambulatory Conditions

urine output, lethargy), onset (abrupt vs. gradual), duration

B. Stool characteristics: Frequency, quantity, consistency, volume, blood, pus, mucus, greasy stools

C. Abdominal pain

D. Exposure: Travel history (developing areas, camping), day care, exposure to persons who are ill, ingestion of raw or undercooked meat or seafood, raw milk, sexual contacts (oral-anal, receptive anal intercourse), visit to farm or petting zoo

E. Med/Drug history: Recent ATBs, laxative use, antacids, excessive alcohol, caffeinated beverages, sorbitol (sugar-free gum or candy)

F. Past medical history: Immunosuppression, HIV/AIDS, prior gastrectomy

G. Other: Headaches, myalgias, confusion

IV. PHYSICAL EXAMINATION

A. General: Temperature, blood pressure, pulse, weight

B. Oral: Dry membranes

C. Skin: Decreased skin turgor, rash, jaundice

D. Abdomen: Guarding, rebound tenderness, hypo- or hyperactive bowel sounds, hepatomegaly, ascites, or masses

E. Rectal: Guaiac stool, note any fistulas

V. EVALUATION

A. Features which are common for infectious diarrhea

1. History: Fever, abdominal pain, tenesmus, bloody stool, nausea/vomiting

2. Physical: Abdominal pain, bloody or heme-positive stool

3. Laboratory: Fecal WBCs > 50 HPF, fecal lactoferrin

B. Indications for stool studies

1. There have been numerous approaches recommended. In numerous studies yield in all cultures is between 1% and 5%

2. Yield may be increased by selective use of studies. Conditions which increase likelihood for infectious diarrhea are listed above

3. Infectious Disease Society of America issued recommendations in 2001 which recommend testing patients with diarrhea lasting > 1 day especially if accompanied by fever, bloody stool, systemic illness, recent use of ATBs, day care center attendance, hospitalization, or dehydration

4. Stool studies may include culture and sensitivity (notify lab if evaluating for E. coli 0157), Shigella, Salmonella, Yersinia, Campylobacter, ova and parasites, C. difficile toxin

C. Additional studies should be tailored to the signs and symptoms and may include CBC, electrolytes, BUN, creatinine, urinalysis, abdominal radiography, anoscopy, flexible sigmoidoscopy, and colonoscopy

D. In patients with persistent diarrhea, consider further evaluation for other entities including inflammatory bowel disease (ulcerative colitis or Crohn’s disease), irritable bowel syndrome, ischemic bowel disease, laxative abuse, partial obstruction, and other entities as mentioned in II. B. above

VI. MANAGEMENT OF INFECTIOUS DIARRHEA  

(Note: Management of other etiologies mentioned in II. above, is tailored to specific diagnosis. Duration of treatment below is for immunocompetent patients)

A. Replace fluid loss orally if possible. In patients with mild diarrhea use clear juices and soups and with more severe diarrhea or dehydration use oral rehydration solutions

B. Avoid antimotility agents in patients with bloody diarrhea or infection with Shiga toxin-producing E. coli. In patients without these entities, consider Imodium: 4mg PO initially, then 2mg after each unformed stool to maximum of 16mg/day or use Pepto-Bismol 2 tabs or 30mL up to QID. Avoid in pregnant women

C. Institute therapy for:

1. Traveler’s diarrhea:
   a. Fluoroquinolone: Cipro 500mg BID × 1–3 days
   b. Azithromycin 500mg QD × 1–3 days or 1000mg × 1 dose, antibiotic of choice
Management of Common Ambulatory Conditions  

66. Diarrhea in Adults

in children (10mg/kg/days × 3 days) and pregnant women, and for quinolone-resistant Campylobacter (such as Thailand, Nepal)
c. Rifaximin (Xifaxan) 200mg TID × 3 days for noninvasive strain of E coli
2. Shigellosis: Cipro 500mg PO BID × 3–5 day or Levoquin 500mg PO QD × 3–5 days; Azithromycin 10mg/kg/days for children
3. Campylobacter: Azithromycin 500mg PO QD × 3 days
4. Giardia: Metronidazole (Flagyl) 250mg PO TID × 5–7 days or Tinidazole (Tindamax) 2g in 1 dose
5. Cholera: Doxycycline 300mg × 1 dose or Ciprofloxacain 1g × 1 dose or Azithromycin 1g × 1 dose (20mg/kg × 1, max 1g)
6. Clostridium difficile: Stop offending ATB. Metronidazole (Flagyl) 250mg PO QID × 10–14 days or Vancomycin 125–500mg PO QID × 10–14 days

D. Not routinely recommended for:
1. Salmonella: Unless patient is > 50yrs or has prosthesis, valvular heart disease, severe atherosclerosis, malignancy, or uremia
2. Yersinia: ATB not usually required unless severe infection or immunocompromised
3. E. coli 0157: Treatment with ATBs has been shown to increase production of Shiga toxin and may increase likelihood of hemolytic uremic syndrome (HUS). Treatment with ATBs has not been shown to ameliorate illness

E. Decrease risk of transmission to contacts with hand washing and good hygiene

CLINICAL PEARLS

- Treatment of salmonella with ATBs may prolong the carrier state. Institute therapy when systemic spread is considered, but not to reduce secondary transmission (can be accomplished with hand washing)
- Traveler's diarrhea can occur from contaminated ice cubes or water used to wash fruits or vegetables
- Patients taking Flagyl for an infectious diarrhea should avoid alcohol (may cause an Antabuse-like reaction)
- Test for HIV in patients diagnosed with Cryptosporidium

References
67. Constipation in Adults

Linda Stone, MD
Michael B. Weinstock, MD
Daniel M. Nedes, MD

I. DEFINITION: Defecation which occurs < 2 ×/week

II. HISTORY AND PHYSICAL EXAM
A. History
   1. Frequency of stools, consistency, need to strain, and pain with defecation
   2. Rectal bleeding (melena vs. bright red blood mixed with stool), weight loss, and abdominal bloating or cramping
   3. Past medical history
      a. Previous patterns of bowel activity
      b. Current meds
      c. History of malignancy or radiation therapy
      d. Previous surgeries
B. Physical exam
   1. Abdomen: Note any surgical scars. Palpate for masses (stool) and hepatosplenomegaly. Check for hernia. Examination results are often normal
   2. Neurologic: Neuro exam if necessary

III. ETIOLOGIES
A. Medications: Opiate analgesics, antihypertensives (calcium channel blockers), iron, calcium, barium, antidepressants, antipsychotics, antispasmodics, antiparkinson meds, antacids
B. Neurologic dysfunction: Hirschsprung’s disease, neurofibromatosis, autonomic neuropathy, Chagas disease, spinal cord lesions, multiple sclerosis, CVA, Parkinson’s disease
C. Metabolic and endocrine: Diabetes Mellitus, hypothyroidism, hypercalcemia, hypocalcemia, hypokalemia, pregnancy
D. Collagen vascular diseases: Amyloidosis, systemic sclerosis, myotonic dystrophy
E. Mechanical difficulties: Colorectal cancer, hernia, diverticulitis, irritable bowel, hemorrhoids, anal fissure, or stricture

IV. EVALUATION: Direct evaluation based on findings in history and physical examination
A. Blood chemistry: Blood glucose, serum electrolytes, calcium, and TSH
B. Fecal occult blood test: Perform during examination and send 3–4 home for patient to check and return
C. Radiology
   1. Sigmoidoscopy or colonoscopy: To detect colon cancer, obstructive lesions, and evidence of laxative abuse (melanosis coli)
   2. Transit study: Radiopaque markers are taken along with a high fiber diet. X-rays are obtained over the subsequent 3 days. Normal patients will pass the marker before 72 hrs. Markers still present ≥ 4 days suggest a colonic problem
   3. Anorectal manometry: Measures sphincter tone; helps to differentiate patients with Hirschsprung’s disease from other neurologic problems

V. MANAGEMENT
A. Lifestyle
   1. Exercise (walking, jogging, swimming, etc.)
   2. Increase fluids intake: 6–8 glasses (8 oz) of water or fruit juice per day
   3. Increase fiber intake to 20–35g of dietary fiber per day
B. Medications
   1. Laxatives
Laxatives for the Treatment of Constipation

<table>
<thead>
<tr>
<th>Laxative Class</th>
<th>Recommendation for Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool softener</td>
<td>Docusate (Colace), 50-200 mg/d in divided doses</td>
</tr>
<tr>
<td>Fiber</td>
<td>Psyllium (Metamucil), 20-30 g/d; Fibercon 2-4 tabs/d</td>
</tr>
<tr>
<td>Osmotic</td>
<td>70% Sorbitol, 15-45mL/d, lactulose 15-30mL qd-QID</td>
</tr>
<tr>
<td></td>
<td>Polyethylene glycol-electrolyte solution (Miralax) 17g qd-QID</td>
</tr>
<tr>
<td>Lubricants</td>
<td>Mineral oil, 15-45 mL/d</td>
</tr>
<tr>
<td>Saline cathartics</td>
<td>Milk of magnesia, 15-45 mL Qhs</td>
</tr>
<tr>
<td>Stimulant cathartics</td>
<td>Bisacodyl (Dulcolax), two to four 5-mg tablets Qhs; Senna, 8.6mg tab, 2-4 tabs/d</td>
</tr>
</tbody>
</table>

2. Lubiprostone (Amitiza):
   a. Activates chloride channel to enhance intestinal fluid secretion
   b. Indicated for chronic idiopathic constipation and opioid-induced constipation in adults with noncancer pain
   c. Dose: 24mcg BID with food
   d. Common adverse events: Nausea, diarrhea, headache, abdominal pain and distention, and flatulence
   e. Pregnancy Category C. A negative pregnancy test prior to beginning therapy is advised

3. Methylnaltrexone (Relistor)
   a. Selective antagonist of opioid binding at the mµ-opioid receptor
   b. Opioid-induced constipation in patients with cancer pain
   c. Dose: 38kg to < 62kg: 8mg sc QOD
      62kg to 114kg: 12mg sc QOD
      weight falling outside those ranges: 0.15mg/kg sc QOD
   d. Common adverse reactions: abdominal pain, flatulence, nausea, dizziness, diarrhea and hyperhidrosis

CLINICAL PEARLS

- New onset of constipation is a warning sign for cancer. Screen for colon cancer with selected patients
- Consider irritable bowel syndrome (IBS) as the cause of constipation
- Fecal impaction is often a common cause of constipation in the elderly

References

68. Hemorrhoids

I. DEFINITION: Hemorrhoids (piles) are varicosities of the rectal venous plexus. Can occur internally (above the pectinate line) or externally (below the pectinate line)
   A. **Internal hemorrhoids** are covered by viscerally innervated mucosa. Uncomplicated internal hemorrhoids are not painful. Internal hemorrhoids are referred to as complicated when the patient presents with painless bleeding, prolapse or thrombosis. Internal hemorrhoids may occasionally become strangulated (massive prolapse and thrombosis, necrosis and ulceration) and the patient presents with severe pain and inability to sit down or defecate
   B. **External hemorrhoids** are covered by somatic innervated mucosa. May be painful or painless. Complications include acute thrombosis or rupture with hematoma formation

II. CLASSIFICATION OF INTERNAL HEMORRHHOIDS
   A. **First degree**: Do not protrude, cannot be palpated by digital rectal exam (DRE), require anoscopy for diagnosis
   B. **Second degree**: Protrude, reduce spontaneously
   C. **Third degree**: Protrude, require manual reduction
   D. **Fourth degree**: Prolapsed, irreducible

III. HISTORY AND PHYSICAL EXAMINATION
   A. History
      1. Rectal itching (from stool residue left secondary to poor wiping because of pain)
      2. Straining with stool
      3. Lump at the rectum
      4. History of constipation
      5. Rectal bleeding
      6. Pain: May be caused by fissure, thrombosis, ulceration or infection
   B. Physical examination
      1. Inspect the rectum for external hemorrhoids or prolapsed internal hemorrhoids with the patient at rest and while straining. Hemorrhoids are usually painless, red or purplish, and protruding from the anus
      2. Examine for fissures, dermatitis, fungal infection and herpes. May use Q-tip to gently separate the edges of the anus to look for fissures
      3. Digital rectal examination (DRE): Detects only thrombosed internal hemorrhoids, but may detect anal cancer/masses which may be confused with hemorrhoids

IV. EVALUATION
   A. **Anoscopy**: May be performed routinely or if diagnosis is in question
      1. Gently insert a lubricated anoscope
      2. Ask the patient to “bear down” (not too forcefully)
      3. Slowly withdraw the anoscope
      4. Watch for internal hemorrhoids to bulge into the anorectal lumen
   B. **Rectal bleeding**: Consider evaluation with colonoscopy or flexible sigmoidoscopy and air contrast barium enema to exclude other sources of GI bleeding including colon cancer, neoplastic polyps, AV malformation, and inflammatory bowel disease

V. MANAGEMENT
   A. **Initial management**: For first to third degree hemorrhoids. If these conservative measures are unsuccessful, then consider definitive management
      1. Lifestyle changes to avoid constipation (see Chapter 67, Constipation in Adults)
         a. Defecation: Patients should not suppress the urge to defecate and should not strain while defecating
b. Diet: Modify diet to increase intake of fiber, fluids, and fruit juices. Decrease fats and meats

c. Exercise: Increase aerobic exercise

2. Sitz bath: Sitting in a warm or cool tub for 20 minutes BID–TID in the acute phase

3. Anusol-HC cream or suppositories (Hydrocortisone Acetate): 1 PR BID × 2 weeks.

For severe cases, may increase to TID

B. Definitive management: Patients with acute thrombosis and prolapse of internal hemorrhoids may require hospitalization and treatment with bed rest, analgesics, stool softeners and often hemorrhoidectomy. Definitive therapy is indicated for fourth degree hemorrhoids and first to third degree hemorrhoids which are not amenable to the above measures

1. Sclerotherapy: For first degree and small second degree bleeding internal hemorrhoids. A sclerosing agent (e.g., quinine urea hydrochloride or phenol) is injected into the superior aspect of the hemorrhoid above the pectinate line. Injection may need to be repeated in several months

2. Ligation: Best suited for third and fourth degrees internal hemorrhoids. Should not be used for external hemorrhoids or internal hemorrhoids complicated by abscess, thrombosis, cryptitis or anal fissure. Cure rates about 80–90%. The hemorrhoid is strangulated by placing a rubber band at the base. Complications include pain (6%), bleeding (3%), and perianal hematoma (3%). May require 2–3 separate ligations. Fatal septicemia has been reported after ligation and may present with triad of perianal pain, fever and urinary hesitancy

3. Excision and evacuation: Indicated for large painful thrombosed external hemorrhoids (small thrombosed external hemorrhoids may respond to conservative management)

   a. Patient is placed in fetal position or on knees with buttocks taped open (the tape pulls one buttock laterally and then goes around abdomen and then placed so that it pulls the other buttock laterally)

   b. Hemorrhoid is anesthetized with 1% Lidocaine with Epinephrine. Use Lidocaine around the edges of hemorrhoid

   c. An elliptical incision is made over lateral edges of hemorrhoid. Hemorrhoid and clot are removed

   d. Sutures are not necessary. Wound is left open to heal by secondary intention

CLINICAL PEARLS

- Simple incision has higher recurrence rate compared to using an elliptical incision to completely excise clotted hemorrhoid
- About ½ of Americans over 50 will seek medical advice for hemorrhoids
- Most common cause of painless rectal bleeding is internal hemorrhoids
- Hemorrhoids are unusual in children and should be viewed with eye toward other disease
- Rectal pruritus may be initial complaint with hemorrhoids, but consider other causes such as fissures, dermatitis (contact or seborrheic), psoriasis, pinworm, Candida, herpes, neurodermatitis, and squamous cell cancer

References

69. Anemia

I. GENERAL: Hemoglobin < 12g/dL in women and < 13g/dL in men (WHO criteria). Classically divided into microcytic (MCV < 83 mcm³), normocytic (MCV 83–100 mcm³), or macrocytic (MCV > 100 mcm³)

II. PHYSIOLOGY OF NORMAL IRON METABOLISM
A. Iron is required for hemoglobin and DNA synthesis. Daily dietary intake of iron in US is approximately 10–20mg/day
B. Most iron absorption takes place in the small intestine
C. Mucosal iron is stored as ferritin and the mucosal transport protein is transferrin
D. Iron storage (as ferritin) is primarily found in the bone marrow, spleen, liver, and skeletal muscle

III. HISTORY
A. Many patients are asymptomatic. May have fatigue, weakness, lightheadedness, headache, irritability, palpitations, paresthesias, gait disturbances, sore tongue, brittle nails, or PICA (desire to eat dirt, ice, paint). Inquire about rectal bleeding, weight loss
B. Alcohol use
C. Meds: Zidovudine (AZT), Dilantin, Phenytoin, OCPs, Sulfa, Trimethoprim, Colchicine, Neomycin
D. Medical history including history of malabsorption syndromes or inflammatory bowel disease
E. Surgeries—partial or total gastrectomy predisposes patient to B₁₂ deficiency—pernicious anemia
F. Chemical or radiation exposure (myelodysplasia)
G. Diet: Strict vegetarians are susceptible to developing B₁₂ deficiency; patients with a high carbohydrate diet (and nothing else) are susceptible to folate deficiency

IV. PHYSICAL: Physical exam may be normal or may include murmur, CHF, papillary atrophy of the tongue, retinal hemorrhages, glossitis, brittle nails, gait disturbance (B₁₂ deficiency) or splenomegaly/ascites/jaundice (liver disease), signs of chronic alcohol abuse

V. EVALUATION: May be considerable overlap, but the evaluation is generally initiated by first determining if it is microcytic (MCV < 80 mcm³), macrocytic (MCV > 100 mcm³), or normocytic (MCV 80–100 mcm³)
A. Microcytic anemia
   1. Differential diagnosis
      a. Iron deficiency anemia (the most common cause of microcytosis)
      b. (Anemia of) chronic disease
      c. Thalassemia
      d. Sideroblastic anemia
      e. Lead toxicity
   2. Labs
      a. Serum iron, total iron binding capacity (TIBC), ferritin
      b. WBC (low count suggests marrow production problem and high count could suggest infection or leukemia)
      c. Peripheral smear: Burr cells (chronic renal failure), spherocytes (hemolytic diseases), dysplastic changes, basophilic stippling (thallasemia, iron deficiency, lead poisoning), Howell-Jolly bodies (asplenia, pernicious anemia, severe iron deficiency)
      d. Reticulocyte count: If < 1% this suggests inadequate production. If > 1%, then calculate the reticulocyte index (% reticulocytes x patient’s hematocrit/normal hematocrit). Reticulocyte index should be > 2 with the presence of anemia
### Anemia

#### Management of Common Ambulatory Conditions

<table>
<thead>
<tr>
<th>ETIOLOGY</th>
<th>SERUM Fe</th>
<th>TIBC</th>
<th>FERRITIN</th>
<th>BONE MARROW Fe STORES</th>
<th>HgbA 2 AND F (FETAL)</th>
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<tbody>
<tr>
<td>Iron Deficiency</td>
<td>Decreased</td>
<td>Increased</td>
<td>Decreased</td>
<td>NONE</td>
<td>Normal</td>
</tr>
<tr>
<td>Chronic Disease</td>
<td>Decreased</td>
<td>Normal or Decreased</td>
<td>Normal or Increased</td>
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<td>Normal</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or Increased</td>
<td>Normal</td>
<td>Increased in b-thal; Normal in a-thal</td>
</tr>
<tr>
<td>sideroblastic anemia</td>
<td>Normal or Increased</td>
<td>Normal or Increased</td>
<td>Normal or Increased</td>
<td>Increased</td>
<td>Normal</td>
</tr>
</tbody>
</table>

3. Etiology of iron deficiency anemia
   a. Blood loss: Gastrointestinal (ulcer, malignancy), menstruation, blood donation
   b. Decreased ingestion or increased requirements (pregnancy, lactation)
   c. Decreased absorption: Malabsorption syndromes, partial gastrectomy
   d. Pulmonary hemosiderosis, polycythemia

4. Management of iron deficiency anemia
   a. Determine etiology and direct initial therapy toward correction
   b. Evaluation of the GI tract in adults (see below)
   c. Adults: FeSO₄ 325mg PO BID-TID; children: 3–6mg elemental Fe/kg/day PO divided TID (e.g., Fer-in-sol). Side Effects: Cramping, nausea, constipation and/or diarrhea

5. Evaluating the gastrointestinal tract in iron deficiency anemia
   a. Idiopathic iron deficiency anemia in adults is commonly from blood loss in GI tract—obtain fecal occult blood test
   b. History and physical directed toward potential areas of blood loss
   c. Endoscopic evaluation (EGD or colonoscopy) depending on patient’s symptoms
   d. For asymptomatic adults, perform colonoscopy first

B. Macrocytic anemia

1. Differential diagnosis
   a. Alcohol abuse
   b. B₁₂ or folate deficiency
   c. Hemolysis or bleeding
   d. Liver disease
   e. Hypothyroidism
   f. Myelodysplasia
   g. Chemotherapeutic agents or other drugs

2. Labs (as indicated)
   a. WBC and peripheral smear—target cells (liver disease), hyposegmented cells (myelodysplasia), hypersegmented cells (B₁₂ or folate deficiency)
   b. B₁₂ and folate (RBC folate is more reliable)
   c. Reticulocytes
   d. TSH and free T₄
   e. LFTs
   f. Consider bone marrow aspirate

3. Management: Directed toward underlying disorder
   a. Causes of B₁₂ deficiency include decreased intake (strict vegan), decreased absorption (pernicious anemia, gastrectomy, gastric atrophy, Crohn’s disease, ileal resection, celiac disease, tropical sprue, chronic pancreatitis, bacterial overgrowth) and decreased utilization (nitrous oxide inhalation, inborn errors of metabolism)
   b. Treatment of B₁₂ deficiency includes oral therapy with Vitamin B₁₂ 1,000–2,000 micrograms PO QD (equivalent to parenteral therapy) or 1,000mcg IM once per week × 8 wk then 1,000mcg IM once monthly
   c. Causes of folate deficiency include decreased intake, decreased absorption (tropical
sprue, celiac disease, short gut syndrome), meds (Dilantin, Phenobarbital, alcohol, OCs, Trimethoprim, Sulfac), increased demands (pregnancy, infancy, hemolytic anemia)

d. Treatment of folate deficiency—**Folate** 1mg PO QD. Note: Ensure that concomitant B₁₂ deficiency does not exist since neurologic symptoms of B₁₂ deficiency may worsen if treated only with folic acid

C. Normocytic anemia

1. Differential diagnosis
   a. Early iron deficiency anemia
   b. Anemia of chronic disease
   c. Chronic renal insufficiency
   d. Endocrine disorders: Thyroid disease, hyperparathyroidism, adrenal insufficiency
   e. Bone marrow failure: Radiation, drugs (chemotherapy), viruses (HIV, Hepatitis B)
   f. Bone marrow replacement: Metastatic cancer, myelofibrosis, leukemia

2. Normocytic anemia may be present due to some of the etiologies which have caused microcytic and macrocytic anemia

3. Labs (as indicated)
   a. WBC and peripheral smear
   b. B₁₂ and folate (RBC folate is more reliable)
   c. Reticulocytes
   d. TSH and free T₄
   e. LFTs
   f. Consider bone marrow aspirate

**CLINICAL PEARLS**

- Most common causes of anemia in the elderly are anemia of chronic disease and iron deficiency anemia
- Neurologic symptoms in patients with B₁₂ deficiency may precede the onset of anemia
- Patients with B₁₂ deficiency may have normocytic or microcytic anemia
- Full term newborns have a 6 month supply of iron, therefore iron deficiency is rarely a cause of anemia in children < 6 months
- G6PD deficiency is present in 13% of black males and 2% of black females
- AAP recommends using iron fortified infant formulas and not to drink whole cow’s milk during child’s first year (may cause occult GI bleeding)

**References**


70. OCULAR DISORDERS & SCREENING

I. INDICATIONS FOR REFERRAL TO OPHTHALMOLOGIST
A. Immediate referral
1. Penetrating trauma: History of missile type injury, high velocity, metal on metal, irregular pupil
2. Acute glaucoma: Red and painful eye, pupil semi-dilated and fixed, hazy cornea decreased vision. May have nausea and abdominal pain
3. Corneal ulcer: Red and painful eye, photophobia, fluorescein staining on cornea. Usually associated with trauma, poor lid apposition, or contact lens wear
4. Postoperative infection/endophthalmitis: Pain, decreased vision, white cell level in anterior chamber, purulent drainage. Can result from any invasive ophthalmologic procedure
5. Iritis: Limbal flush, photophobia, small pupil, sore eye. Usually post-traumatic
6. Floaters or flashes: Differential includes retinal detachment or hole, posterior vitreous detachment
7. Sudden decreased vision: Occlusion of the retinal vein or artery, trauma, or stroke
8. Orbital cellulitis: Fever, pain or restriction of eye movements, endophthalmitis, periorbital swelling
9. Chemical exposure with alkali
B. Referral within several days: Poor healing of corneal abrasion, unresponsive conjunctivitis, double vision or any visual problem that does not improve with treatment

II. HISTORY
A. Onset and duration of symptoms (sudden, gradual), and associated symptoms including pain, redness, itching, burning, crusting/matting
B. Change in vision: Floaters, halos, scotoma (zigzags), photopsia (flashing lights), specific visual field defects
C. Photophobia
D. Pain, with or without eye movement
E. Diplopia (double vision)
F. Systemic symptoms of CVA/TIA, nausea, vomiting, abdominal pain (from the severe pain), fever, temporal pain
G. Contact lens wear
H. Night blindness or vision decrease (combined with myopia, cataracts, retinitis pigmentosa)
I. Recent eye surgery or trauma (if so, was the patient wearing safety glasses)

III. PHYSICAL EXAMINATION
A. Check visual acuity of each eye with correction. If corrective lenses not available, use pinhole (patient reads visual acuity chart through a pinhole which should compensate for any uncorrected refractive errors)
B. Check pupils
1. Size: Anisocoria (unequal pupils) may be acute or chronic (secondary to old trauma, surgery or a normal variant)
2. Reactivity: Sluggish versus rapidly reactive
3. Swinging flashlight test: Checks consensual response in opposite pupil (evaluation for optic nerve damage, i.e., glaucoma, retrobulbar neuritis)
C. Inspect lids for lid eversion (ectropion), lid inversion (entropion), lash growth toward the cornea (trichiasis), chalazion (see below). Also check for lash loss (hypothyroid) or crusting. May need to evert lid to check for foreign body, signs of blepharitis
D. Extraocular muscle function: Motility and position
1. Cranial nerve III: Innervates medial, inferior, and superior rectus and inferior oblique as well as levator muscle of lid
2. Cranial nerve IV: Innervates superior oblique
3. Cranial nerve VI: Innervates lateral rectus
4. Strabismus: Misalignment of the eyes

E. Fluorescein staining: Will stain areas of denuded or damaged epithelium (corneal abrasion, ulceration, etc.)
F. Tonometry: Average intra-ocular pressure is < 21 mmHg

G. Funduscopic Exam
1. Dilation: Eyes may be dilated if anterior chamber is not shallow (observed by shining light beam across the anterior chamber). Dilate with Neo-Synephrine 2.5% or 1% Mydriacyl (avoid Atropine due to long duration of action). Dilation causing an attack of acute angle closure glaucoma is extremely uncommon
2. Exam
   a. Red reflex: If unequal, consider cataract, vitreous hemorrhage, tumor
   b. Hemorrhages (e.g., diabetes, hypertension, trauma or renal disease)
   c. Retinal detachment
   d. Cotton wool spots: Infarctions of nerve fibers
   e. Cherry red spot in macula: Central retinal artery occlusion
   f. Papilledema, A-V nicking, cup/disc ratio (average is 0.3)

H. Confrontation visual field: To detect peripheral vision defects

I. Slit lamp exam: To examine anterior segment of eye, remove foreign bodies, and check for inflammatory cells in anterior chamber:
   Hyphema: Blood in anterior chamber
   Hypopyon: Layered white cells in anterior chamber (seen in iritis or infection)
   Flare: Light scatter caused by inflammatory cells or proteins in the aqueous fluid

IV. MANAGEMENT

A. Conjunctivitis
1. Bacterial: Purulent drainage, red eye, minimal pain, no change in vision. Use 1 drop to affected eye Q 2hrs while awake × 2 days, then QID × 3–5 days. Many choices including:
   a. Aminoglycosides such as Tobramycin or Bacitracin
   b. Quinolone such as Ofloxacin (Ocuflax) or Ciprofloxacin (Ciloxan) for more severe infections
   c. Neosporin containing drops (Neomycin, Polymyxin B, and Gramicidin) may cause allergic reactions
   d. Encourage hand washing
2. Viral: No treatment necessary except infection control
3. Allergic: Itchy, red eyes. Bilateral. Many options, including:
   a. Antihistamine/decongestant: Vasocon-A
   b. Mast cell stabilizer: Crolom Solution 4%, (Cromolyn Sodium) 1 GTT QID, Beopotastine 1.5% (Beprepe) 1 GTT BID, Alomide (Lodoxamide 0.1%) 1–2 GTTS QID, Aloril (Nedocromil 2%) 1–2 GTTS BID
   c. Histamine antagonist: Levocabastine (Livostin 0.05%) 1 GTT QID
   d. Anti-histamine/Mast-cell stabilizer: Emedastine (Emadine) 1–2 GTTS BID
   e. Antihistamine/Mast-cell stabilizer/Eosinophil inhibitor: Zaditor (Ketotifen 0.025%) 1 GTT Q8–12hr
   f. NSAID: Ketorolac 0.5 (Acular), 1 GTT QID
   g. Steroid eye drops, not for extended use
   h. Systemic antihistamines: See Chapter 71, Allergic Rhinitis/Seasonal Allergies

B. Corneal abrasion: History of mild trauma (e.g., fingernail scratch, tree branch, contact lens), photophobia, conjunctival injection, involuntary lid closure, increased tearing, decreased vision if abrasion is located at center of cornea. Distinguish from corneal foreign body, herpes simplex (dendritic appearance to corneal stain), or corneal ulcer (infiltrate around corneal defect)
1. Use slit lamp to facilitate exam. If no slit lamp available, magnification of ophthalmo-scope may be used for direct observation or by localizing the abrasion or foreign body against red reflex
2. Topical anesthetic (to relieve discomfort and facilitate examination): 1 drop of Tetracaine 0.5% or Proparacaine (Alcaine 0.5%) will lead to immediate relief of pain. Do not send anesthetic drops home with patient
3. Prophylactic eye drops (ATBs) may be prescribed. If severe discomfort, may also give Cycloplegic such as Cyclogyl 1% (Cyclopentolate) or Homatropine 2% or 5% TID which will make patient more comfortable
4. Patient should follow-up in 1–2 days if not healed

C. Corneal foreign body
1. Topical anesthetic as used in corneal abrasion (see IV. B. above.)
2. Remove corneal foreign body with blunt instrument, cotton swab, or forceps
3. Patient may return to normal activities immediately. No need to patch eye
4. If a rust ring remains or foreign body cannot be removed, then refer

D. Conjunctival foreign body
1. No anesthetic necessary
2. Evert upper eyelid and remove foreign body with cotton swab
3. May see linear, vertical corneal abrasions (ice-skate track abrasions) indicating retained foreign bodies in the superior tarsal conjunctiva

E. Blepharitis: History of burning, excessive tearing (epiphora), foreign body sensation with erythema of lid margin, dandruff-like deposits on lashes, fibrinous scales around individual lashes (collarettes), lash loss, recurrent mild conjunctivitis. Caused by seborrhea, staph infection, and/or meibomian gland dysfunction and frequently recurs
1. Antibacterial eye drops, treat 7–10 days (chronic cases may require intermittent ATB/steroid drops)
2. Wash lids every day with baby shampoo (eyes closed)
3. Warm compresses to eye TID
4. Wash hands after touching eyes

F. Sudden onset double vision: Distinguish monocular from binocular double vision; binocular will resolve when either eye is covered. Monocular is secondary to uncorrected refractive error, dry eye, corneal scar, or cataract. Binocular diplopia may be secondary to nerve palsies (III, IV, or VI), decompenated strabismus, diabetes, cerebral aneurysm, tumor, myasthenia gravis, thyroid eye disease, orbital blow-out fractures
1. Patch either eye for symptomatic relief while awaiting definitive diagnosis
2. Evaluate for above mentioned entities and refer to ophthalmologist

G. Chalazion: Firm well-demarcated nodule just below lid margin; may have grayish discoloration on conjunctival surface which is secondary to a lipogranulomatous inflammation of meibomian gland
1. May be symptom-free, or nodule may be tender and erythematous
2. Treatment includes frequent warm compresses and ATB drops initially. After 1 month ophthalmologist may inject, lance, or excise the chalazion

H. Stye (hordeolum): Painful, erythematous, often pointed nodule on surface of skin (external stye) or on conjunctival surface (internal stye) which is usually caused by a staph infection of a sebaceous gland of the lid. Treatment includes warm compresses and topical ATB drops

I. Open-angle glaucoma
1. Refers to a group of diseases with progressive optic nerve damage and visual field loss, usually with associated elevations in intraocular pressure. Prevalence 0.5% of the population. More severe in African-Americans. Increased incidence with positive family history
2. Average intraocular pressure is < 21mmHg
3. Damage from glaucoma is manifested by optic nerve “cupping” (caused by loss of neurons and glial tissue). Cup-to-disc ≥ 0.6 or greater is one sign of glaucoma
4. Visual field loss over time (usually spares the central visual field until late)

J. Angle-closure glaucoma: Women > men, may have acute severe eye pain and blurry vision, with associated nausea, vomiting, diaphoresis, abdominal pain. May see halos around lights. Requires immediate medical therapy followed by laser iridectomy

V. PRIMARY/PREVENTIVE OPHTHALMOLOGY SCHEDULE

A. Neonates
1. Ophthalmologic screen for retinopathy of prematurity if birth weight <1500g, <33 weeks gestation, or received O2 therapy for > 48hrs at birth
2. In all other neonates, red reflexes should be checked at birth and every visit thereafter
to screen for congenital cataracts, retinoblastoma, congenital glaucoma. Cataracts should be treated before the age of 3 months to prevent amblyopia. In more darkly pigmented individuals, the red reflex may look dull orange or whitish orange—make sure this is symmetric and uniform across entire reflex.

B. Preschool
1. Screen for strabismus (exotropia and esotropia) with cover-uncover test and pupillary light reflex test (normally both light reflexes should be centered in each pupil). Begin screening at birth—prior to 4 months of age infants may show variable crossing or drifting out of the eyes due to underdevelopment of the macula. If strabismus not picked up early, it may lead to amblyopia (decreased vision in 1 eye). Refer for ophthalmologic evaluation
2. Vision screening is feasible at around age 3½ yrs; will initially use the Allen test (pictures) until child is able to read numbers or letters

C. School-aged children: Should have vision screen at least every 2–3yrs if asymptomatic

D. Adults
1. Routine “glaucoma” exam (Funduscopic exam and IOP) at 35 then every 2yrs (yearly if family history of glaucoma)
2. Funduscopic exam at least yearly in patients at increased risk—diabetes mellitus, family history of retinal detachments, or glaucoma corticosteroid therapy, Plaquenil, Mellaril, Ethambutol (visual acuity)
3. Age > 65; full eye exam every 1–2yrs regardless of risk factors
4. African-American (Recommendation of the Comprehensive Adult Eye Evaluation)—Comprehensive eye evaluation by an ophthalmologist:
   a. 20–39: Every 3–5yrs
   b. 40–64: Every 2–4yrs
   c. 65 or older: Every 1–2yrs

E. Diabetes: Examine type 1 diabetics within 3–5yrs of diagnosis and type 2 diabetics shortly after diagnosis. Subsequent exams annually

VI. SPECIFIC PEDIATRIC OPHTHALMOLOGIC DISORDERS
A. Conjunctivitis
1. In neonates, may be toxic conjunctivitis from routine perinatal prophylaxis
2. Infectious conjunctivitis may be caused by staph, chlamydia, herpes virus, gonorrhea. If discharge is purulent and excessive, gonorrhea is probable; blindness can result in 24–48hrs, should be immediately referred

B. Nasolacrimal duct obstruction (congenital)
1. Obstruction is common. It is usually unilateral which is often congenital due to lack of patency of the inferior ostium of the nasolacrimal duct. The tear lake is elevated, and the eye appears weepy
2. May get bacterial superinfection: Eyelids will be adherent with purulent matter on awakening. Lids are red with tearing of the eye. Infections will recur in spite of topical ATBs, unless duct opens or is opened up with massage and/or probing
3. Approximately 75% spontaneously open within first 6 months of life. Should be referred for duct probing after 6 months if no resolution. If persistent purulent drainage, then refer earlier
4. Can put pressure on nasolacrimal sac with a cotton swab or finger; if expression of mucopurulent material is seen from the puncta, then nasolacrimal duct obstruction is the diagnosis
5. Parent should massage over the duct 3–4 ×/day; this will relieve most obstructions

C. Strabismus (see V. Primary/Preventive schedule, above)
1. Inward, outward, or upward deviation of 1 or both eyes; pupils are misaligned
2. Any patient with constant deviation, or deviation that develops after the first 3–4 months of life, should be referred to ophthalmologist
3. Therapy usually involves patching of good eye and/or corrective lenses (after evaluation to rule-out tumor, cataract, etc.)
4. Ideally, eyes should be straightened before age 2 to increase chance of stereopsis (normal depth perception)
Vertically oriented, linear corneal abrasions may indicate a conjunctival foreign body under the upper lid. Evert the upper lid with a cotton swab.

Never send anesthetic eye drops home with patients with corneal abrasions; they delay healing by preventing re-epithelialization of the cornea, and may damage the cornea, resulting in blindness.

Always check vision before examination and treatment.

Be alert for herpes simplex; dendritic appearance under fluorescein staining.

*Neomycin* can cause allergic reaction in up to 10% of patients.

**References**


**Allergic Rhinitis**

I. **Overview**

A. Allergic rhinitis is an immunologically mediated disease. It is initiated by a type I antigen-antibody reaction. Inhaled allergens interact with T and B cell lymphocytes to produce IgE antibodies which then attach to mast cells and basophils resulting in the release of histamine and chemotactic factors and allergic rhinitis symptoms.

B. Allergic rhinitis is one of the most common primary care problems and affects 10–30% of adults and up to 40% of children. Annual estimates of direct medical costs of treating allergic rhinitis is up to $4.5 billion.

C. Guidelines from the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology defines rhinitis as “inflammation of the membranes lining the nose, and is characterized by nasal congestion, rhinorrhea, sneezing, itching of the nose and/or postnasal drainage.” Rhinitis is characterized by 1 or more of the following symptoms: nasal congestion, rhinorrhea, sneezing and itching.

D. Allergic rhinitis is associated with headaches, fatigue, poor concentration, loss of sleep, fatigue, adverse effects of medical therapies and possible development of other medical conditions such as asthma, sinusitis or otitis media.

E. Rhinitis may be caused by allergic, non-allergic, infectious, hormonal, occupational or other factors.

II. **History**

A. Seasonal prevalence

B. Paroxysmal sneezing, rhinitis, dry, watery or pruritic eyes, pharyngeal itch, cough

C. Triggering exposures

D. Anosmia (decreased sense of smell)
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E. Age at onset  
F. Med use (inquire specifically about intranasal decongestants, also see list below; VI. B.)  
G. History of atopy  
H. Family history of allergies, asthma, atopic dermatitis, and mucociliary dysfunction disorders, inflammatory/autoimmune conditions  
I. Surgical history of previous ENT operations  
J. Social history should assess for exposures to tobacco or smog

III. PHYSICAL EXAM (intranasal examination should be performed using a speculum)  
A. Rhinorrhea and/or nasal congestion  
B. Pale, boggy, blue-gray, edematous nasal turbinates which may be coated with clear secretions  
C. Nasal crease (“allergic salute”)  
D. Infraorbital venous dilation (dark circles under eyes/allergic shiner)  
E. Mouth breathing; dry lips indicating mouth breathing as a result of impaired nasal airflow  
F. Skin folds under eyes (Denies lines)  
G. Cobblestoning of posterior pharynx  
H. Scleral/conjunctival injection and/or edema

IV. LABS/TESTING  
A. Percutaneous testing (prick testing): Small amount of antigen is pricked into the skin; can easily be done in office if supply of antigens is available. Preferred for initial testing because more rapid, less painful, less expensive, and less likely to cause systemic reactions  
B. Intradermal testing: Antigen is injected into the dermis. Greater reproducibility and greater sensitivity than prick testing. Higher false positive rate than prick testing  
C. RAST (radioallergosorbent testing): Blood is analyzed for specific anti-IgE antibodies to known antigens; useful for patients with extensive eczema, dermatographism or prior anaphylaxis, young, or cannot discontinue antihistamines  
D. Nasal smears: Eosinophilia can be supportive but is not diagnostic

V. DIFFERENTIAL DIAGNOSIS: May mimic symptoms of allergic rhinitis  
A. Vasomotor rhinitis: Related to autonomic dysfunction and more common in women  
B. Infectious rhinitis: Viral (up to 98% of acute rhinitis, especially in children), bacterial  
C. Rhinitis medicamentosa: Tachyphylaxis after use of nasal decongestant or cocaine. Nasal mucosa bright red and swollen  
D. Eosinophilia syndrome: Nasal eosinophils in patients who have perennial symptoms and occasionally loss of sense of smell  
E. Hormonal rhinitis: Menstrual, pregnancy (usually second trimester to term, resolving after delivery) and hypothyroidism  
F. Drug-induced rhinitis: ACEi, PDE-5i, Aspirin, Clonidine, Hydralazine, Labetalol, Propranolol, Methylpapa, Prazosin, Terazosin, Reserpine, NSAIDS, oral contraceptives  
G. Gustatory rhinitis: Occupational: grain, dusts, irritants, chemicals; can be allergic/mixed  
H. Anatomic: Nasal polyps (often unilateral and associated with asthma and aspirin sensitivity), septal deviation, tumors, hypertrophy of adenoids or nasal turbinates  
I. Ciliary dysfunction: Primary (Kartagener's syndrome, cystic fibrosis) secondary (viral)  
J. Atrophic: caused by continuous nasal hygiene, lavage, and debridement  
K. Other: Alcoholism, cocaine abuse, nasal septal deviation, tumors, adenoidal hypertrophy, hypertrophy of the nasal turbinates

VI. MANAGEMENT  
A. Environmental controls  
   1. Indoor: Avoid active and passive tobacco smoke, remove bedroom carpet, foam pillows, enclose mattress and box springs in plastic, use air conditioning  
   2. Dust mites: Control bedroom: wash bedding weekly, impermeable covers on pillows and mattresses, keep humidity below 50%, HEPA (high density particulate air) filter  
   3. Molds: Remove any visible mold/mildew, treat with a retardant, frost-free refrigerator, keep firewood outside, avoid house-plants, clean heating and cooling systems,
remove old books
4. Animals: Avoid furry animals and birds or eliminate carpeting and keep floors polished and upholstery frequently cleaned. HEPA vacuum. Animals should stay out of the bedroom

B. Pharmacotherapy
1. Local meds: Often helpful in conjunction with oral antihistamines
   a. Steroid nasal inhalers: First line treatment. Intranasal steroids onset of effect is within 24 hours, but maximal effect is not for a few weeks. Ciclesonide and Fluticasone Furoate have less than 1% systemic bioavailability and are less likely to have systemic effects than older intranasal steroids
      i. Beclomethasone Dipropionate (Beconase AQ): 1–2 sprays in each nostril BID to QID. May decrease to QD once therapeutic
      ii. Fluticasone Propionate (Flonase): 2 sprays in each nostril QD or 1 spray in each BID
      iii. Triamcinolone (Nasacort AQ): 2 sprays each nostril QD
      iv. Flunisolide (Nasalide, Nasarel): 2 sprays each nostril BID
      v. Budesonide (Rhinocort Aqua): 2 sprays each nostril QD
      vi. Mometasone Furoate (Nasonex): 2 sprays each nostril QD
      vii. Ciclesonide: Omnaris—2 sprays each nostril QD. Zetonna—1 actuation per nostril QD
   b. Intranasal anticholinergic: Ipratropium (Atrovent Intranasal 0.03%, 0.06%): useful in treatment of anterior watery rhinorrhea. Dose 2 sprays per nostril 3–4 times daily
   c. Intranasal antihistamine—Azelastine (Astelin), Olopatadine (Patanase): 2 sprays each nostril BID
   d. Mast cell stabilizers—Cromolyn Sodium (NasalCrom): 1 spray each nostril 3–6 ×/day
   e. Saline nasal spray—Safe, inexpensive, helps thin mucous, use 3–6 ×/day, e.g., Saline X, Ocean Nasal Mist, NaSal
   f. Nasal vasoconstrictors—Should not use more than 3–4 days secondary to rebound vasodilatation and worsening of symptoms (Rhinitis medicamentosa). May be helpful in acute sinusitis or for airplane flights
      i. Neo-Synephrine (Phenylephrine): 0.25, 0.5 or 1.0%: 2–3 sprays in each nostril PRN
      ii. Oxymetazoline (Afrin): 2–3 sprays each nostril BID; do not use for more than 3 days
2. Non-sedating antihistamines: the most commonly used and preferred antihistamines
   a. Fexofenadine (Allegra)
      i. 60mg PO BID or 180mg QD
      ii. Approved for children 6 months to <2 years: 15mg PO BID; children 2–11 years: 30mg PO BID; children >12 years: refer to adult dosing
      iii. Onset of action: 60 minutes
      iv. Also available as Allegra-D 12 hour (60mg Fexofenadine and 120mg Pseudoephedrine) PO BID and Allegra-D 24 hour (180mg Fexofenadine and 240mg Pseudoephedrine) 1 PO QD
   b. Cetirizine (Zyrtec): Available OTC; children 6–12 months: 2.5mg PO daily; children 12 months to 2 years: 2.5mg PO daily, can increase to 2.5mg PO BID; children >6 years: refer to adult dosing
      i. Dose: 5–10mg PO QD (slightly sedating in some patients)
      ii. Approved for children 2–5yrs, 2.5mg QD with increases to 5mg QD (available 5mg/5cc). Dose for children 6–11yrs is 5–10mg QD
      iii. Onset of action: 15–30 minutes
   c. Loratadine (Clarinit)
      i. Dose: 10mg PO QD
      ii. Approved for children 2–5 years: 5mg QD, >6yrs, 10mg QD (available 5mg/5cc)
      iii. Onset of action: 1–3hrs
      iv. Also available as Claritin D 12hr (5mg Loratadine/120mg Pseudoephedrine)
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BID and Claritin D 24hr (10mg Loratadine/240mg Pseudoephedrine) QD
d. Desloratadine (Clarinex)
i. Dose: 5mg PO QD
ii. Approved for children 6–11yrs: 2.5mg QD; 12mo–5yrs 1.25mg QD; 6–11mo: 1mg QD
iii. Also available in 2.5mg/5mL syrup
c. Levocetirizine (Xyzal)
i. Dose 5 mg PO QHS
ii. Children 2–5 years: 1.25mg PO QHS; 6-11 years: 2.5 mg PO QHS; over age 12 years: refer to adult dosing.
iii. Onset of action 1 hour

3. Sedating antihistamines: Caution in patients with BPH and in the elderly secondary to urinary retention and risk of glaucoma. The FDA panel recommends OTC cold medicines should not be used in children <2 years of age because of risks of potentially life threatening side effects
a. Diphenhydramine (Benadryl, Banophen, Diphenhist)
i. Adults: 25–50mg PO TID–QID
ii. Children children 2 to <6 years: 6.25mg every 4 hrs, maximum 37.5mg/day; children 6 to <12 years: 12.5mg every 4 hrs, maximum 75mg/day, and children >12 years: 25mg every 4 hrs, maximum 150mg/day
b. Chlorpheniramine (Chlor-Trimeton, Allerchlor)
i. Adults: 4mg PO TID–QID PRN
ii. Children 6–11yrs: maximum dose 12mg/24 hrs
iii. Children 2–5yrs: maximum doses 6mg/24 hrs
c. Hydroxyzine (Atarax, Vistaril): 25mg PO QID PRN
4. Oral decongestants: Stimulatory CNS effects may offset sedative effects of sedating antihistamines
a. Phenylephrine
b. Pseudoephedrine—e.g., Sudafed (now sold “behind the counter” as part of the fight against illegal drug production)

5. Leukotriene receptor antagonists (LTRA)
a. Montelukast (Singulair) is the only LTRA approved for the treatment of seasonal allergic rhinitis in ≥2 yr and perennial allergic rhinitis in ≥6 mo
Dose: Adults and children ≤15 yr: 10mg QD; 6–14 yr: 5mg QD; ≤5 yr: 4mg QD
b. Inhaled corticosteroids

6. Ophthalmic solutions: Should not be used with soft contact lenses
a. Antihistamines are used for allergic conjunctivitis: Azelastine (Optivar 0.05%), Olopatadine (Patanol 0.1%)—1 GTT OU BID
b. Vasoconstrictor/antihistamine (Naphcon-A, Visine-A): 1 GTT OU Q6h PRN
c. NSAIDs; only Ketorolac 0.05% (Acular) is indicated for seasonal conjunctivitis. Dose 1 GTT QID/7 days

7. Systemic steroids: Rarely necessary, but may be helpful in severe cases of complete nasal obstruction. Short course of Prednisone for 1 week or less

C. Immunotherapy

1. Indications
a. Unable to manage symptoms with environmental modification or meds
b. Patients who require meds for greater than 6 months of the year
c. Intolerable side effects to meds
d. Caution in initiating injection immunotherapy in children < 5 years
2. Perform RAST testing or skin testing to identify the offending allergen
3. Weekly injections are initiated with a small amount of antigen, which is gradually increased. Length of time between injections is also gradually increased to once every 3–4 weeks
4. Often able to discontinue after 3–5 seasons and have persisting benefit for several years after completion of therapy

CLINICAL PEARLS
• It may often be helpful with copious rhinitis to give an oral decongestant (Pseudoephedrine, Phenylephrine) along with an antihistamine and intranasal med
72. ACUTE SINUSITIS

I. GENERAL

A. Definition: Inflammation of the mucosa of 1 or more of the paranasal sinuses. The term rhinosinusitis has been suggested to replace acute sinusitis. Acute bacterial rhinosinusitis is usually a secondary infection resulting from sinus ostia obstruction or impairment of mucus clearance mechanisms caused by an acute viral upper respiratory tract infection.

B. Rhinosinusitis is 1 of the 10 most common diagnoses in ambulatory care and resulted in approximately 25 million US physician office visits in 1995. Most common sinuses involved are the maxillary and ethmoid sinuses.

C. Most cases presenting in the ambulatory setting are caused by viruses and not bacteria.

D. Patients with acute bacterial rhinosinusitis (ABRS) have one of the 3 clinical presentations:
   1. Persistent signs and symptoms, lasting ≥10 days without any clinical improvement
   2. Severe symptoms (fever ≥39°C, purulent nasal discharge or facial pain) lasting ≥3–4 days
   3. Worsening or “double-sickening” (≥3–4 days)

E. Sinus radiography is not recommended.

F. Most cases resolve without antibiotic (ATB) treatment. ATB should be reserved for those with severe symptoms. The most narrow spectrum ATB against *S. pneumoniae* and *H. influenzae* should be used.

II. ETIOLOGY

A. Bacterial pathogens: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, and *S. pyogenes*

B. Viral: Multiple pathogens.
III. PHYSICAL EXAMINATION
A. Purulence in the nares or nasopharynx (not always visible)
B. Irritation of the nasal mucosa: Leads to inflammation with a bright red, irregular appearance
C. Nasal polyps: Prolonged nasal inflammation may lead to polypoid degeneration of nasal mucosa and formation of polyps
D. Facial tenderness to palpation or percussion
   1. Maxillary: Subzygomatic over cheek and upper teeth
   2. Ethmoid: Periorbital
   3. Frontal: Forehead above eyebrow
   4. Sphenoid
      a. Usually retrobulbar, often not well localized
      b. Infection in sphenoid sinus may lead to pain and tenderness over vertex of skull, mastoid bones, and occipital portion of head
E. Periorbital tissue swelling or erythema of skin overlying affected sinus may be seen

IV. CLASSIFICATION
A. Acute: Symptom duration <4 weeks
B. Subacute: Symptom duration 4–12 weeks
C. Recurrent acute: ≥4 episodes per year with complete resolution between episodes; each episode lasts ≥7 days
D. Chronic: Symptom duration >12 weeks

V. DIAGNOSTIC PROCEDURES
A. Radiography
   1. Plain films. No longer recommended due to the poor sensitivity and specificity
   2. Sinus CT Scan
      a. In general, high sensitivity but poor specificity as many patients with viral rhinosinusitis and viral URIs will have positive sinus CTs. However, 1 study found that when characteristic CT findings are combined with a high clinical likelihood, the positive predictive value is about 90%
      b. Not necessary to obtain in an uncomplicated acute sinusitis. Should be performed when diagnosis is in question
B. Rhinoscopy (flexible): Allows a detailed examination of the upper nasal cavities and posterior nasopharynx. Technique is also valuable in identifying polyps in the high nasal vault, and structural abnormalities
C. Transillumination: Technique has been unreliable in diagnosing acute sinusitis

VI. MEDICAL TREATMENT
A. Empiric antibiotic therapy should be initiated as soon as the clinical diagnosis of acute bacterial rhinosinusitis (ABRS) is established
B. When choosing an antibiotic, consider risk for antibiotic resistance, efficacy, and cost
C. Risk for antibiotic resistance:
   1. Age <2 or >65, daycare
   2. Prior antibiotics within the past month
   3. Prior hospitalization past 5 days
   4. Comorbidities
   5. Immunocompromised
D. If no risk for antibiotic resistance, the first-line antibiotic therapy is Amoxicillin-Clavulanate (Augmentin) 500mg/125mg PO TID or 875mg/125mg PO BID. If improvement occurs after 3–5 days, complete 5–7 days of ATB therapy
E. If there is risk for antibiotic resistance, use high-dose Amoxicillin-Clavulanate (Augmentin XR) 2000mg/125mg PO BID. If improvement occurs after 3–5 days, complete 7–10 days of ATB therapy
F. If worsening or no improvement after 3–5 days of ATB therapy, switch to high-dose Amoxicillin-Clavulanate (Augmentin XR) 2000mg/125 mg PO BID or a respiratory Fluoroquinolone (Levofloxacin) 500mg QD or Moxifloxacin 400mg QD
G. Alternative to high-dose Amoxicillin-Clavulanate: Doxycycline 100mg BID or 200mg BID
H. In beta-lactam allergy, use one of the following:
1. Doxycycline 100mg BID or 200mg BID
2. Levoﬂoxacin (Levaquin) 500mg PO QD
3. Moxiﬂoxacin (Avelox) 400mg PO QD

I. Macrolides (Clarithromycin and Azithromycin) are no longer recommended for empiric therapy due to high rates of resistance among S. pneumoniae (~30%)

J. Trimethoprim-Sulfamethoxazole (Bactrim) is not recommended for empiric therapy because of high rates of resistance among both S. pneumoniae and Haemophilus influenzae (~30%-40%)

K. Second- and third-generation oral Cephalosporins are no longer recommended for empiric monotherapy of ABRS due to variable rates of resistance among S. pneumoniae. Combination therapy with a third-generation oral Cephalosporin (Cefixime or Cefpodoxime) plus Clindamycin may be used as second-line therapy for children with non-type I penicillin allergy or from geographic regions with high endemic rates of PNS S. pneumoniae

L. In children:
1. First line: Amoxicillin-Clavulanate 45mg/kg/day PO BID
2. Second-line: Amoxicillin-Clavulanate 90mg/kg/day BID
3. Beta-lactam allergy:
   a. Type I hypersensitivity: Levoﬂoxacin 10–20mg/kg/day PO Q12–24h
   b. Non-type 1 hypersensitivity: Clindamycin 30–40mg/kg/day PO TID plus Cefixime (Suprax) 8mg/kg/day PO BID or Cefpodoxime (Vantin) 10mg/kg/day PO BID
4. Risk for antibiotic resistance or failed initial therapy:
   a. Amoxicillin-Clavulanate 90mg/kg/day BID, or
   b. Clindamycin 30–40mg/kg/day PO TID plus Cefixime (Suprax) 8mg/kg/day PO BID or Cefpodoxime (Vantin) 10mg/kg/day PO BID
   c. Levoﬂoxacin 10–20 mg/kg/day PO Q12–24h

M. Adjunctive therapies:
1. Analgesics: Acetaminophen or a NSAID given alone or in combination with an opioid is appropriate for mild to moderate pain
2. Decongestants: May be used to reduce mucosal edema and facilitate aeration and drainage during acute episodes. The effect of decongestants is limited in the nasal cavity and does not extend to the paranasal sinuses. Topical decongestants should not be used longer than 3 days because of the risk of rebound nasal congestion (rhinitis medicamentosa)
3. Antihistamines should be reserved for patients with known allergies
4. Saline nasal irrigation may be used to soften viscous secretions and improve mucociliary clearance. Use a bulb syringe to irrigate TID-QID PRN
5. Guaifenesin, a mucolytic, is not recommended due to lack of evidence for its effectiveness
6. Intranasal steroids are minimally absorbed and have a low incidence of systemic adverse effects. The data on intranasal corticosteroid monotherapy for acute sinusitis are limited. They may be effective in patients with less severe symptoms at baseline. Current guidelines consider them an option based on individualized decision

N. Failure despite above approaches
1. CT scan to obtain definitive diagnosis—sensitive but not specific. Note: No role or minimal role for plain films
2. ATBs: Consider using a different second line agent for 4–6 weeks in conjunction with nasal steroids and a decongestant
3. Referral to an allergist or ENT

VII. RECURRENT OR CHRONIC SINUSITIS

A. In children the most common cause of recurrent sinusitis is recurrent viral upper respiratory infection

B. Other conditions predisposing patients to chronic sinusitis include allergic inflammation, cystic fibrosis, immunodeficiency disorders (insufficient or dysfunctional immu-
noglobulins), ciliary dyskinesia (immotile cilia syndrome, Kartagener’s syndrome),
nasal polyps, or an anatomical problem
C. Evaluation of children with recurrent or chronic sinusitis may include consulting an
allergist, a sweat test, measurement of immunoglobulins and their subclasses, and pos-
sibly a mucosal biopsy (to assess ciliary function and structure)

VIII. COMPLICATIONS OF ACUTE SINUSITIS (AND TREATMENT)
A. Periorbital cellulitis: Manifested by eye swelling, exophthalmos, and imparted/painful
extraocular movements
B. Intracranial abscess: Manifested by signs of increased intracranial pressure, meningeal
irritation, and focal neurologic deficits
C. Meningitis

IX. INDICATIONS FOR SURGERY OR REFERRAL
A. Patients with chronic or recurrent sinusitis who have failed an extended course of ATBs,
nasal steroids and allergy management
B. Patients with chronic sinusitis and worsening pulmonary disease
C. Patients with severe asthma which is exacerbated by recurrent sinus symptoms

CLINICAL PEARLS
• Before committing a patient to the diagnosis of chronic sinusitis, consider radiologic studies
• 3 most common causes of chronic cough (90–95%) are post-nasal drip (often secondary
to sinusitis), asthma and gastroesophageal reflux disease (GERD)
• Acute rhinosinusitis is often viral in origin. Physicians prescribe an ATB 85–98% of the time
• Pseudomonas may be a pathogen in patients with cystic fibrosis
• Patients with HIV can present with recurrent sinusitis

References
Chow AW, et al. IDSA Clinical practice guideline for acute bacterial rhinosinusitis in children
2007;137:S1–S31.
Hirschmann JV. Antibiotics for common respiratory tract infections in adults. Arch Int Med
2002;162:256.
Hickner JM, et al. Principles of appropriate antibiotic use for acute rhinosinusitis in adults:
Piccirillo JF, et al. Impact of first-line vs second-line antibiotics for the treatment of acute
73. DIFFERENTIAL DIAGNOSIS OF ARTHRITIS

I. EVALUATION WITH HISTORY, PHYSICAL EXAM, AND COMMON CONDITIONS
Differentiate between mono-arthritis (1 joint involvement) and polyarthritis (> 1 joint involved)—see II. Differential Diagnosis and V. Lab Tests for Polyarthritis

A. Mechanical vs. inflammatory
1. Mechanical (Internal derangement, fracture, trauma, or loose body) is suggested by rapid onset of pain (over seconds or minutes), pain that occurs only after use, improves with rest, and involves weight-bearing joints
2. Inflammatory arthritis is suggested by onset from hours to days, intermittent pain unrelated to patterns of use, including fluctuations of pain and swelling, and morning stiffness

B. Exclude infectious arthritis
1. Joint sepsis produces dramatic inflammation followed quickly by irreversible destruction of cartilage and bone. Most develop from hematogenous spread
2. Infection should be suspected with the presence of systemic risk factors such as corticosteroid therapy, immunodeficiency or immunosuppression, diabetes, or intravenous drug abuse and local pathology such as effusions, penetrating trauma, previous injection of corticosteroids, prosthetic joint
3. Patient complains of intense local pain and may resist attempts to examine the affected joint. Infected peripheral joints are swollen, warm, very tender, and sometimes red, and they have markedly restricted range of motion; large joints are more frequently affected than small ones in the absence of local trauma or peripheral vascular disease
4. Gonococcal infection tends to manifest as an inordinately painful monarthritis or polyarthritis and often is preceded by a migratory arthritis
5. Lyme arthritis occurs weeks to months after initial exposure and after the development of the early syndrome of fevers, arthralgias, lymphadenopathy, and rash

C. Crystal induced arthritis
1. Usually a history of recurrent, self-limited attacks of inflammation of the same joint. Clinical features include extremely rapid onset of severe pain and inflammation with extension of the inflammatory process into surrounding tissues, producing appearance of cellulitis
2. Gout is present when urate crystals are identified in synovial fluid or confirmed by documentation of urate crystals in a tophus
3. Pseudogout: Calcium pyrophosphate dihydrate (CPPD) deposition is associated with acute or chronic inflammatory arthritis

D. Other—Non-inflammatory monoarticular arthritis
1. Osteoarthritis frequently manifests as monoarthritis, particularly in the knee, hip, acromioclavicular joint, first radiocarpal joint, or first metatarsophalangeal joint
2. Hip symptoms in a young patient suggest congenital dysplasia of hip or slipped capital femoral epiphysis
3. Osteochondritis dissecans should be suspected in a child or teenager who, after minor trauma, has relatively severe knee pain followed by mechanical dysfunction
4. Osteonecrosis is a common cause of monoarthritis of the hip, shoulders, and knees in young people with systemic diseases who require corticosteroid therapy
5. Hemarthrosis may occur in patients with clotting disorders or on anticoagulant therapy

II. DIFFERENTIAL DIAGNOSIS: MONOARTICULAR VS. POLYARTICULAR ARTHRITIS (common presentations)
A. Monoarticular
1. Septic arthritis: Bacterial, tuberculous, fungal, Lyme disease
2. Crystal disease: Gout, pseudogout
3. Mechanical: Internal derangement, trauma, overuse, loose body, osteochondritis dissecans, stress fracture
4. Ischemic necrosis
5. Hemarthrosis: Coagulopathy, Warfarin (Coumadin)
6. Pauciarticular juvenile: Rheumatoid arthritis
7. Neoplastic: Osteogenic sarcoma, metastatic tumor
8. Other: Congenital hip dysplasia, reflex sympathetic dystrophy, Paget’s disease involving joint, osteomyelitis

B. Polyarticular
1. Rheumatoid arthritis
2. Osteoarthritis
3. Psoriatic arthritis
4. Reiter’s syndrome (idiopathic and human immunodeficiency virus)
5. Calcium pyrophosphate deposition disease
6. Chronic articular hemorrhage
7. Most juvenile rheumatoid arthritis and juvenile spondylitis
8. Erythema nodosum/sarcoid
9. Serum sickness: Acute hepatitis B, rubella
10. Henoch-Shönlein purpura
11. Systemic lupus erythematosus
12. Lyme disease
13. Parvovirus

III. DIAGNOSTIC STUDIES
A. Synovial fluid analysis: To differentiate between inflammatory, non-inflammatory and septic arthritis in patients with monoarthritis. See IV. table below
B. Cultures: Culture synovial fluid if septic arthritis is suspected. If gonococcal arthritis is a consideration, cervicourethral, rectal, and pharyngeal samples should be obtained
C. X-rays: Plain radiographs of the affected joints should be obtained; common findings are soft tissue calcification, osteoarthritis, chondrocalcinosis, loose bodies, fracture, malignancy, osteomyelitis, or Paget’s disease
D. Nuclear Medicine: Useful when it is important to search for a site of infection that cannot be detected or localized, fibrocartilaginous joints in which range of motion is poorly tested, or the spine
E. MRI: Superior to other imaging modalities in the diagnosis of ischemic necrosis of bone; occult fractures, meniscal and cruciate ligament injuries
F. Ultrasound: Useful for aspirating almost any joint
G. Synovial biopsy: May play a role in the diagnosis of chronic, unexplained monoarticular arthritis; tuberculous or fungal synovitis is more frequently identified by staining and culture of open biopsy material than by similar studies of synovial fluid
H. Laboratory tests for polyarthritis—see V. table below

IV. EXAMINATION OF JOINT FLUID

<table>
<thead>
<tr>
<th>Measure</th>
<th>Normal</th>
<th>Group I (Noninflammatory)</th>
<th>Group II (Inflammatory)</th>
<th>Group III (Purulent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (mL) (knee)</td>
<td>&lt; 3.5</td>
<td>Often &gt; 3.5</td>
<td>Often &gt; 3.5</td>
<td>Often &gt; 3.5</td>
</tr>
<tr>
<td>Clarity</td>
<td>Transparent</td>
<td>Transparent to opaque</td>
<td>Opaque</td>
<td></td>
</tr>
<tr>
<td>Color</td>
<td>Clear</td>
<td>Yellow</td>
<td>Yellow to opalescent</td>
<td>Yellow to green</td>
</tr>
<tr>
<td>WBC (per µL)</td>
<td>&lt; 200</td>
<td>200–300</td>
<td>3000–50,000</td>
<td>&gt; 50,000/³</td>
</tr>
<tr>
<td>Polymorphonuclear leukocytes</td>
<td>&lt; 25%</td>
<td>&lt; 25%</td>
<td>50% or more</td>
<td>75% or more/³</td>
</tr>
<tr>
<td>Culture</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Usually positive</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>Nearly equal to serum</td>
<td>Nearly equal to serum</td>
<td>&gt; 25, lower than serum</td>
<td>&lt; 25, much lower than serum</td>
</tr>
</tbody>
</table>

³Counts are lowered with infections caused by organisms of low virulence or if antibiotic therapy has been started.

## V. LABORATORY TESTS FOR POLYARTHRITIS

<table>
<thead>
<tr>
<th>Test</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid factor</td>
<td>Helpful in young persons, in whom background positivity is low</td>
<td>Prognostic significance only, not helpful in individual cases</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>High titer, suggestive of a rheumatic disease</td>
<td>Virtually rules out active systemic lupus</td>
</tr>
<tr>
<td>Uric acid</td>
<td>Elevated levels, indicating that gout is possible</td>
<td>If repeated levels are normal, gout unlikely</td>
</tr>
<tr>
<td>Antistreptolysin O</td>
<td>Recent streptococcal exposure</td>
<td>Rheumatic fever unlikely</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>Possibly marginally useful in early-onset ankylosing spondylitis</td>
<td>No benefit</td>
</tr>
<tr>
<td>Anti-Borrelia</td>
<td>Only helpful if pretest probability is high</td>
<td>Chronic Lyme disease unlikely</td>
</tr>
</tbody>
</table>


### CLINICAL PEARLS
- Rapid development of OA symptoms—consider the possibility of fracture related to osteopenia, an adjacent destructive process such as metastatic tumor, or avascular necrosis
- Untreated infectious arthritis can destroy a joint in 1–2 days
- Intravenous drug abuse increases the risk of septic arthritis through the introduction of infectious material into the intravascular space with subsequent hematogenous spread to the joints; most commonly caused by *Staphylococcus aureus* and *Pseudomonas*

### References
74. Osteoarthritis

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Miriam Chan, PharmD

74. Osteoarthritis

I. INTRODUCTION
A. Osteoarthritis (degenerative joint disease—DJD) is the most common form of joint disease. It affects over 25 million in the US and occurs more frequently with age. Characterized by marked loss of cartilage and joint space
B. Etiology—unknown. Risk factors include increased age, genetics, obesity, female sex and a prior history of trauma. It is more common in the presence of other joint disorders such as Rheumatoid arthritis (RA), gout and Paget’s disease
C. 2 types
1. Primary: Most often affects the hands (DIP and PIP joints, knees, hips, spine (neck and lower back). Also can be found in MTP joint of the great toe
2. Secondary: May occur at any joint after an articular injury or secondary to a congenital or developmental cause, genetic defects, infectious causes or other rheumatological diseases

II. SYMPTOMS AND SIGNS
A. Pain worsens with weight bearing and with more advanced disease, after prolonged movement of the affected joint
B. Pain improves with rest
C. Morning stiffness lasting less than 30 minutes
D. Joint stiffness after sitting in one position for a long period of time
E. Joint instability
F. Loss of function
G. Joints enlarge and are tender to palpation
H. Often have crepitus and limited ROM, possibly with effusions
I. Heberden’s nodes (DIP joints) and Bouchard’s nodes (PIP joints)
J. Note: Systemic signs should prompt exploration for other causes

III. X-RAY: Used to confirm. Findings do not always correlate with pain
A. Joint space narrowing/collapse
B. Osteophyte formation
C. Bony sclerosis
D. Cyst formation

IV. MANAGEMENT: Goal of treatment is to control pain, improve joint function, maintain normal body weight, and achieve a healthy lifestyle
A. Non-pharmacologic
1. Weight loss and joint protection
2. Muscle strengthening and stretching
3. Routine non-impact training, i.e., cross-training to include biking and swimming
4. Joint un-loaders, orthotics
5. Knee brace or sleeve
6. Ambulation assistive devices
7. CAM treatment: acupuncture
8. Surgery for end-stage knee and hip arthritis
B. Pharmacologic
1. Acetaminophen is equally effective compared to NSAIDs for knee OA. Should be tried first line due to side effects associated with NSAIDs. Use for mild-moderate pain. Dose up to 4g/day (3g/day for elderly)
2. **NSAIDs.** Use in patients who have an inadequate response to Acetaminophen. Take with food. Can be used with a GI protective agent (PPI or Misoprostol) in patients at risk of peptic ulcers. Use for mild-moderate pain, e.g., **Ibuprofen 200–800mg** PO 3–4 ×/day, **Naproxen 200–500mg PO BID**

3. **Topical NSAIDs**
   a. **Voltaren (Diclofenac) 1% Gel:** Topical NSAID gel approved for OA of the knee and hands. Lower extremities: 4g QID max 16g/day; upper extremities 2g QID max 8g/day. Max total dose 32g/day
   b. **Pennsaid (Diclofenec) 2% topical solution:** approved for OA of the knees; 2 pumps 2 times daily per knee

4. **Celecoxib (Celebrex):** COX-2 inhibitor. Use for patients at high risk of GI complications. Dose 100–200mg/day

5. **Tramadol (µ-opioid receptor agonist).** Use for moderate to moderately severe pain. Dose 50mg Q6hrs, up to 300mg/day

6. **Narcotic pain medications.** Use for severe pain

7. **Intra-articular steroids.** Use when conventional therapy fails. Examples: **Depo-Medrol** or **Kenalog-40,** dose 20–40mg for knee and hip. Patients should rest 48 hrs after injection. Wait at least 8–12 wks between injections. Up to 2–3 injections per joint per year

8. **Intra-articular hyaluronic acid derivatives (e.g., Euflexxa, Orthovisc, Synvisc).** Use as viscosupplementation and indicated for OA of the knee. Series of 3–5 weekly injections, depending on product

9. **Topical Capsaicin cream 0.025–0.075%**. Use as an adjunct. Available OTC. Apply 3–4 ×/day. May cause transient burning on application. Avoid contact with eyes

10. **Glucosamine:** 1500mg/day and **Chondroitin:** 1200mg/day. Available as dietary supplement. Evidence suggests possible efficacy for knee OA only

C. **Surgery**

1. **Indications:**
   a. Removal of loose pieces of bone and cartilage from the joint if they are causing symptoms of buckling or locking
   b. Patients who have failed more conservative therapy

2. **Types of Surgery**
   b. Total joint arthroplasty: Use for patients with severe pain who have failed medical management or have a significant decrease in activities of daily living. Implants last 10–15 years or longer
   c. Chondrocyte grafting: Use for younger patients with localized osteoarthritis or chondral defect

**CLINICAL PEARLS**

- One of the most important factors in preventing osteoarthritis is maintaining appropriate body weight
- Many patients with radiographic evidence of osteoarthritis feel no pain
- Osteoarthritis is the most common cause of impaired mobility in the elderly; 70–90% of Americans age 75 or older have arthritis in at least 1 joint
- If the patient has knee pain at night, this could be due to inflammatory arthritis, tumors, infections, or crystal disease

**References**


Feeley BT, Gallo RA, Sherman S, Williams RJ. Management of osteoarthritis of the knee in the
75. Rheumatoid Arthritis

I. DEFINITION: A chronic, systemic inflammatory connective tissue disease characterized by symmetric, erosive synovitis and sometimes multisystem involvement. Etiology is unknown

II. EPIDEMIOLOGY
A. Estimated prevalence of 1% of US population
B. Prevalence increases with age
C. Women 2 × as often as men
D. Much higher concordance in monozygotic twins compared to dizygotic twins, suggesting genetic predisposition; also higher incidence with certain HLA subtypes (DR4 and DR1)

III. SIGNS AND SYMPTOMS
A. Insidious development of symptoms over several weeks
B. Symmetric inflammation of smaller joints, esp. MCP, PIP, and MTP joints, but may also affect large joints, particularly later in the disease (involvement of DIP joints is more typical of osteoarthritis and psoriatic arthritis)
C. Morning stiffness often lasting over 1 hr
D. Joint deformity: Caused by laxity of ligaments and tendons around the joints
   1. Swan-neck: flexion of PIP and hyperextension at DIP joints
   2. Ulnar deviation of MCP joints
   3. Atlantoaxial subluxation of cervical spine: May cause myelopathy or even death (esp. if in car accident or other trauma with subluxation)
E. Joint destruction: Often not apparent on x-ray until 1 yr after onset of disease; initially osteopenia followed by erosion of bone and decalcification
F. Rheumatoid nodules: Occur over pressure points and may be confused with tophi
G. Sjögren’s syndrome: May occur secondarily, especially in older patients with longstanding disease
H. Anemia: Often have mild normochromic, normocytic anemia
I. Other: May also have vasculitis, pulmonary manifestations, nerve entrapment syndromes (e.g., carpal tunnel), low-grade fever, malaise, fatigue, and weight loss

IV. DIAGNOSIS
A. Rheumatoid Factor: Nonspecific but present in up to 90% of patients with RA, usually associated with more severe, erosive disease
B. Inflammatory markers: ESR and C-reactive protein elevated but very nonspecific, however, may be used to clinically follow disease with changes in treatment
C. Synovial fluid analysis: WBC count typically 10,000–20,000 with 60–75% PMNs
D. Diagnosis: Based on American College of Rheumatology Criteria

The 1987 American College of Rheumatology Revised Criteria for Classification of Rheumatoid Arthritis (Traditional Format)

**CRITERION** | **DEFINITION**
--- | ---
1. Morning stiffness | Morning stiffness in and around the joints lasting at least one hour before maximal improvement
2. Arthritis of three or more joint areas | At least three joint areas with simultaneous soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible joint areas are right or left PIP, MCP, wrist, elbow, knee, ankle and MTP joints
3. Arthritis of hand joints | At least one joint area swollen as above in a wrist, MCP or PIP
4. Symmetric arthritis | Simultaneous involvement of the same joint areas on both sides of the body; bilateral involvement of PIP, MCP or MTP joints is acceptable without absolute symmetry
5. Rheumatoid nodules | Subcutaneous nodules, over bony prominences, or extensor surfaces, or juxta-articular regions, observed by a physician
6. Serum rheumatoid factor | Demonstration of abnormal amounts of rheumatoid factor by any method that has been positive in less than 5% of normal control subjects
7. Radiologic changes | Radiologic changes typical of rheumatoid arthritis on postanterior hand and wrist roentgenograms, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

**NOTE:** For classification purposes, a patient shall be said to have rheumatoid arthritis if at least 4 of the 7 criteria are present. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as “classic,” “definite” or “probable” rheumatoid arthritis is not made.


V. MANAGEMENT
A. Goals
1. Relief of symptoms
2. Preservation of function
3. Prevention of structural damage and deformity
4. Maintenance of a normal life-style

B. Education: Explain goals of therapy and chronic disease course to patients; enroll help of family members and other support groups

C. Physical and occupational therapy

D. Systemic rest: Depends on the severity of disease (e.g., mild disease may require only 2hrs of rest per day)

E. Articular rest: Relaxation and stretching of the hip and knee muscles to prevent contractures

F. Exercise: To preserve joint motion, and enhance muscular strength and endurance

G. Assistive devices: Raised toilet seat, gripping bar, cane, crutches, etc. (see Chapter 114, Falls in the Elderly)

H. Weight loss: Will aid with arthritis of the lower extremities

I. Local therapies
1. Heat and cold: For analgesic effects (heat or cold) and muscle-relaxing effects (prior to exercising or stretching—local moist heat or warm tub baths)

2. Injections of corticosteroids (see Chapter 94, Corticosteroid Injection of Joints)

3. Splints: To provide joint rest, reduce pain, prevent contracture. Should be applied for the shortest period of time possible and should be removed at least twice per day for stretching and range of motion exercises. May coordinate with physical or occupational therapist

J. Medications

1. Non-steroid anti-inflammatory drugs (NSAIDs): Do not affect the disease outcome, but they have immediate analgesic and anti-inflammatory effects. They are now used mainly as bridge drugs for relief of pain until onset of action of DMARDs occur
   a. Some patients may respond to or tolerate one NSAID better than another. Most common side effects are GI and renal toxicity. NSAIDs except COX-2 inhibitors can interfere with platelet function and prolong bleeding time. In addition, NSAIDs except Naproxen may increase thrombotic risk
   b. Aspirin: inexpensive; 650–975mg QID. High dose aspirin may have more GI toxicity than traditional NSAIDs; use enteric coated aspirin and give with a PPI. Nonacetylated salicylates have less GI toxicity than aspirin
   c. COX-2 inhibitors: Celecoxib (Celebrex) 100–200mg BID; use in patients at high risk of GI toxicity such as elderly patients, history of GI bleeding or peptic ulcer disease, high dose NSAID therapy, and those receiving anticoagulants or systemic corticosteroids. GI prophylaxis with chronic NSAID use: Misoprostol (Cytotec), a proton pump inhibitor, or a double dose of a H2 blocker may be used to reduce the incidence of NSAID induced GI toxicity
   d. Misoprost 1 (Cytotec)
      i. Dose: 200mcg PO QID (may decrease to 100mcg QID or 200mcg BID if not well tolerated
      ii. Side effects: Diarrhea and bloating. Note: Contraindicated in pregnancy
   e. Proton pump inhibitors
      i. Omeprazole (Prilosec) 20mg QD
      ii. Lansoprazole (Prevacid) 15mg QD
      iii. Rabeprazole (Aciphex) 20mg QD
      iv. Esomeprazole (Nexium) 20mg QD
      v. Pantoprazole (Protonix) 40mg QD

2. Glucocorticoids
   a. Oral corticosteroids: Use low dose (5–7.5mg QD), short course for symptomatic relief until beneficial effects of DMARDs become apparent
   b. Adverse effects of systemic steroids include osteoporosis, weight gain, fluid retention, cataracts, GI toxicity, poor wound healing, hyperglycemia, hypertension, adrenal suppression and increased risk of infection
   c. Patients on chronic Prednisone (≥7.5mg/day) should receive a bisphosphonate, such as Alendronate (Fosamax) or Risedronate (Actonel) 5mg QD to prevent steroid-induced osteoporosis. Calcium and Vitamin D supplements should be given concurrently
   d. Intra-articular injection of a steroid such as Triamcinolone (Artisotopan) can relieve joint pain with minimal adverse effects in a patient who does not have generalized disease

3. Disease-modifying antirheumatic drugs (DMARDS)
   a. Used to control symptoms and delay or possibly stop progression of the disease
   b. Most DMARDS have a slow onset of action and require regular monitoring of adverse effects
   c. The American College of Rheumatology (ACR) recommends:
      i. The use of DMARD monotherapy in patients with early RA (disease duration <6 mo) who have low disease activity, or moderate/high disease activity with the absence of poor prognostic features, and in patients with established RA who have low disease activity without poor prognosis
      ii. The use of DMARD combination therapy (including double and triple therapy) in patients with early RA who have moderate or high disease activity plus poor prognostic features, and in patients with established RA who have low
Management of Common Ambulatory Conditions 75. Rheumatoid Arthritis

d. Methotrexate (MTX) is usually the first DMARD of choice in mild, moderate or severe RA. The effect is usually apparent within 4-6 weeks, but it may take longer.

e. Leflunomide (Arava) can be used as initial monotherapy or in patients who do not tolerate MTX.

f. Hydroxychloroquine is well tolerated and may be appropriate in milder cases. It is often used in combination with MTX and Sulfasalazine. It may take 3–6 months to see its effect.

g. Minocycline may offer some benefit in milder cases of RA, but can cause drug-induced lupus and is contraindicated in children <8y and pregnant women.

h. Sulfasalazine causes more toxicity than Hydroxychloroquine.

4. Biologic agents: TNF inhibitors and Non-TNF inhibitors

a. The American College of Rheumatology (ACR) recommends:

i. Use of a TNF inhibitor with or without MTX in patients with early RA who have high disease activity with poor prognostic features. Infliximab is the only TNF inhibitor that should be used in combination with MTX.

ii. Add or switch to a biologic agent in patients with moderate or high disease level after 3 months of inadequate response to DMARDs.

b. Tumor necrosis factor (TNF) is a pro-inflammatory cytokine present in the synovium of patients with RA. The medications relieve symptoms and is effective in limiting joint destruction. They may be more effective than DMARDs and also act faster than DMARDs. Use of TNF inhibitor in combination with MTX has synergistic beneficial effects. TNF inhibitors are the first-line biologic therapy and are the most studied. However, simultaneous use of more than one biologic therapy is not recommended due to additive adverse effects.

i. Patients who do not respond to one TNF inhibitor may respond to another.

ii. Common side effects with TNF inhibitors include injection-site reactions, infusion reactions and serious infections.

iii. TNF inhibitors are contraindicated in patients with hepatitis B, multiple sclerosis or demyelinating disease.

c. Non-TNF inhibitors

i. Abatacept (Orencia) is a genetically engineered fusion protein that interferes with T-cell activation.

ii. Rituximab (Rituxan) is a genetically engineered chimeric monoclonal antibody against CD20, a B-cell specific surface antigen. It is commonly given concurrently with MTX or another DMARD.

iii. Tocilizumab (Actemra) is a humanized monoclonal antibody that competitively inhibits the binding of the pro-inflammatory cytokine interleukin-6 to its receptors.

iv. Anakinra (Kineret) is a human recombinant IL-1 receptor antagonist. It is considered the less effective biologic agent for RA and is not recommended.

v. Tofacitinib (Xeljanz) is a Janus kinase inhibitor. It is currently the only oral biologic agent that is approved for the treatment of patients with moderate-to-severe RA who have had an inadequate response or intolerance to MTX. It may be used as monotherapy or in combination with MTX or other conventional DMARDs.

d. Patients should be screened for latent TB (PPD or interferon-gamma blood test) before initiation and annually during treatment with a biologic agent.

e. Complete blood counts should be monitored regularly.

f. All patients on biologic agents should receive a pneumococcal vaccine, annual influenza vaccination, hepatitis B, HPV, and herpes zoster vaccination. They should not receive live vaccines (Zostavax, MMR, varicella or intranasal influenza) during treatment. If needed, live vaccines should be given at least one month before initiating treatment.

g. The average cost for a biologic agent is between $3000 to $5000 per month.

5. ACR recommendations on choice of biologic agents in patients with:

a. Hepatitis C: Etanercept

b. Hepatitis B (untreated or Child-Pugh class B or higher): Do not use any biologic agent.

c. Malignancy
Commonly Used DMARDs and Biologic Agents

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dosage</th>
<th>Adverse Effects</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate (Rheumatrex, generics)</td>
<td>7.5-25 mg/wk PO, SC or IM</td>
<td>Common: Nausea, diarrhea, fatigue, mouth sores, rash, alopecia, elevated LFTs. Rare: myelosuppression, pneumonitis, hepatic fibrosis, cirrhosis, risk of infections.</td>
<td>CBC, platelet, AST, albumin, SCr q4-8 wks</td>
</tr>
<tr>
<td>Hydroxychloroquine (Plaquenil, generics)</td>
<td>200 mg qd-bid</td>
<td>GI upset, HA, myopathy, retinal damage (rare).</td>
<td>Vision changes; visual field q12 mo</td>
</tr>
<tr>
<td>Sulfasalazine (Azulfidine, Azulfidine EN, generics)</td>
<td>2-3 g/day in 2-4 doses</td>
<td>Rash, GI upset, hemolysis in G6PD deficiency, elevated LFTs, contact lens staining, reversible oligospermia, myelosuppression (rare).</td>
<td>CBC q2-4 wk x 1st 3 mo, then q3 mo. Periodic LFTs</td>
</tr>
<tr>
<td>Leflunomide (Arava)</td>
<td>100 mg/d x 3 days, then 10-20 mg qd</td>
<td>Diarrhea, rash, alopecia, teratogenic, liver toxicity, thrombocytopenia (rare).</td>
<td>CBC, ALT q4-8 wk</td>
</tr>
<tr>
<td>Minocycline (Minocin, generics)</td>
<td>50-200 mg/day in 2 doses</td>
<td>Dizziness, GI upset, photosensitivity, skin discoloration, hepatitis (rare).</td>
<td>Not defined</td>
</tr>
<tr>
<td>TNF Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab (Humira)</td>
<td>40 mg q2 wks SC</td>
<td>Infusion site reactions, HA, rash, increased infection risks including TB and Hep B reactivation, pancytopenia, malignancies, heart failure, demyelinating disease, lupus-like syndrome.</td>
<td>PPD at baseline and annually; CBC and LFTs at baseline and q3-6 mo</td>
</tr>
<tr>
<td>Certolizumab pegol (Cimzia)</td>
<td>400 mg SC at 0, 2, and 4 wks, then 200 mg every other wk or 400 q4wk</td>
<td>Infusion site reactions, upper respiratory tract infection, rash, urinary tract infection, infection risks including Hep B virus reactivation, malignancies, heart failure, demyelinating disease, lupus-like syndrome.</td>
<td>PPD at baseline and annually; CBC and LFTs at baseline and q3-6 mo</td>
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<tr>
<td>Etanercept (Enbrel)</td>
<td>25 mg 2x/wk or 50 mg once/wk SC</td>
<td>Infusion site reactions, increased risk of infections, pancytopenia, malignancies, heart failure, demyelinating disease, lupus-like syndrome.</td>
<td>PPD at baseline and annually; CBC and LFTs at baseline and q3-6 mo</td>
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<tr>
<td>Golimumab (Simponi)</td>
<td>50 mg SC once/mo</td>
<td>Infusion site reactions, upper respiratory tract infection, nasopharyngitis, infection risks including Hep B virus reactivation, malignancies, hepatotoxicity, heart failure, demyelinating disease, hypersensitivity reactions.</td>
<td>PPD at baseline and annually; CBC and LFTs at baseline and q3-6 mo</td>
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<tr>
<td>Infliximab (Remicade) (use with Methotrexate)</td>
<td>3 mg/kg at 0, 2, and 6 wks; then q8 wks IV</td>
<td>Infusion reactions, HA, abdominal pain, infections including Hep B virus reactivation, pancytopenia, malignancies, heart failure, demyelinating disease, lupus-like syndrome, hypersensitivity reactions.</td>
<td>PPD at baseline and annually; CBC and LFTs at baseline and q3-6 mo</td>
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<td>Non-TNF Inhibitors</td>
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<tr>
<td>Abatacept (Orencia)</td>
<td>&lt;60kg: 500 mg; 60-100 kg: 750 mg; &gt;100 kg: 1000 mg IV infusion at 0, 2, and 4 wk then q4 wk or 125 mg SC once/wk</td>
<td>HA, upper respiratory infections, nasopharyngitis, nausea, increased risk of infections, hypersensitivity reactions, malignancies.</td>
<td>Screen patient at high risk of hepatitis B and TB</td>
</tr>
<tr>
<td>Rituimab (Rituxan)</td>
<td>1000 mg IV twice, 2 wk apart</td>
<td>Infusion reactions, upper respiratory tract infection, nasopharyngitis, urinary tract infection, bronchitis, serious infections, cardiovascular events, progressive multifocal leukoencephalopathy, Hep B virus reactivation.</td>
<td>Screen patient at high risk of hepatitis B and TB</td>
</tr>
<tr>
<td>Tocilizumab (Actemra)</td>
<td>4 mg/kg IV q4 wk, may increase to 8 mg/kg q4 wk</td>
<td>Upper respiratory tract infections, nasopharyngitis, HA, hypertension, neutropenia, elevated LFTs, dyslipidemia, injection reactions, serious infections, GI perforation, hypersensitivity reactions.</td>
<td>Neutrophils, platelets, lipids, and LFTs; screen for latent TB</td>
</tr>
<tr>
<td>Tofacitinib (Xeljanz)</td>
<td>5 mg po BID</td>
<td>Upper respiratory tract infections, headache, diarrhea, nasopharyngitis, serious infections, GI perforations, elevated LFTs and lipids, neutropenia, lymphopenia.</td>
<td>Screen for latent TB and Hep B; monitor CBC, neutrophils, lipids, and LFTs; drug interactions with P450 3A4 and 2C19</td>
</tr>
</tbody>
</table>

75. Rheumatoid Arthritis

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i. Treated solid tumor or nonmelanoma skin cancer, >5 y ago: any biologic agent
ii. Treated solid tumor or nonmelanoma skin cancer, within the last 5 y: Rituximab
iii. Treated skin melanoma: Rituximab
iv. Treated lymphoproliferative malignancy: Rituximab

d. Congestive heart failure (NYHA III/IV and EF ≤50%): Do not use TNF inhibitors
CLINICAL PEARLS

- Asking about length of morning stiffness, e.g., “How long does it take in the morning for you to feel as good as you’ll be?” is a useful way of following the severity of the disease as the duration of morning stiffness correlates with the degree of joint inflammation.
- Since Methotrexate is teratogenic, male patients should wait 3 months after stopping therapy, and female patients should wait at least 1 ovulatory cycle before attempting to get pregnant.
- Anti-TNF therapy should be discontinued if serious infection occurs. Screen for latent TB before therapy with anti-TNF agents.
- DMARDS do not have immediate analgesic effects.

References


Drugs for rheumatoid arthritis. Treatment Guidelines from the Medical Letter. May 2012.


Steve Brook, MD
Thomas D. Armsey, Jr., MD
Phil Favia, MD

76. GOUTY ARTHRITIS

I. DEFINITION

A. Gout

1. Inflammatory disease characterized by tissue deposition of monosodium urate crystals
2. Incidence (cases per 1000 person-years is 1.4 for women and 4.0 for men. Women tend to be affected after menopause)

B. Hyperuricemia: Defined as a level > 7.0mg/dL and resulting from either overproduction or underexcretion of uric acid. Men are 6 × as likely as women to have a uric acid level > 7mg/dL.

II. ETIOLOGY

A. Primary Gout

1. Underexcretion of uric acid (90% of patients): Primary idiopathic
2. Overproduction of uric acid (10% of patients)
   a. Primary idiopathic
   b. Hypoxanthine-guanine phosphoribosyltransferase deficiency
   c. Phosphoribosylpyrophosphate synthetase overactivity
   d. Glucose 6-phosphatase deficiency

B. Secondary Gout

1. Underexcretion of uric acid
   a. Renal disease (chronic renal failure, renal insufficiency, lead nephropathy, polycystic kidney disease)
   b. Meds (ASA, diuretics, Niacin, Levodopa, Ethambutol)
   c. Alcohol
   d. Dehydration
   e. Starvation/metabolic abnormalities
   f. Other: HTN, obesity, hypothyroidism, Down’s syndrome
2. Overproduction of uric acid
   a. Purine-rich diet (organ meats, sardines, anchovies, bacon, turkey, venison, veal, scallops)
### 76. Gouty Arthritis

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b. Alcohol  
c. Obesity  
d. Exercise  
e. Other: Myeloproliferative disorders, lymphoproliferative disorders, hemolytic disorders, psoriasis, chemotherapy

#### III. Differential Diagnosis:
Infectious arthritis, cellulitis, bursitis, tendinitis, osteoarthritis, rheumatoid arthritis, pseudogout, amyloidosis, type IIa hyperlipidemia

#### IV. Signs and Symptoms: Differ depending on the stage

**A. Asymptomatic hyperuricemia**
1. No symptoms present  
2. Serum uric acid level elevated (>7.0mg/dL)

**B. Acute gouty arthritis**
1. Classic presentation: Acute, nocturnal onset of pain, swelling, warmth, and erythema  
2. Monoarticular involvement is most common, with the first MTP joint affected in 50% of cases. Other joints affected include the forefoot, heel, ankle, wrist, fingers, and elbow  
3. Older adults, particularly women, may have a polyarticular presentation  
4. Fever and chills may be present in severe attacks  
5. Peak intensity occurs within 24–36hrs  
6. Resolution of symptoms without treatment occurs in days to weeks  
7. Absence of symptoms between acute attacks (termed interval gout)

**C. Interval gout**
1. The asymptomatic period between acute attacks. May last weeks to years (50% patients experience another acute attack within 1 year)  
2. Tophi (subcutaneous or interosseous collections of urate crystals) may be present in up to 10% of patients if the disease has progressed to the chronic stage

**D. Chronic tophaceous gout**
1. Increasingly rare due to modern therapy  
2. Locations include: Ear helix, proximal ulnar olecranon, Achilles tendon, and prepatellar bursa  
3. Acute exacerbations are frequent and often polyarticular  
4. Morning stiffness and joint deformity are common

#### V. Evaluation

**A. Joint aspiration**
1. Identification of negatively birefringent monosodium urate crystals under polarizing microscopy remains the gold standard of diagnosis but is not routinely done in clinical practice  
2. If a septic joint is suspected, aspiration followed by culture and sensitivity is essential  
3. The white blood cell count may also be elevated within the synovial fluid (10,000–60,000) with neutrophils predominating

**B. 24hr urine for uric acid**
1. Important test to direct treatment and determine if patient is overproducer or underexcretor of uric acid. Perform after acute attack resolves  
2. Patients on normal diet with 24hr uric acid excretion >800mg are classified as overproducers. Value of <600mg classifies patient as underexcretor

**C. Other labs**
1. Serum uric acid: Often not helpful in the diagnosis of acute gout (normal in 10% of patients). Useful in monitoring response to urate-lowering therapy  
2. Creatinine, CBC, LFTs, lipid profile, and UA

**D. Imaging**
1. Plain radiographs are not useful in diagnosing acute gout. Usually only soft tissue swelling is seen  
2. Classic radiographic findings in chronic gout: “punched-out” bony lesions, cortical erosions with overhanging margins, and joint space preservation  
3. In general, gout must be inadequately treated for approximately 12yrs before x-ray changes are seen

#### VI. Management
A. Asymptomatic hyperuricemia
1. No medical treatment is indicated
2. Secondary causes of hyperuricemia should be sought and adjusted accordingly:
   a. Weight loss
   b. Reduction in dietary purines
   c. Reduction in alcohol consumption
   d. Avoidance of dehydration (diuretics) and repetitive trauma
   e. Control HTN and hyperlipidemia

B. Acute gouty arthritis
1. Treatment should be initiated as early as possible (preferably within 24hrs). Immobilization and ice are important adjuncts to medical therapy
2. Monotherapy: Mild to moderate attacks involving 1–2 joints are treated with either Colchicine, NSAIDs or systemic corticosteroids depending on patient factors and preference
3. Combination therapy: In cases with severe pain involving multiple joints or failed monotherapy, the following combinations can be used:
   a. Colchicine + NSAIDs
   b. Colchicine + oral steroids
   c. Intra-articular steroids + all other modalities
   d. Combinations can be 2 full dose preparations or 1 full dose therapy and another prophylaxis dosed medication
4. Colchicine (Colcrys): Used only if started within 36 hours of an attack
   a. Dosing: 1.2mg followed by 0.6mg 1 hour later then prophylaxis dosing of 0.6mg once or twice daily
   b. Dose must be adjusted in chronic kidney disease and adjusted or avoided when used with high potency P450 3A4 and P-glycoprotein inhibitors such as Clarithromycin, Erythromycin, Cyclosporine and Disulfiram
5. NSAIDs
   a. Full dose should be used until complete resolution of symptoms, though tapering is optional in patients at risk of complications from NSAIDs. Examples:
      i. Ibuprofen: 600mg PO TID
      ii. Naproxen: 500mg PO BID
6. Corticosteroids—Prednisone: 40mg PO daily for 5 days
7. Urate lowering therapy (ULT): Patients on ULT should continue their regimen during an acute attack. Initiating therapy during an acute attack could exacerbate symptoms

C. Chronic therapy
1. Includes anti-inflammatory prophylaxis and ULT to decrease the patient’s disease burden
2. Chronic therapy is indicated in patients with tophi on exam or imaging studies, 2 or more attacks per year and should be considered in patients with either CKD (stage 2 or worse) or past urolithiasis (both level C evidence)
3. Anti-inflammatory prophylaxis: is started as an acute attack subsides and/or ULT is initiated and includes low dose Colchicine at 0.6mg QD to BID, low dose NSAIDs such as Naprosyn 250mg PO BID. Therapy should be continued until there is no inflammatory activity and the uric acid lowering goal has been obtained
4. ULT: goal is a urate level at which there is no disease activity, which is typically less than 6 but is often as low as < 5
   a. Diet modification is recommended for all patients initially
      i. Avoid alcohol overuse (especially beer), organ meats and high fructose corn syrup-sweetened foods and beverages
      ii. Limit alcohol, beef, lamb, pork, shell fish, sardines, sugar, fruit juices, sucrose and sodium
   b. ULT includes the Xanthine oxidase inhibitors (XOI) Allopurinol and Febuxostat (Uloric), uricosuric agents such as Probencid and the new biologic agent Pegloticase
   c. Can be started during an acute attack as long as there is concurrent anti-inflammatory therapy to control symptoms
   d. Monitoring (symptoms and urate levels) every 2–5 weeks initially then every 6
months once goal urate level is obtained
e. Xanthine oxidase inhibitors (XOI): Allopurinol (Febuxostat considered when Allopurinol not tolerated)
   i. Starting dose of 100mg/day (50mg/day in CKD stage 4 or worse). Higher doses are more likely to precipitate an attack
   ii. Titration is every 2–5 weeks to reach goal as long as no signs of Allopurinol hypersensitivity syndrome (AHS: rash, pruritis, LFT elevation). The final dose may be >300mg/day, even in patients with CKD (>30mL/min)
   iii. Consider screening for HLA-B *5801 (associated with high risk of AHS) in Koreans with CKD 3 or worse, and Han Chinese and Thai irrespective of renal function
f. Uricosuric therapy: 
   Probenecid, Losartan and Fenofibrate (the latter two are off-label)
   i. Typically prescribed as monotherapy when XOI are not tolerated or contraindicated
   ii. Can be prescribed in combination with an XOI in order to reach therapeutic goals
   iii. Should not be used in patients with history of nephrolithiasis, elevated baseline urinary uric acid and should not be first line therapy when CrCl is < 50mL/min
   iv. Dilution (increased fluid intake) and alkalinization (with potassium citrate) of urine should be considered to prevent stones
g. Pegloticase (Krystexxa): A novel, IV administered biologic agent used in only severe gout cases refractory to oral agents

CLINICAL PEARLS
• Although hyperuricemia and gout are frequently associated, the 2 conditions are not mutually exclusive—some patients with gout have normal uric acid levels, and some patients with hyperuricemia never develop gout
• Any therapy for gout should include lifestyle modifications such as weight loss, low purine diet, and reduction in alcohol consumption
• If patients currently treated with Allopurinol or Probenecid experience an acute attack do not adjust the doses. Treat with NSAIDs or Colchicine
• If gout is present in patients <30, consider a genetic disorder

References
Osteoporosis

I. GENERAL
A. Osteoporosis (WHO definition): Bone mineral density (BMD) T-score of less than or equal to 2.5 standard deviations below the mean at the total hip, femoral neck, or lumbar spine (posterior-anterior).

B. Osteopenia (WHO definition): BMD T-score of between 1.0 and 2.5 standard deviations below the mean.

C. Osteoporosis is the most common bone disorder and affects more than 10 million people in the United States and 200 million women worldwide. 33% of men will be affected by osteoporosis by age 75.

D. Osteoporosis accounts for greater than 1.5 million fractures annually at a cost of $17 billion to the U.S. health care system. 50% of postmenopausal women will develop an osteoporotic fracture during their lifetime.

E. Hip fractures are associated with a 10–20% mortality in the first year with nearly 50% having some long-term loss of mobility.

F. Categorized as primary or secondary.
   1. Primary Osteoporosis: Bone loss that occurs with aging.
   2. Secondary Osteoporosis: Secondary to medical disorders, hematologic disorders, hypogonadal states, and certain medications that adversely affect bone health and contribute to and/or exacerbate osteoporosis.

### Secondary Causes of Bone Loss

<table>
<thead>
<tr>
<th>Medications</th>
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<tr>
<td>Aromatase inhibitors</td>
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<td>Cytotoxic agents</td>
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<td>Excessive thyroxine doses</td>
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<td>Gonadotropin-releasing hormone agonists or analogues</td>
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<td>Heparin</td>
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<td>Immune suppressives (eg, cyclosporine)</td>
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<tr>
<td>Intramuscular medroxyprogesterone</td>
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<tr>
<td>Long-term use of certain anticonvulsants (eg, phenytoin)</td>
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<td>Oral or intramuscular use of glucocorticoids for 93 mo</td>
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<td>Genetic disorders</td>
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<td>Hemochromatosis</td>
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<td>Hypophosphatasia</td>
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<td>Osteogenesis imperfecta</td>
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<td>Thalassemia</td>
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<td>Disorders of calcium balance</td>
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<td>Hypercalcia</td>
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<td>Vitamin D deficiency</td>
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<td>Endocrinopathies</td>
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<td>Cortisol excess</td>
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<td>Cushing’s syndrome</td>
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<td>Gonadal insufficiency (primary and secondary)</td>
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<td>Hyperthyroidism</td>
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<tr>
<td>Primary hyperparathyroidism</td>
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<td>Type 1 diabetes mellitus</td>
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<td>Gastrointestinal diseases</td>
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<td>Billroth I gastroenterostomy</td>
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<tr>
<td>Chronic liver disease (eg, primary biliary cirrhosis)</td>
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<td>Malabsorption syndromes (eg, celiac disease, Crohn’s disease)</td>
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<tr>
<td>Total gastrectomy</td>
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<tr>
<td>Other disorders and conditions</td>
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<tr>
<td>Ankylosing spondylitis</td>
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<tr>
<td>Chronic renal disease</td>
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<tr>
<td>Lymphoma and leukemia</td>
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<td>Multiple myeloma</td>
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<tr>
<td>Nutritional disorders (eg, anorexia nervosa)</td>
<td></td>
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<tr>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Systemic mastocytosis</td>
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</table>

**77. Osteoporosis**

*Management of Common Ambulatory Conditions*

**G. Risk Factors**

1. Clinical factors: Low peak bone mass, advancing age, thinness (low body weight or low body mass index-BMI), prior fracture history at any site, early menopause, hypogonadism, family history of osteoporotic fracture, osteopenia on radiograph, systemic glucocorticoid (≥5mg/d) use for greater than 3 months, proton pump inhibitor

2. Lifestyle factors: cigarette smoking, low level of physical activity, prolonged immobilization, heavy alcohol consumption (7 or more ounces per week), excessive caffeine intake, propensity to fall

3. Nutritional factors: low calcium or vitamin D intake, malabsorption syndromes

**II. HISTORY AND PHYSICAL EXAM**

A. History: Evaluate for risk factors listed above, including secondary risk factors. Include history of fracture in the patient or in a first-degree relative. Assess for acute or chronic back pain. Evaluate history of falls, fainting, or loss of consciousness that may indicate increased risk of falls. Medication history

B. Physical examination

1. Height: Loss of height of greater than 3 cm increases likelihood of vertebral fracture and should be evaluated with a lateral thoracolumbar radiograph

2. Weight: Weight less than 57 kg or BMI less than 21 kg/m² is associated with increased fracture risk

3. Kyphosis: Abnormal curvature of thoracic spine as a result of multi-level severe vertebral compression fractures

4. Evaluate grip strength, visual acuity, gait stability and speed, balance, muscle strength and coordination

5. Assess for features that may reveal secondary causes of osteoporosis

**III. DIAGNOSIS**

A. Bone Mineral Density (BMD): Used as a proxy for overall bone strength, which is related to bone density and bone quality. BMD is the technical standard for diagnosing osteoporosis

B. Dual-energy x-ray absorptiometry scanning (DEXA, DXA): Gold standard for measuring BMD

1. Advantages: high precision and accuracy, inexpensive, low radiation exposure (90% less than standard chest radiograph)

2. Recommended Sites: total hip, femoral neck, and posterior-anterior lumbar spine

3. Results:
   a. T-score: Difference between an individual’s BMD and the mean BMD for a normal, young adult population of the same gender. Score of +1 is 1 standard deviation above the mean and –1 is 1 standard deviation below the mean. Osteoporosis is a T-score less than –2.5
   b. Z-score: Difference between an individual’s BMD and the BMD of others in a population of same gender, age, and ethnicity
   c. BMD is the single best predictor of fracture risk

4. Peripheral sites: Distal radius and calcaneus. Less useful in predicting fracture risk and therefore are not sufficient for diagnosis and treatment decisions. Cannot apply WHO criteria to these sites, therefore use should be limited to when DEXA is not available

5. Other radiographic methods such as qualitative ultrasound or computed tomography may assist in the diagnosis of osteoporosis, but they have not yet been accepted as sole methods to be used for diagnosis or treatment determinations

C. Labs

1. Routine laboratory tests used to evaluate for secondary causes of osteoporosis: CBC, serum calcium, serum 25-hydroxyvitamin D, serum albumin, serum alkaline phosphatase, urinary calcium excretion

2. Biochemical markers of bone turnover: Currently available markers include bone-specific alkaline phosphatase and osteocalcin, the most useful markers presently. The value of these markers in routine clinical practice has not been established, but is likely to be in combination with other important risk factors, such as BMD

**IV. SCREENING:** No controlled studies have evaluated the effect of screening on fractures or
Management of Common Ambulatory Conditions 77. Osteoporosis

fracture-related morbidity

A. U.S. Preventive Services Task Force (USPSTF) Recommendations for Routine Screening:
   1. Women ages 65 and older (B recommendation)
   2. Women ages 60 and older and at increased risk (B recommendation)
   3. No recommendations regarding screening for women ages 60–64 without increased risk for osteoporotic fractures (C recommendation)
   4. The National Osteoporosis Foundation also recommends screening younger postmenopausal women who have had a fracture or who have one or more risk factors identified, adults with a fracture after age 50, adults with a condition or taking a medication associated with bone loss, and men ≥70y

B. North American Menopause Society Recommendations for Routine Screening
   1. Postmenopausal women with medical causes of bone loss, regardless of age
   2. Postmenopausal women at least 65 years of age, regardless of additional risk factors
   3. Consider screening for healthy postmenopausal women less than age 65 with the following risk factors: fracture (other than skull, facial bone, ankle, finger, and toe) after menopause, history of hip fracture in a parent, current smokers, or low weight (see II. B. 2.)

C. Number needed to screen: The USPSTF estimates that the number needed to screen to prevent 1 hip fracture is 1,856 for women ages 60–64 and 143 for women ages 75–79

D. Screening Frequency: No studies have been done to evaluate the optimum screening intervals. Generally accepted to re-screen untreated postmenopausal women in 3–5 years. For women receiving osteoporosis treatment screening may be useful after 2 years

E. WHO Fracture Risk Algorithm (FRAX): The FRAX algorithms give the 10-year probability of a hip fracture and the 10-year probability of a major osteoporotic fracture. The algorithm is available at www.nof.org as well as at www.shef.ac.uk/FRAX

V. OSTEOPOROSIS IN MEN

A. Epidemiology
   1. 1 to 2 million men in the US have osteoporosis, and an additional 8 to 13 million have osteopenia
   2. 13% of white men over 50 years will experience at least one osteoporotic fracture in their lifetime

B. Risk factors
   1. Low body weight (body mass index of less than 25kg per m²)
   2. Weight loss of more than 10 percent of body weight
   3. Physical inactivity
   4. Corticosteroid use
   5. Androgen deprivation therapy
   6. Spinal cord injury

C. Screening
   1. The US Preventive Services Task Force does not make any specific recommendations on osteoporosis screening in men
   2. The American College of Physicians proposes that physicians initiate periodic risk assessment in older men before the age of 65 years; based on a meta-analysis, it recommends dual-energy x-ray absorptiometry (DEXA) in men at increased risk of osteoporosis who are candidates for drug therapy

D. Treatment—Similar to women. Note: Testosterone therapy increases BMD in men who have low levels of testosterone

VI. MANAGEMENT: All postmenopausal women should be counseled in non-pharmacologic approaches to prevent bone loss and fractures. Pharmacologic therapy should be offered to specific populations

A. Lifestyle Modification
   1. Nutrition: Balanced diet, adequate protein intake (Protein supplementation of 20g/day may shorten hospitalization in older patients following hip fracture)
   2. Calcium: Role in increasing BMD and improving efficacy of therapeutic agents. No positive effect on fracture risk. Requirements of dietary calcium increase with age
      a. Dietary sources: should be primary source. Dairy products are the best
      b. Calcium supplements and calcium-fortified foods: for women unable to consume enough dietary calcium. Calcium supplements should be taken in divided
doses. Calcium citrate is more effective than calcium carbonate
i. The Institute of Medicine recommends:
   Men 50–70y: 1000mg/d
   Men ≥71y: 1200mg/d
   Women ≥51y: 1200/d

3. Vitamin D: Essential for intestinal absorption of calcium. May decrease vertebral and nonvertebral fractures. Sources: sunlight, dairy products, fatty fish, and supplements
a. NDF Recommendation: 800–1,000 IU/d Vitamin D intake
b. Treatment of Vitamin D deficiency: 50,000 IU Vitamin D₃ or D₂ daily) × 8–12 wks followed by 1,500–2,000 IU/d to maintain the target blood level of 25(OH)D ≥30 ng/mL

4. Exercise: Impact and nonimpact exercises have a positive impact on the lumbar spine. Impact exercise probably has a positive impact on the femoral neck. Strength training has significant benefits on bone mass. Balance exercises have been shown to decrease fall risk

5. Fall prevention: Focus on exercises to improve balance and muscle strength. Adjust medications and reduce fall hazards in the home by improving lighting and removing obstacles in the home, particularly in bathrooms, stairs and hallways

6. Smoking cessation: Recommended for all smokers

7. Alcohol avoidance: Postmenopausal women should drink only in moderation and less than 7 drinks per week. Moderate consumption (1–2 ounces per week) in women aged 65 or older is actually associated with higher BMD and decreased risk of hip fracture

B. Pharmacologic Management

1. Bisphosphonates
   a. Mechanism: Inhibit the activity of osteoclasts, reducing bone resorption. Significantly increase BMD in a dose-dependent fashion. Reduction of risk of vertebral fractures by 40–50%
   b. Indications: First-line therapy for prevention in postmenopausal women with low BMD, treatment for postmenopausal women with osteoporosis, prevention and treatment of glucocorticoid related bone loss, first-line therapy in men with low BMD or osteoporosis
   c. Contraindications: Patients with esophageal abnormalities that delay esophageal emptying. Patients who are unable to sit or stand upright for 30 to 60 minutes after medication administration. Creatinine clearance less than 30mL/min
d. Side Effects: Dysphagia, esophagitis, esophageal and gastric ulcers, and flu-like illness with large doses of IV bisphosphonates. Osteonecrosis of the jaw, primarily seen after dental extraction and with large doses related to treatment of cancer-related bone diseases
e. Dosing
   i. Daily, weekly, or monthly formulations of bisphosphonates are available
   ii. Bisphosphonate tablets must be taken on an empty stomach, first thing in the morning, with 8 ounces of plain water
   f. IV formulations
      i. Ibandronate (Bonvia) 3mg IV q 3 months
      ii. Zoledronic Acid (Reclast) 5mg IV infusion over ≥15 min once a year for treatment and once every other year for prevention. Patients should be well hydrated and pre-treated with acetaminophen to reduce the risk of an acute phase reaction
g. Duration of treatment
   i. Evidence of efficacy beyond 5 years is limited. On the other hand, rare safety concerns such as ONJ and atypical femur fractures are more common beyond 5 years
   ii. Treatment duration should be individualized with a comprehensive risk assessment. It is reasonable to discontinue bisphosphonates after 3–5 years in people who have a modest risk of fracture. However, those who have a high risk for fracture, continued treatment with a bisphosphonate or an alternative therapy should be considered
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Effectiveness of Medications on Reducing Risk of Listed Fracture Types for Postmenopausal Women with Osteoporosis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Vertebral</th>
<th>Nonvertebral</th>
<th>Hip</th>
<th>Wrist</th>
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<tbody>
<tr>
<td>Bisphosphonates</td>
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<tr>
<td>Alendronate</td>
<td>Reduced (A)</td>
<td>Reduced (A)</td>
<td>Reduced (A)</td>
<td>Reduced (C)</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Reduced (A)</td>
<td>Reduced (A)</td>
<td>Reduced (A)</td>
<td>Reduced (C)</td>
</tr>
<tr>
<td>Zoledronic acid</td>
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<td>Reduced (A)</td>
<td>Reduced (A)</td>
<td>Not specified</td>
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<tr>
<td>Ibandronate</td>
<td>Reduced (A)</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td>Reduced (A)</td>
<td>Reduced (A)</td>
<td>Reduced (A)</td>
<td>Not specified</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Reduced (A)</td>
<td>Reduced (B)</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Reduced (A)</td>
<td>Did not reduce (A)</td>
<td>Did not reduce (A)</td>
<td>Did not reduce (A)</td>
</tr>
</tbody>
</table>

A= High level of evidence; B= moderate level of evidence; C= Low level of evidence


2. Raloxifene (Evista)
   a. Mechanism: Selective estrogen receptor modulator with benefits on BMD, but with a lower risk for breast cancer, endometrial cancer, and cardiovascular disease when compared to estrogen. Reduction of risk of vertebral fractures
   b. Indications: For prevention in postmenopausal women with low BMD, treatment for postmenopausal women with osteoporosis
   c. Side Effects: Venous thromboembolic disease, pulmonary embolism, and hot flashes
   d. Reduction in risk of invasive breast cancer
   e. Dosing: 60mg/day oral formulation

3. Salmon Calcitonin (Miacalcin)
   a. Mechanism: Reduction in bone resorption. Increases BMD and reduces lumbar spine fractures
   b. Indications: Treatment for reduction of acute bone pain from osteoporotic vertebral compression fractures. Second-line therapy for postmenopausal women with osteoporosis
   c. Dosing: Nasally at 200 IU/day. Also available as a subcutaneous injection
   d. There are concerns about an increased risk of malignancies from Calcitonin. Continued therapy should be evaluated on a regular basis. The FOA advisory committee has recommended that Calcitonin no longer be used as a treatment for osteoporosis

4. Hormone Therapy (HT)
   a. Mechanism: Systemic estrogens promote preservation and increased BMD. Reduction of fracture risk
   b. The Woman's Health Initiative (WHI) found that 5 years of HT reduced the risk of clinical vertebral fractures and hip fractures by 34% and other osteoporotic fractures by 23%. However, there was increased risks of MI, stroke, invasive breast cancer, pulmonary emboli and DVT during 5 years of HT
   c. The primary indication for HT is for women with moderate to severe menopausal symptoms
   d. Dosing: General rule = lowest dose for shortest duration

5. Conjugated estrogen/Bazedoxifene (Duavee)
   a. It is a tissue-selective estrogen complex
   b. Indicated for women who suffer from moderate-to-severe hot flashes associated with menopause and to prevent osteoporosis after menopause
   c. Dose: One 0.45mg/20mg tablet taken once daily
   d. Side effects: Muscle spasms, nausea, diarrhea, dyspepsia, upper abdominal pain, oropharyngeal pain, dizziness, and neck pain
   e. Same Boxed Warning and Precautions as other estrogen products

6. Teriparatide (Forteo)
   a. Mechanism: Recombinant human parathyroid hormone that stimulates osteoblastic bone formation. Reduction of vertebral fracture by 67%
b. Indications: Treatment of postmenopausal women who are at high risk for fracture or for whom other therapies have failed.

c. Contraindications: Patients with hypercalcemia, bone metastases, or disorders that predispose to bone tumors such as Paget’s Disease or skeletal irradiation.

d. Side effects: Muscle cramps, hypercalcemia, nausea and dizziness.

e. Recommended dose 20mcg/day subcutaneously for no longer than 18–24 months.

7. Denosumab (Prolia)

a. A receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL) inhibitor.

b. Indications:

i. Treatment of postmenopausal women and men with osteoporosis at high risk of fracture or patients who have failed or are intolerant to other available osteoporosis therapies.

ii. For bone loss in men with prostate cancer.

iii. For bone loss in women with breast cancer.

c. Dose: 60mg SC once every 6 months, administered by a health provider.

d. Side effects: Hypocalcemia, increased risk of serious skin infections (cellulitis) and skin rash, musculoskeletal pain, pain in extremity, osteonecrosis of the jaw and atypical femur fractures (rare).

### Medications Used for Prevention or Treatment of Osteoporosis

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication</th>
<th>Mechanism of action</th>
<th>Trade name</th>
<th>Indications</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>Alendronate</td>
<td>Antiresorptive; inhibits osteoclast activity by inducing osteoclast apoptosis</td>
<td>Fosamax</td>
<td>Prevention and treatment of postmenopausal osteoporosis, treatment of glucocorticoid-induced osteoporosis, treatment of osteoporosis in men</td>
<td>5 mg/d or 35 mg/wk + vitamin D3 (2800-5600 IU D3/wk)</td>
</tr>
<tr>
<td></td>
<td>Ibandronate</td>
<td></td>
<td>Boniva</td>
<td>Prevention and treatment of postmenopausal osteoporosis</td>
<td>5 mg/d or 35 mg/wk or 35 mg/wk+citric acid</td>
</tr>
<tr>
<td></td>
<td>Risedronate</td>
<td></td>
<td>Actonel</td>
<td>Prevention and treatment of postmenopausal osteoporosis</td>
<td>5 mg/d or 35 mg/wk or 35 mg/wk+citric acid</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Calcitonin</td>
<td>Parathyroid hormone decreases skeletal release of calcium, phosphorus, and hydroxyproline; antiresorptive; decreases bone loss, increases bone density; may reduce pain from insufficiency fracture; reduces risk of spine fracture</td>
<td>Micacalcin, Calcimar, Fortical</td>
<td>Prevention and/or treatment of postmenopausal osteoporosis</td>
<td>Nasal spray 200 IU/d or Injection 100 IU/d</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Estrogen</td>
<td>Antiresorptive; specific mechanism of action obscure; reduces bone loss; increases bone density; reduces risk of spine fracture</td>
<td>Multiple brand names available</td>
<td>Prevention of osteoporosis</td>
<td>Pill or skin patch, 0.3 mg/d (low dose) or 0.625 mg/d (standard dose)</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>Teriparatide</td>
<td>Stimulates new bone formation; possibly by maintaining viability of osteocytes; increases intestinal calcium absorption; decreases urinary calcium excretion; increases production of 25-vitamin D-3; increases bone mineral density; reduces risk of spine fracture in women and men</td>
<td>Forteo</td>
<td>Treatment of postmenopausal osteoporosis; treatment of men at high risk for fracture</td>
<td>20mcg SQ/d</td>
</tr>
<tr>
<td>Selective estrogen receptor modulators (SERMs)</td>
<td>Raloxifene</td>
<td>Antiresorptive; increases bone mass; reduces risk of spine fracture</td>
<td>Evista</td>
<td>Prevention and treatment of postmenopausal osteoporosis</td>
<td>60 mg/d</td>
</tr>
<tr>
<td>Mineral supplement</td>
<td>Calcium</td>
<td></td>
<td></td>
<td></td>
<td>1000–1200 mg/d</td>
</tr>
<tr>
<td>Vitamin supplement</td>
<td>Vitamin D</td>
<td></td>
<td></td>
<td></td>
<td>850–1000 IU/d</td>
</tr>
</tbody>
</table>

CLINICAL PEARLS

- Osteoporosis is diagnosed by a BMD T-score of less than or equal to 2.5 standard deviations below the mean. DEXA is the gold standard for diagnosis.
- The USPSTF recommends screening women aged 65 and older and women aged 60 and older considered at increased risk with a DEXA scan.
- All postmenopausal women should be counseled in lifestyle modification to prevent bone loss and fractures.
- Medications should be started for patients with a T-score -2.0 or lower by hip DEXA with no risk factors, or those with T-score of -1.5 or lower and one or more risk factors.

References


Miriam Chan, PharmD
Ivan Wolfson, MD
Michael B. Weinstock, MD
Joyce Miller, PA-C
78. UTIs

Management of Common Ambulatory Conditions

- a. Greater than 5 WBC per high power field
- b. Bacteriuria is present
- c. Nitrite is positive
- d. Note: False positives occur with leukocyte esterase because of vaginal leukocytes

3. Urine culture: Only necessary if there is a strong likelihood of UTI despite negative urine dip, screen or micro, atypical clinical features, suggestion of a complicated UTI, patient is a child, is immunosuppressed, has recurrent UTIs, or is status post ATB treatment of UTI

4. Follow-up: For uncomplicated UTIs, no follow-up culture or visit is necessary unless symptoms persist, recur, or patient is pregnant

### Sensitivity and Specificity of Components of the Urinalysis, Alone and in Combination

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity % (Range)</th>
<th>Specificity % (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte esterase</td>
<td>83 (67-94)</td>
<td>78 (64-92)</td>
</tr>
<tr>
<td>Nitrite</td>
<td>53 (15-82)</td>
<td>98 (90-100)</td>
</tr>
<tr>
<td>Leukocyte esterase or nitrite positive</td>
<td>93 (90-100)</td>
<td>72 (58-91)</td>
</tr>
<tr>
<td>Microscopy: WBCs</td>
<td>73 (32-100)</td>
<td>81 (45-98)</td>
</tr>
<tr>
<td>Microscopy: bacteria</td>
<td>81 (16-99)</td>
<td>83 (11-100)</td>
</tr>
<tr>
<td>Leukocyte esterase or nitrite or microscopy positive</td>
<td>99.8 (99-100)</td>
<td>70 (60-92)</td>
</tr>
</tbody>
</table>


F. Management

1. Duration of therapy
   - a. 3 day course is as effective as 7 days with half the number of side effects. Single dose therapy is not recommended
   - b. A 7–14 day course is recommended for an uncomplicated UTI if patient is: diabetic, >65, febrile, pregnant (7 days), has had a UTI within 6 weeks, has had symptoms >7 days, diaphragm user

2. First-line Antibiotics: choice should be based on patient allergy and compliance history, local practice patterns, local resistance prevalence, availability, cost, and tolerance
   - a. Nitrofurantoin (Macrobid) 100mg BID × 5 days (with meals)
     i. 93% efficacy. Minimal resistance to E coli. May use in pregnancy (Pregnancy category B)
     ii. Side effects: nausea, headache, flatulence
   - b. TMP/SMX (Bactrim) 1 DS tab (160/800mg) BID × 3 days
     i. 93% efficacy. Avoid if resistance is >20% or if used for UTI in previous 3 mo
     ii. Pregnancy category D
     iii. Side effects: N/V, anorexia, rash, urticaria, hematologic complications, and photosensitivity
   - c. Trimethoprim (TMP) 100mg BID × 3 days. Similar efficacy as TMP/SMX.
     Pregnancy category C
   - d. Fosfomycin (Monurol) 3-g sachet in a single dose
     i. 91% efficacy based on 1 trial, but it appears to be less effective than TMP/SMX or Fluoroquinolones. Avoid if early pyelonephritis suspected
     ii. Pregnancy category B
     iii. Side effects: diarrhea, nausea, headache, and vaginitis

3. Second-line Antibiotics
   - a. Fluoroquinolones: More expensive. Use if local resistance to TMP/SMX is high and for patients with recurrent, chronic or complicated UTIs. Not for use in pregnant women or if patients aged <18y
     i. 90% (85–98%) efficacy. Resistance prevalence in the US is rising and high prevalence in some regions in the world
     ii. Pregnancy category C
iii. Side effects include N/V, diarrhea, headache, drowsiness and insomnia
iv. Dosing
   • Ciprofloxacin (Cipro) 250mg BID × 3 days
   • Levofloxacin (Levaquin) 250mg QD × 3 days
   • Ofloxacin (Floxin) 200mg BID × 3 days

b. β-lactam antibiotics
   i. 89% (79–98%) efficacy; less effective than TMP/SMX or Fluoroquinolones. Few efficacy data on first generation Cephalosporins (e.g., Cephalixin); avoid empirical Amoxicillin or Ampicillin due to high prevalence of resistance
   ii. Side effects: diarrhea, N/V, rash, and urticaria
   iii. Dosing: Treat for 3–7 days
      • Amoxicillin-Clavulanate (Augmentin) 500/125mg BID
      • Cefaclor (Ceclor) 250mg TID
      • Cefpodoxime (Vantin) 100mg BID
      • Cefdinir (Omnicef) 100mg BID (off-label use)

4. Relief of dysuria
   a. Pyridium (Phenazopyridine) 100–200 mg TID. Side effects include headache, rash, pruritus, GI disturbance, urine discoloration, and staining of contact lenses
   b. Urised: 2 tabs PO QID (PC and HS)

II. ACUTE UNCOMPLICATED PYELONEPHRITIS
A. Signs and symptoms
   1. Dysuria, frequency, urgency
   2. CVA/back pain
   3. Fever/chills
   4. Abdominal pain
   5. Nausea/vomiting

B. Etiology: E. coli—80%, also Proteus, Klebsiella, Enterobacter
C. Evaluation: Urinalysis and consider culture. Pyuria almost always present, gram negative bacteria, WBC casts may be present
D. Indications for hospitalization
   1. Nausea/vomiting
   2. Ill appearing/dehydrated
   3. Age > 65
   4. Pregnancy
   5. Immunosuppression

E. Outpatient treatment
   1. Fluoroquinolones:
      a. Ciprofloxacin 500mg BID or Cipro XR 1g QD × 7 days
      b. Levofloxacin 750 mg QD × 5 days
   2. TMP-SMX 160/800 mg (1 DS tab) BID × 14 days
   3. Oral β-lactams × 10–14 days. Use only when other recommended agents cannot be used. If it is used, an initial IV dose of 1g Ceftriaxone or a 24-h dose of Aminoglycoside is recommended

III. COMPLICATED UTIs
A. Complicated UTIs occur in the presence of structural abnormalities and in certain patient populations. In these cases, pathogens are more variable and may be more resistant to ATBs
   1. Abnormalities may include vesicourethral reflux, stones or obstruction
   2. Patient populations at risk include patients with diabetes, sickle cell disease, polycystic kidneys, renal transplant recipients, patients on immunosuppressive therapy, pregnancy, neurologically impaired

B. Evaluation: Obtain urinalysis and urine cultures and sensitivities
C. Treatment with Fluoroquinolone or TMP-SMX (as above): Begin while awaiting culture and sensitivities
D. Hospitalization: Severely ill patients should be hospitalized and covered for Pseudomonas and Enterococcus
IV. RECURRENT UTIs

A. Epidemiology: Occur in ~20% of young women
   1. Etiology: 90% are due to exogenous reinfection, typically months apart. Since rarely due to anatomic or functional abnormalities or urinary tract, imaging studies are of little use. Inquire about hygiene, diaphragm use, wiping pattern (back to front) and use of hot tubs. If diaphragm/spermicide use, consider another form of contraception
   2. Evaluation: Obtain culture and sensitivity

B. Management
   1. Initiate with a broader-spectrum antibiotic such as a Fluoroquinolone
   2. Episodes of UTIs that occur at least 1 month after successful treatment of a UTI should be treated with a first-line short-course regimen
   3. If the recurrence is within 6 months, consider a first-line agent other than the one that was used originally, especially if TMP/SMX was used, because of possible resistance
   4. Non-antibiotic preventive strategies
      a. Abstinence or reduction in frequency of intercourse
      b. If spermicides are used, change to another method of contraception
      c. Change behaviors: Urinate soon after intercourse, drink fluids liberally, not routinely delay urination, wipe front to back after defecation, avoid tight-fitting underwear, avoid douching
      d. Drink cranberry juice, capsules, or tablets
      e. Use topical Estrogen
      f. Use Adhesion blockers (D-mannose, available in health-food stores)
   5. Antibiotic prophylaxis: Reduces risk of recurrence by about 95%
      a. Self-diagnosis and self-treatment: A first-line antibiotic regimen is prescribed for future use. The patient is educated to take it at onset of UTI symptoms
      b. Postcoital antibiotic prophylaxis: Single dose of antibiotic as soon as feasible after intercourse
         i. Nitrofurantoin 50–100mg
         ii. TMP/SMX 40/200mg or 80/400mg
         iii. TMP 100mg
         iv. Cephalexin 250mg
      c. Continuous antibiotic prophylaxis: Daily bedtime dose (except Fosfomycin)
         i. Nitrofurantoin 50–100mg
         ii. TMP/SMX 40/200mg (3×/wk is also effective)
         iii. TMP 100mg
         iv. Cephalexin 125–250mg
         v. Fosfomycin 3g every 10 days
            • Long-term exposure to Nitrofurantoin may cause rare toxic effects which include pulmonary hypersensitivity, chronic hepatitis, and peripheral neuropathy

V. UTIs IN YOUNGER MEN

A. Rare if < 50 years. It used to be thought that UTIs in men were caused by urologic abnormalities, but now studies suggest that these UTIs are due to the same strains of E. coli that affect women. Need to differentiate from prostatitis and STD by obtaining a good sexual history and performing a rectal exam
B. Patients present with symptoms of cystitis, but may mimic urethritis with urethral discharge. Obtain urine culture and sensitivity on all patients. If there is urethral discharge, obtain culture before obtaining urine specimen
C. Risk factors: Homosexuality, sexual partner with vaginal colonization by uropathogen, immunosuppressed patients, bladder outlet obstruction
D. Adult men who respond to ATBs with their first UTI do NOT need further urologic evaluation. Subsequent UTIs do need further work-up
E. If indicated, further workup includes renal ultrasound, IVP, helical CT, or cystourethrogram
F. Treat with 7 day course of ATBs

VI. CATHETER-ASSOCIATED URINARY TRACT INFECTION (CA-UTI)

A. Prevention: Sterile insertion, prompt removal, and use of a closed collecting system
B. **Bacteriuria:** If catheter is in > 30 days, most patients will have bacteriuria
   1. Intermittent catheterization has resulted in lower rates of bacteriuria than long-term indwelling catheter
   2. Distinguish between bacteriuria and infection (pain, fever, CVA tenderness, etc.)

C. **Management**
   1. If the catheter has been in place >2 wk at the onset of CA-UTI and is still indicated, the catheter should be replaced. Obtain urine culture from the freshly placed catheter prior to antibiotic therapy
   2. If use of the catheter can be discontinued, obtain a culture of a voided midstream urine specimen prior to the antibiotic therapy to help guide treatment
   3. Urine cultures are used to confirm that an empiric therapy provides appropriate coverage and to allow tailoring of therapy base on susceptibility data
   4. Antibiotic treatment is indicated for symptomatic patients with culture showing >100,000 CFU. Treat with a **Fluoroquinolone** (*Ciprofloxacin* or *Levofloxacin*)
   5. No treatment for patients with asymptomatic bacteriuria. Antibiotic treatment may be considered in patients with asymptomatic bacteriuria that persists 48 hr after removal of a short-term indwelling catheter
   6. Duration of treatment
      a. 7 days for patients with CA-UTI who have prompt resolution of symptoms and 10–14 days for those with a delayed response, regardless of whether the patient remains catheterized or not
      b. 5-day regimen of **Levofloxacin** for patients with CA-UTI who are not severely ill
      c. 3-day antibiotic regimen for women aged ≤65 y who develop CA-UTI without upper UTI symptoms after an indwelling catheter has been removed

VII. **ASYMPTOMATIC BACTERIURIA**
   A. Treat patients with asymptomatic bacteriuria prior to traumatic urologic procedures with mucosal bleeding
   B. Pregnant women with asymptomatic bacteriuria are at an increased risk for adverse outcome
      1. Pregnant women should be screened for bacteriuria by urine culture at least once in early pregnancy
      2. They should be treated if test results are positive
      3. Oral antibiotics: *Amoxicillin/Clavulanate, Cefuroxime (Ceftin)*, or *Nitrofurantoin*
      4. The duration of antibiotic therapy should be 3–7 days
      5. Periodic screening for recurrent bacteriuria should be undertaken following therapy

**CLINICAL PEARLS**
- Dysuria may also be secondary to urethritis infections, irritant, contact, vaginitis, prostatitis, renal stone, hematuria, or concentrated urine
- Children/infants may present with fever and/or irritability instead of urinary symptoms
- Leukocytes and/or leukocyte esterase may be from vaginal leukocytes and not from cystitis

**References**
79. Hematuria

Management of Common Ambulatory Conditions

Daniel M. Neides, MD

I. DEFINITION: The presence of red blood cells (RBCs) in the urine

II. INDICATIONS FOR WORKING-UP HEMATURIA
A. > 3 RBCs/HPF on 2 of 3 clean catch specimens
B. 1 episode of gross hematuria
C. 1 episode of large microhematuria (> 100 RBCs/HPF)

III. DIFFERENTIAL DIAGNOSIS
A. ABC mnemonic:
   A = Anatomic (renal cysts, AV malformation, obstruction with hydronephrosis, BPH)
   B = Boulders (nephrolithiasis, hypercalciuria, hyperuricosuria)
   C = Cancer (renal cell, bladder, prostate in adults; Wilms' tumor or leukemia in children)
   D = Drugs (prescribed and illicit drugs)
   E = Exercise (contact and noncontact sports)
   F = Familial or foreign body (indwelling catheter, trauma, Alport's syndrome—family history of deafness and renal disease)
   G = Glomerulonephritis (post-strep, Goodpasture's, SLE, Berger's, Henoch-Schönlein purpura)
   H = Hematology (hemoglobinopathies, coagulopathies)
   I = Infection (bacterial, viral or fungal)
B. Most common etiology in elderly: Men–BPH; women–squamous metaplasia of the trigone

IV. HISTORY
A. Genitourinary history
   1. Dysuria, nocturia, or increased frequency
   2. Vaginal or penile discharge (obtain sexual history)
   3. Recent trauma or vigorous exercise
   4. Previous urologic surgery
   5. Flank pain or prior nephrolithiasis
   6. Last menstrual period
B. Painful vs. painless hematuria
   1. Etiologies of painful hematuria: UTI, endometriosis, nephrolithiasis, papillary necrosis, obstruction, passage of clots
   2. Etiologies of painless hematuria: Bladder tumor, staghorn calculus, polycystic kidneys, hydronephrosis, sickle cell anemia, hypercalciuria, anticoagulation
C. Recent Infections
   1. Fever, sore throat, or rash
   2. Tooth extraction or other invasive procedures
   3. Recent travel (schistosomiasis)
D. Relation of gross hematuria to urinary stream
   1. Initial: Distal urethra
   2. Terminal: Bladder neck or prostatic urethra
   3. Total: Upper tract or bladder proper
E. Clots
   1. Large and thick: Bladder
   2. Small and stringy: Ureter (upper tract)
F. Family history
   1. Renal disease
   2. Sickle cell anemia
   3. Deafness (Alport's syndrome—familial nephritis)
   4. Bleeding disorders (hemophilia, von Willebrand's disease, Vitamin K deficiency, liver disease)
G. Meds: Many drugs may cause hematuria (including Cyclophosphamide, Warfarin (Coumadin), NSAIDs, Aspirin, PCN)
H. Risk factors for urologic cancer: Age > 40, tobacco use, exposure to rubber or aniline dyes, schistosomiasis, pelvic radiation, family history of urologic cancer, or analgesic abuse

V. PHYSICAL EXAMINATION
A. General: Temperature and vital signs
B. Oropharynx: Tonsillar enlargement
C. Abdomen: Masses, hepatomegaly, or suprapubic tenderness
D. Back: CVA tenderness
E. Extremities: Supraclavicular, axillary, or inguinal adenopathy
F. Skin: Rash or ecchymoses
G. Rectal: Masses and prostate size, guaiac stool

VI. EVALUATING HEMATURIA
Directed by results of the history and physical exam: Processes which may yield a false positive dipstick result include contamination of the urine specimen with menstrual blood, dehydration, exercise, ascorbic acid (Vitamin C) or vitamins, high concentrations of oxidants, foods (beets, rhubarb, fava beans, blackberries), meds (Rifampin, Pyridium, Quinine), and Porphyria

A. Asymptomatic microscopic hematuria
1. Obtain UA and screening chemistries (see below)
2. If negative UA and screening chemistries, repeat UA in 3 months
3. If microscopic hematuria persists, then obtain radiologic study (U/S or IVP, with tomograms) and urologic consult

B. Asymptomatic gross hematuria
1. Obtain UA and screening chemistries (see below)
2. Obtain radiologic study (IVP or U/S) and obtain urologic consult for cystoscopy

C. Laboratory
1. Urinalysis +/- culture and sensitivity
   a. Pyuria, WBC casts (infection)
   b. Proteinuria, RBC casts (glomerular disease)
2. Screening chemistries, as clinically indicated
   a. BUN, creatinine, electrolytes
   b. CBC, platelets, PT/PTT
   c. PSA
3. If evidence of glomerular disease (i.e., presence of proteinuria or RBC casts):
   a. Serum ANA, Anti-GBM (glomerular basement membrane—Wegener’s disease), C3, C4, ASO titers (post-strep), ESR, and serum protein electrophoresis
   b. 24hr urine for protein and CrCl
4. If the microscopic examination indicates an absence of RBCs then an evaluation for hemoglobinuria or myoglobinuria should be initiated

D. Radiology
1. Helical CT: Sensitivity and specificity for evaluation of nephrolithiasis/ureterolithiasis possibly exceeding IVP without the need for IV contrast
2. Renal ultrasound: Good for evaluation of kidney (cystic or solid masses or hydro-nephrosis) but limited evaluation of ureteral disease
3. Intravenous pyelography (IVP)—rarely done due to advent of CT
   a. Useful in defining the anatomy of the urinary tract and evaluation of obstruction. Also gives an estimation of function
   b. Increase sensitivity by adding tomograms or renal CT scan (will detect smaller lesions or those not encroaching the collecting system)
   c. Consider ultrasound if contrast nephropathy is a concern

E. Endoscopy—Cystoscopy: Useful for evaluating the lower urinary tract

F. Pathologic
1. Urinary cytology (low sensitivity, high specificity)
   a. Useful in detecting transitional cell cancer of the bladder (high grade or CIS)
   b. With in situ bladder lesions, cytology can be positive before visualization via cystoscopy
   c. False positives can occur with nephrolithiasis or UTIs
2. Renal biopsy
   a. Indications are unclear
   b. May not affect prognosis or treatment unless hematuria is accompanied by HTN, proteinuria, or decreased CrCl

VII. FOLLOW-UP EXAMINATIONS

Patients with a negative initial work-up will need close follow-up

A. Urologic cancer has been found on follow-up exam in 1–3% of patients with microscopic hematuria and 18% of patients with recurrent gross hematuria

B. The following should be considered as long as hematuria persists:
   1. Every 6 months: Urinalysis and cytology
   2. Every year: IVP and cystoscopy

CLINICAL PEARLS

- Patients with gross hematuria have approximately 5 times the yield of life-threatening conditions when compared to those with microhematuria
- Hematuria will be present in about 85% of patients with renal stones
- Serratia marcescens may cause a “red diaper” in healthy infants. Performing a UA proves the absence of hemoglobin in the urine
- Consider factitious hematuria (narcotic seekers complaining of kidney stones or Münchausen’s disease) in patients with persistent undiagnosed hematuria
- Pyridium may cause a red-orange discoloration of alkaline urine
- Most common etiology in elderly men is BPH and in women is squamous metaplasia of the trigone

References

80. PROTEINURIA

I. DEFINITION
A. Normal excretion of protein in urine
   1. ≤ 150mg/day
   2. Total protein excretion comprised of 5–15mg albumin, >30 different plasma proteins, and glycoproteins from distal tubule cells, i.e., Tamm-Horsfall protein (most prevalent, excreted at 50–75mg/day)
B. “Pathologic” proteinuria: ≥150mg/day. Massive proteinuria is defined as >3.5gm/day. This leads to large albumin loss and other manifestations of nephrotic syndrome (edema, hypoalbuminemia, hyperlipidemia)

II. MECHANISM OF PROTEIN LOSS
A. Tubular/Overflow: Low-molecular weight proteins (β2 microglobulin, lysozyme, light chains, insulin) are usually filtered by glomeruli and reabsorbed by tubules. If tubules are damaged (tubular or interstitial disease), these proteins are excreted, usually in the range of 1–3g/24hrs. High serum protein levels can also “overwhelm” tubules and overflow into urine (i.e., Bence-Jones protein associated with multiple myeloma)
B. Glomerular: Normal glomeruli filter little albumin or globulin. Glomerular disease disrupts this barrier; excretion of mostly albumin on urine electrophoresis signifies a glomerular lesion. Urinary excretion of > 2g/24hrs is usually a result of glomerular disease

III. APPROACH TO EVALUATION AND MANAGEMENT
A. If Dipstick > 1(+) proteinuria, then collect 24hr urine
B. If proteinuria > 2g/24hr
   1. History: Pre-existing disease, HIV risk factors, systemic complaints (fatigue, polydipsia, polyuria, back pain, joint pain, weight loss, rash), family history (diabetes, polycystic kidney disease)
   2. Physical exam: Blood pressure, weight, funduscopic exam, edema, skin and joint exam (vasculitis/rheumatologic disease), ophthalmologic exam for diabetic retinopathy
   3. Labs
      a. Microscopic exam of urine sediment (casts, crystals)
         i. Casts: Formed when proteins gel inside renal tubules, trapping WBCs and RBCs
            aa. Hyaline casts: Found with concentrated urine, fever, diuretic use
            bb. RBC casts: Glomerulonephritis
            cc. WBC casts: Pyelonephritis, interstitial nephritis
            dd. Renal tubular casts: ATN, interstitial nephritis
            ee. Coarse granular casts: Degeneration of cast with cellular elements, non-specific
            ff. Broad waxy casts: Chronic renal failure. Stasis in collecting tubule
         ii. Crystals: Should be visualized when urine is freshly voided and still warm. Uric acid, phosphate, and oxalate crystals are seen in normal patients as well as stone formers
      b. BUN and creatinine, CBC
      c. Serum protein immunoelectrophoresis (SPE) to identify any paraproteins in the serum which could be overwhelming the tubules. Obtain urine protein electrophoresis simultaneously to quantify the amount of each protein type in the urine (important to consider in patient age >40)
      d. ANA, Hepatitis B, Hepatitis C, cryoglobulins, complement levels (C3 and C4) to screen for vasculitis as etiology of glomerular damage (depending on patient’s associated symptoms)
      e. HIV test
80. Proteinuria

Management of Common Ambulatory Conditions

f. Blood glucose, Hemoglobin A1C
g. Blood cultures: Screen for subacute bacterial endocarditis (can cause only pro-
tenuria and/or hematuria)

C. If proteinuria < 2g/24hrs
   1. History: Recent fever, increase in exercise, other systemic complaints (back pain or
      other bone pain, fatigue) to screen for multiple myeloma
   2. Physical: Same as above
   3. Labs: Same as above
   4. Transient proteinuria
      a. Associated with fever, stress, exercise (within last 48hrs)
      b. Recheck after confounding factors have resolved
      c. If <150mg/24hrs, then no work-up
      d. If >150mg/24hrs, then check yearly BP, UA, and Cr
   5. Orthostatic proteinuria: Usually a benign process
      a. <1g/24 hrs; if greater, should consider other etiologies
      b. More common in children and adolescents
      c. Can obtain urine dipstick on first void in AM, then check again after patient has
         been upright for 2hrs. Or do a split 24hr urine collection (16hrs daytime speci-
         men and an 8hrs overnight specimen)
      d. Should follow yearly BP, UA, and creatinine, especially in children

D. Nephrotic syndrome
   1. Definition: Proteinuria >3.5g/24hrs, hypoalbuminemia (serum albumin <3.0g/dL),
edema, and hyperlipidemia (fasting level >200)
   2. Common end point due to a variety of disease processes: DM, amyloidosis, SLE, idiopathic
      renal disease such as focal glomerular sclerosis, membranous nephropathy, nil disease, etc.
      Arises due to an alteration in the permeability of the glomerular capillary wall
   3. Common to all diseases causing nephrotic syndrome is the presence of oval fat bodies seen
      on microscopic exam of urine; caused by degenerating tubular epithelial cells filled with
      cholesterol esters. Under polarized light will appear as “Maltese Crosses”
   4. Loss of antithrombin III and other proteins can lead to a hypercoagulable state, particularly
      venous involvement (DVT, PE, renal vein thrombosis)

IV. SPECIFIC DISEASES

A. Diabetes Mellitus
   1. Most common cause of end-stage renal disease in US. Higher incidence of renal
      complications in Hispanics, blacks, and Native Americans
   2. 20–30% risk of developing diabetic nephropathy
   3. Early renal changes of increased GFR, increased renal blood flow, and renal
      hypertrophy can be reversed with good glycemic control. Sustained hyperglycemia
      and HgbA1c > 9 correlates with hyperfiltration and hypertrophy
   4. Recommendation: Yearly urine microalbuminuria screening. Allows for detection of
      small amounts of albumin which are not detected on routine urine dipstick test.
      Persistent or increasing microalbuminuria indicates early diabetic nephropathy
   5. 24hr urine should be obtained if urine microalbumin screen is positive
   6. ACE inhibitor should be initiated in both hypertensive and normotensive type 1
      diabetic patients with urine microalbuminuria. Blood pressure should be aggressively
      reduced to < 130/80. Check creatinine and potassium 1 week after initiating ACE
      inhibitor. In hypertensive Type 2 diabetic patients with microalbuminuria, ACE
      inhibitors and ARBs have been shown to delay progression to macroalbuminuria;
      ARBs have been shown to delay the progression of nephropathy in patients with Type
      2 diabetes, hypertension, and macroalbuminuria
   7. Blood glucose should also be aggressively controlled to delay progression to persist-
      ent proteinuria
   8. Microalbuminuria is highly predictive for subsequent retinopathy development

B. Hypertension
   1. Hypertensive patients constitute 20% of the dialysis population. The 2 groups at
      highest risk for hypertensive ESRD are blacks of all ages and the elderly

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2. A complete urinalysis should be performed yearly on all hypertensive patients. If positive for protein, a 24hr urine should be obtained. Other causes of proteinuria should also be considered. In addition to aggressive blood pressure management, patient should follow a no-added salt restriction.

3. Meds: Diuretics and ACE inhibitors are most beneficial for patients with renal damage secondary to hypertension.

4. Consider renal artery stenosis as a possible diagnosis in elderly hypertensives with unexplained deterioration of renal function.

**CLINICAL PEARLS**

- In patients with proteinuria and altered renal function, try to avoid NSAIDs.
- Smoking cessation has been shown to decrease albumin excretion.
- When to refer to a nephrologist: Proteinuria greater than 1g/24hrs, unless the etiology is known (i.e., diabetes mellitus) and already being aggressively treated.
- Proteinuria on initial dipstick analysis is found in as high as 17% of selected populations; < 2% have serious and treatable urinary tract disorders.

**References**


David Beckstead, MD
Daniel M. Neides, MD
Michael B. Weinstock, MD

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**81. BENIGN PROSTATIC HYPERPLASIA**

**DEFINITION:** Nodular enlargement of the prostate occurring in the periurethral region of the gland generally among men > 50 yrs.

**I. GENERAL**

A. Is present in 50% of men > 50 and 90% of men > 80 yrs

B. At 75, half of men have symptoms of BPH

C. Pathology of BPH is hyperplastic growth pattern of stroma and epithelium

**II. HISTORY**

A. Lower Urinary Tract Symptoms—must assess for two categories:

1. **Obstructive voiding symptoms:** Delay in initiation, urinary hesitancy, involuntary interruption of stream, weak stream, straining to void, a sensation of incomplete voiding, postvoid dribbling

2. **Hyperactive bladder symptoms:** Nocturia, urinary frequency, urgency, urge incontinence, bladder pain or dysuria

B. Previous surgeries and other therapies used for BPH

C. Symptoms of UTI, cancer (blood in stool or urine, weight loss)

D. Meds which may increase symptoms including diuretics, anticholinergics, opioids, caffeine, OTC decongestants

E. See American Urological Association (AUA) Symptom Index Chart below

F. Family history of prostate cancer

G. History of diabetes, Parkinson's disease, stroke
The AUA Symptom Index

A. For each of the seven questions below, please check the one box that best describes your symptoms. (Note: Numbers within boxes are for health care provider’s use only.)

<table>
<thead>
<tr>
<th>Over the past month...</th>
<th>Not at All</th>
<th>Less Than 1 Time in 5</th>
<th>Less Than Half the Time</th>
<th>About Half the Time</th>
<th>More Than Half the Time</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How often have you had a sensation of not emptying your bladder completely after you finished urinating?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. How often have you had to urinate again less than 2 hours after you finished urinating?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. How often have you found you stopped and started again several times when you urinated?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. How often have you found it difficult to postpone urination?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. How often have you had a weak urinary stream?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. How often have you had to push or strain to begin urination?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7. How many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?</td>
<td>0 (None)</td>
<td>1 (1 time)</td>
<td>2 (2 times)</td>
<td>3 (3 times)</td>
<td>4 (4 times)</td>
<td>5 (5 or more times)</td>
</tr>
</tbody>
</table>

Instructions to Health Care Provider: To calculate the patient’s total AUA Symptom Score, add up the numbers for all boxes checked in questions 1 through 7. AUA Symptom Score: ________ Degree of Severity: □ Mild (0-7) □ Moderate (8-19) □ Severe (20-35)


III. PHYSICAL EXAM

A. Abdominal exam (distended bladder)
B. Digital rectal exam for enlargement. Note that prostate size on exam correlates poorly with symptoms, but correlates well with potential response to therapy (prostates ≥40mL respond better to 5 α-reductase inhibitors). Consistency of prostate is rubbery, firm, but not hard or nodular.
C. Focused neurological exam

IV. INDICATIONS FOR INTERVENTION IN BPH

A. Urinalysis (infection or hematuria)
B. Consider serum creatinine or postvoid residual only if urinary retention is severe
C. Prostatic specific antigen—Optional but many national organizations have recommended against as there is a significant increase in morbidity and expense and no significant decrease in mortality. The risks and benefits should be discussed with the patient and the strategy of “shared decision making” should be employed
D. Consider renal US to evaluate for hydronephrosis

V. MANAGEMENT

A. Behavioral: No fluids after dinner, no caffeine after noon, decrease or stop alcohol; minimize potential exacerbating meds. Timed voiding and double voiding
B. Watchful waiting: Progression is not inevitable. 31–55% will improve with no therapy. Approximately 7% will develop urinary retention over the next 4yrs

C. Medical therapy

1. General Algorithm: Gradually increase doses over 4–6 weeks to decrease orthostatic effects. Note: α-adrenergic antagonists work fastest and 5α-reductase inhibitors require long-term therapy.
   a. Predominantly obstructive voiding symptoms:
      i. Small gland (<40cc) and/or PSA <1.5ng/mL: use α-blockers
      ii. Large gland (≥40cc), and/or PSA >1.5ng/mL: use α-blocker and/or 5α-reductase inhibitor (combination therapy has been shown to be more effective than monotherapy, but may be limited due to increased side-effects)
   b. Mixed obstructive voiding and bladder hyperactivity symptoms:
      i. Use combination antimuscarinic and α-blocker therapy

2. α-adrenergic antagonists: Takes 2–4 weeks for full effect
   a. Selective (theoretically less extra-gonadal side-effects)
      i. Tamsulosin (Flomax): 0.4mg to be taken ½ hr after the same meal each day and may increase to 0.8mg after 2–4 wks
      ii. Silodosin (Rapaflo): 8 mg daily with a meal
   b. Nonselective (theoretically more extra-gonadal side-effects)
      i. Doxazosin (Cardura): Start with 1mg QHS for 7 days. If well tolerated, gradually increase dose to 8mg QD
      ii. Terazosin (Hytrin): Start with 1mg QHS for 7 days. If well tolerated, gradually increase dose to 20mg QD
      iii. Alfuzosin (Uroxatrol): 10mg once daily with food
   c. Side effects
      i. Gonadal: Erectile dysfunction, retrograde ejaculation
      ii. Extra–gonadal: Dizziness, orthostatic hypotension (avoid taking within 4 hours of a Phosphodiesterase inhibitor), fatigue, headache, nasal congestion, dry mouth

3. 5α-reductase inhibitors: Decrease conversion of testosterone to dihydrotestosterone. Takes 2–6 months for full effect
   a. Finasteride (Proscar): 5mg PO QD
   b. Dutasteride (Avodart): 0.5mg PO QD
   c. Side effects: Erectile dysfunction, decreased libido, abnormal ejaculation, gynecomastia, decreases PSA level by 50%, 6% decreased risk of prostate cancer (but if patient does get prostate cancer these medicines increase the risk of it being a high-grade cancer)

4. Antimuscarinic agents: Takes 12 weeks for full effect
   a. Selective (for the bladder detrusor muscle, less extra–urinary anticholinergic side effects)
      i. Solifenacin (Vesicare): 5–10mg PO daily
      ii. Darifenacin (Enablex): 7.5–15mg PO daily
   b. Nonselective (more extra–urinary anticholinergic side effects)
      i. Oxybutynin (Ditropan): 5mg PO BID, or 5–20mg CX PO daily
      ii. Trospium (Sanctura): 20mg PO BID, or 60mg XR PO daily
      iii. Tolterodine (Detrol): 2mg PO BID, or 2–4mg XR PO daily
      iv. Fesoterodine (Toviaz): 4–8mg PO daily

5. Phosphodiesterase–5 inhibitor: Only one has FDA approval for BPH. Works through smooth muscle relaxation (the Phosphodiesterase–5 enzyme is located in prostate tissue). Takes 4 weeks for full effect
   a. Tadalafil (Cialis): 2.5–5mg daily

6. Alternative Therapies: Saw Palmetto (Serenoa repens), Rye grass pollen extract (Cernilton), Pygeum
   a. All have conflicting evidence, although each has several poorly designed studies showing efficacy. The American Urologic Association does not endorse the use of any of these products for the treatment of BPH

D. Surgical therapy: Indications include medical treatment failure, obstructive renal failure, bladder stones, chronic UTIs
1. Transurethral resection of the prostate (TURP)—improvement in 75–96% with impotence in 5–10% and retrograde ejaculation in 75%
2. Transurethral incision of the prostate (TUIP)
   a. Patients with moderate to severe symptoms and small prostates
   b. Improvement in 78–83%, with less retrograde ejaculation than TURP (25%)
3. Open prostatectomy
   a. Usually done when prostate is too large to be done by TURP/TUIP
   b. Improvement in 94–100%
   c. Impotence in 5–39%, incontinence in <1%, retrograde ejaculation in 36–95%

E. Minimally invasive therapy
1. Laser Prostatectomy: Advantages include less blood loss and outpatient surgery. Disadvantages include lack of tissue for pathology and more irritative voiding complaints
2. Transurethral needle ablation of the prostate (TUNA): A catheter is placed in the urethra and radiofrequencies are used to heat the tissue resulting in coagulative necrosis
3. Transurethral electrovaporization of the prostate: High current densities cause a cavity in the prostatic urethra
4. Hyperthermia: Microwave hyperthermia with transurethral catheter
5. High-intensity focused ultrasound (HIFU): Thermal tissue ablation
6. Intraurethral stents: For patients with poor surgical risk
7. Transurethral balloon dilation of the prostate: Most effective in small prostates

CLINICAL PEARLS
- Utilize the symptom assessment to quantitate and follow prostatism
- For mild symptoms, reassurance and reassessment are appropriate management
- Distinguish between overactive bladder and obstructive symptoms to guide management
- Of all these medicines, 5 α-reductase inhibitors take the longest to start working, but they are the only BPH medicines that have been shown to decrease the risk of acute urinary retention and the rate of progression to surgical therapy

References
82. CA\text{LCIUM DISORDERS}

— PART ONE: HYPERCALCEMIA —

I. DEFINITION: Total calcium $>10.5\text{mg/dL}$ or ionized calcium $>5.3\text{mg/dL}$. False positives may be caused by hemoconcentration during blood collection or elevation in serum proteins, particularly albumin

II. ETIOLOGY

A. Malignancy
1. Osteolytic hypercalcemia: Tumor cell products, such as cytokines, act locally to stimulate osteoclastic bone resorption. Occurs with extensive bone involvement by tumor, usually due to breast cancer, myeloma, and lymphoma
2. Humoral hypercalcemia: Tumor products act systemically to stimulate bone resorption and to decrease calcium excretion. Most often caused by squamous cell carcinoma of the lung, head and neck, or esophagus, or by renal, bladder, or ovarian cancer

B. Primary hyperparathyroidism: Most common etiology in ambulatory care with annual incidence of 2 in 1000. 85% of cases are due to an adenoma of a single gland, 15% to hyperplasia of all 4 glands, and 1% to parathyroid carcinoma

C. Sarcoidosis (occurs secondary to increased absorption of calcium) and other granulomatous diseases

D. Paget’s disease

E. Immobilization (due to suppression of the parathyroid-vitamin axis)

F. Vitamin D intoxication (due to increased absorption of calcium) and milk-alkali syndrome

G. Meds: Thiazide diuretics (increased renal reabsorption of calcium) and Lithium

H. Other causes: Addison’s disease, renal failure, familial hypocalciuric hypercalcemia, hyperthyroidism, Vitamin A intoxication, disseminated SLE, pheochromocytoma, prolonged immobilization

I. Multiple endocrine neoplasias (MEN) syndromes
1. MEN I: Parathyroid, pituitary and pancreatic islet cell adenoma
2. MEN IIA: Hyperparathyroid, pheochromocytoma, medullary cell CA of the thyroid

III. HISTORY AND PHYSICAL EXAM: Most patients are asymptomatic at time of diagnosis. Symptoms vary with degree of hypercalcemia and rapidity of development, but usually evident when serum calcium $>12\text{mg/dL}$

A. General: Weakness, fatigue, pruritus, hypertension, myopathy, weight loss, night sweats (malignancy)

B. Duration of symptoms (primary hyperparathyroidism is usually etiology of symptoms present $>6$ months without obvious cause)

C. Diet: Intake of milk and antacids (milk-alkali syndrome), thiazides, Vitamin A or D, Lithium

D. Evidence of Neoplasm: (e.g., breast or ovarian) Ectopic soft tissue calcification (may be seen when calcium levels rise $>13\text{mg/dL}$)

E. CNS: Confusion, depression, psychosis, stupor, coma, headache, hyporeflexia, hypotonia, apathy, mental retardation (infants)

F. GI: Constipation, nausea, vomiting, anorexia, abdominal pain (pancreatitis, PUD)

G. GU: Nephrolithiasis, nocturia, polyuria, renal failure (may be seen when calcium levels rise $>13\text{mg/dL}$)

H. Musculoskeletal: Bone pain (metastatic disease, multiple myeloma), deformities, fractures, myopathy, pseudogout, muscle atrophy, bone pain with palpation, proximal muscle weakness

I. Eye: Band keratopathy (found in medial and lateral margin of cornea)
IV. DIAGNOSTIC TESTING
A. Lab tests
1. CBC, electrolytes, BUN, creatinine (renal insufficiency)
2. Ionized calcium, albumin, phosphate, magnesium, alkaline phosphatase
3. 24hr urine calcium
4. Parathyroid hormone (PTH) level: Elevated in more than 90% of patients with primary hyperparathyroidism. Serum PTH levels are suppressed in patients with hypercalcemia due to malignancy or other causes (except familial hypocalciuric hypercalcemia which is distinguished by documenting low urinary calcium clearance)
5. 1, 25–dihydroxyvitamin D level (with history of excessive ingestion of fat soluble vitamins such as Vitamin D)
B. ECG: Shortening of QT interval, wide T waves, Digoxin sensitivity
C. Bone survey: May show subperiosteal bone resorption (PTH excess)
D. Bone scan: May show lytic lesions

V. MANAGEMENT: Differs between acute symptomatic hypercalcemia and chronic hypercalcemia
A. Acute hypercalcemia: Symptomatic patients or those with serum calcium > 13mg/dL are generally admitted for IV therapy and observation
B. Chronic hypercalcemia
1. High fluid intake: Should consume 3–5 L/day of fluids to increase renal calcium excretion
2. Glucocorticoids: Inhibit intestinal absorption of calcium and increases urinary calcium excretion. Effect usually evident after 48–72hrs. Effective in hypercalcemia due to myeloma, hematologic malignancies, breast cancer, Vitamin D intoxication, and sarcoidosis
3. Oral phosphates: Promotes calcium deposition in bone and soft tissue as well as inhibiting GI calcium absorption. Use only in patients with normal renal function
   a. Dose: 1–3g/day in divided doses
   b. E.g., Neutra-Phos, Phos-tabs, Fleet Phospho-soda
   c. Side effects: Diarrhea, nausea, soft tissue calcification
4. Dietary calcium restriction
C. Hypercalcemia due to specific conditions
1. Vitamin D toxicity: Treat with a low calcium diet (<400mg/day). May take up to 2 months for effects of Vitamin D to subside
2. Sarcoidosis: Prednisone 10–20mg/day
3. Primary hyperparathyroidism: Parathyroidectomy is the only effective treatment. Indications for surgery include symptoms of hypercalcemia, nephro lithiasis, bone mass reduction greater than 2 standard deviations, age <50, serum calcium >12mg/dL
4. Malignancy: Interval between detection of hypercalcemia and death is often <6 months

— PART TWO: HYPOCALCEMIA —

I. DEFINITION: Serum calcium <9mg/dL or ionized calcium <4.6mg/dL

II. ETIOLOGY
A. Hypoalbuminemia: Most common cause of low total serum calcium. Each decrease of 1g in serum albumin will decrease serum calcium by 0.8mg/dL, but will not change free (ionized) calcium
B. Renal insufficiency: Decreased production of 1,25-dihydroxyvitamin D, increased serum phosphate levels cause calcium deposits in bone and soft tissue
C. Vitamin D deficiency: Malabsorption, decreased production of 1,25-dihydroxyvitamin D, inadequate intake
D. Hypomagnesemia: Decreased PTH secretion
E. Hyperphosphatemia
F. Drugs: Pentamidine, Ketoconazole, Foscarnet, Cisplatin, Cytosine Arabinoside
G. Other: Acute pancreatitis, rhabdomyolysis, tumor lysis syndrome, pseudohypoparathyroidism (PTH resistance), multiple citrated blood transfusions, sepsis

III. HISTORY AND PHYSICAL EXAM
A. General: Weakness, depression, lethargy
B. Neuro: Paresthesias, impaired cognitive function, seizures
C. Psychiatric: Depression
D. Musculoskeletal
   1. Symptoms consistent with pseudohypoparathyroidism: Short metacarpals and short stature
   2. Symptoms consistent with idiopathic hypoparathyroidism: Hypothyroidism, candidiasis, vitiligo, adrenal failure
   3. Soft tissue calcifications
E. Neurological: Tetany, seizures, psychosis
   1. Chvostek’s sign: Facial twitching after tapping the facial nerve
   2. Trousseau’s sign: Carpopedal spasm after inflation of blood pressure cuff (over the patient’s systolic blood pressure) for 2–3 minutes
F. Cardiovascular: Dysrhythmias, CHF, hypotension
G. Ophthalmologic: Cataracts
H. Meds (listed above)
I. Past medical/surgical history: Previous neck surgery, history of diseases associated with idiopathic hypoparathyroidism (hypothyroidism, adrenal failure) or Vitamin D deficiency
J. Family history of hypocalcemia: Familial hypocalcemia, hypoparathyroidism, or pseudohypoparathyroidism

IV. LABORATORY
A. Ionized calcium and magnesium
B. Phosphorus: Usually elevated in hypocalcemia except in Vitamin D deficiency
C. BUN/creatinine
D. Parathyroid hormone (PTH)
E. Alkaline phosphatase
F. Albumin

V. MANAGEMENT
A. Severe acute hypocalcemia: Admission
B. Chronic hypocalcemia: Objective is to maintain serum calcium levels between 8–9mg/dL. If hypercalciciuria develops at serum calcium levels < 8.5mg/dL, Hydrochlorothiazide 50mg PO QD can be used to reduce urinary calcium excretion
   1. PO: Calcium Carbonate (Tums, Os-Cal, Biocal, Caltrate) 500–1000mg PO TID
   2. Renal failure
      a. Use phosphate binding antacids to reduce hyperphosphatemia (e.g., Amphojel)
      b. Oral calcium supplementation 0.5–1.0g PO TID with meals. Tums provides 500mg elemental calcium and is the least expensive
      c. For long term therapy, Vitamin D supplementation with Calcitriol (Rocaltrol) is best choice for most patients due to its lower risk of toxicity. Initial dose is 0.25µg PO QD. Most patients maintained with 0.5–2.0µg PO QD
   3. Hypoparathyroidism or Vitamin D deficiency: Vitamin D and oral calcium supplementation as noted above
C. Hypomagnesemia
   1. Severe hypomagnesemia (with serum calcium < 0.8mg/dL): Treat as a medical emergency in hospital setting
   2. Chronic hypomagnesemia: Magnesium Oxide 400mg PO BID–QID
**CLINICAL PEARLS**

- Patients who take Digoxin and are hypocalcemic should be monitored on telemetry, as hypocalcemia potentiates Digoxin toxicity
- 20% of patients with gram negative sepsis have hypocalcemia
- Calcium is 2% of the normal body weight

**References**


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**83. Potassium Metabolism**

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**PART ONE: HYPERKALEMIA**

**I. DEFINITION:** Serum potassium ≥5.5 mmol/L

**II. SIGNS AND SYMPTOMS**

A. Patient may have weakness and flaccid paralysis, abdominal distension and diarrhea. Primarily diagnosed by laboratory and ECG changes (see below)

**III. ETIOLOGY**

A. Increased potassium intake: May result from salt substitutes, foods with high potassium content, or iatrogenic parenteral replacement

B. Decreased potassium excretion: Usually due to impaired secretion resulting from either:
   1. Impaired sodium re-absorption—decreased aldosterones (as seen in Addison’s disease, use of potassium sparing diuretics, ACE inhibitors, NSAIDs, Heparin, or Cyclosporine)
   2. Increased chloride reabsorption: Renal insufficiency and diabetic nephropathy
   3. Decreased distal flow rate—seen in protein malnourished patients

C. Intra/Extracellular shift: Metabolic acidosis, insulin deficiency, exercise-induced hyperkalemia, tumor lysis syndrome, rhabdomyolysis, β-blockers, or Digoxin toxicity

D. Tissue damage: Crush injuries, rhabdomyolysis

E. Other causes (mechanism not clear): Lupus nephritis, chronic pyelonephritis, renal transplantation, acute glomerulonephritis

F. Pseudohyperkalemia: Lab error, thrombocytosis and leukocytosis, hemolysis (tourniquets, finger stick, delay between blood draw and analysis in lab)

**IV. EVALUATION:** Electrocardiogram is single most important factor in determining seriousness of patient’s hyperkalemia

A. Review history looking for iatrogenic or physiologic reasons for hyperkalemia

B. Obtain ECG
   1. Earliest changes are peaked T waves, with potassium level >6.5 mEq/L
   2. Potassium level > 7–8 mEq/L results in loss of P waves and widening of QRS complex
   3. Potassium level > 8–10 mEq/L may result in cardiac arrest

C. Repeat test if lab does not correlate with clinical picture

D. Do not delay ECG and/or treatment while waiting for repeat labs to come back!
V. MANAGEMENT

A. Emergency management: Indicated for hyperkalemia associated with cardiac toxicity, muscular paralysis or with severe hyperkalemia (> 6.5–7.0) without ECG changes.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Calcium gluconate 10% or calcium carbonate 5%</td>
<td>1 ampule IV (10 mL = 1 g)</td>
<td>0-5 minutes</td>
<td>1 hour</td>
<td>Stabilizes cardiac membranes</td>
</tr>
<tr>
<td>2. Sodium bicarbonate</td>
<td>1-2 ampules (44-88 mEq) IV</td>
<td>15-30 minutes</td>
<td>1-2 hours</td>
<td>Shifts K+ into cells</td>
</tr>
<tr>
<td>3. Regular Insulin</td>
<td>5-15 units IV</td>
<td>15-60 minutes</td>
<td>4-6 hours</td>
<td>Shifts K+ into cells</td>
</tr>
<tr>
<td>4. D50 (dextrose)</td>
<td>1 ampule (50 g) IV</td>
<td>15-60 minutes</td>
<td>4-6 hours</td>
<td>Works with insulin</td>
</tr>
<tr>
<td>5. Kayexalate*</td>
<td>15-60 g in 20% sorbitol PR or PO</td>
<td>1-4 hours</td>
<td>This is the definitive treatment</td>
<td></td>
</tr>
<tr>
<td>6. Hemodialysis*</td>
<td>— Indicated for refractory cases or in patients with renal failure</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*These are the definitive treatments that will remove potassium from the body. Insulin and D50 should be used together.

Note: Calcium only to be used with ECG changes.

B. Non-emergency management:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kayexalate</td>
<td>PO: 15-30g in 20% sorbitol</td>
<td>Blinds potassium in bowel</td>
</tr>
<tr>
<td></td>
<td>Rectal: 15-60g in 20% sorbitol</td>
<td></td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>Furosemide (Lasix) 40-160mg IV or PO</td>
<td>Increased renal potassium excretion</td>
</tr>
<tr>
<td>Hemo or pento dialysis — Patients in acute or chronic renal failure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


— PART TWO: HYPOKALEMIA —

I. DEFINITION: Serum Potassium level <3.5 mEq/L.

II. SIGNS AND SYMPTOMS

A. Potassium of 2.0–2.5 mEq/L: Muscle weakness, hyporeflexia, fatigue, cramps.

B. Potassium of <2.0 mEq/L: May cause areflexic paralysis, and respiratory insufficiency may occur. Rate at which potassium declines has direct relationship to severity of muscular abnormality.

III. ETIOLOGY OF HYPOKALEMIA

A. Excess renal loss

1. Mineralocorticoid excess: Primary or secondary aldosteronism, renovascular HTN, Bartter’s syndrome
2. Diuresis
3. Chronic metabolic alkalosis
4. ATBs: Gentamicin, Amphotericin B
5. Renal tubular acidosis
6. Hypomagnesemia
7. Other: Acute leukemia, urererosigmoidostomy

B. Gastrointestinal losses: Vomiting, diarrhea

C. ECF→ICF shifts: Acute alkalosis, hypokalemic periodic paralysis, barium ingestion, insulin therapy or increased postprandial secretion of insulin, Vitamin B₁₂ therapy

D. Inadequate intake

IV. EVALUATION

A. Review history looking for iatrogenic or physiologic reasons for hypokalemia.

B. If unexplained hypokalemia (e.g., young patient taking no meds, no history of vomiting), obtain a urinary potassium before repleting (hyperaldosteronism). If patient is hypertensive, obtain a renin and aldosterone level (mineralocorticoid excess).
C. Consider checking ABG (pH and bicarbonate) in the unexplained hypokalemic patient

D. **ECG changes** associated with hypokalemia affect primarily repolarization segments of the electrocardiogram
   1. ST segment depression
   2. T wave inversion
   3. Elevation of the U wave

E. **Hypokalemia** greatly increases the incidence of Digitalis toxicity including junctional rhythms or heart block

V. MANAGEMENT

A. Mild hypokalemia which is not symptomatic can be treated with PO replacement
   1. **K-Dur** 20–40mEq PO QD—Sustained release: Not to be used in critical situations
   2. **Slow-K** 8mEq—Sustained release: Not to be used in critical situations
   3. **K-Lyte** (powder) 25–50mEq PO/NG: May be used for treating hypokalemia acutely

B. If patient is severely hypokalemic (< 3.0), or with evidence of cardiac symptoms, replacement should be IV (on telemetry) with frequent lab checks

C. Potassium deficit by level of serum potassium:
   1. K⁺ = 3.0–3.5 Replace with 50–75mEq KCl
   2. K⁺ = 2.5–3.0 Replace with 100–150mEq KCl
   3. K⁺ = 2.0–2.5 Replace with 150–250mEq KCl

D. If magnesium level is low, **Magnesium Oxide** 400mg PO TID × 3–5 days

**CLINICAL PEARLS**

- Consider replacing magnesium or calcium in patients with refractory hypokalemia because potassium replacement will be ineffective if patient is also hypomagnesemic or hypocalcemic
- Because ECG manifestations of hypokalemia are often subtle, electrocardiogram should not be used as a guide to replacement therapy
- Arrhythmias may be more likely to occur in patients with hypokalemia who are also taking Digoxin
- Total amount of potassium in the body is 50 mcg/kg. About 95% is intracellular

**References**


I. DRUG INTERACTION MECHANISMS
A. Absorption of 1 drug can be reduced by another drug, e.g., Cholestyramine
B. Protein/tissue binding displacement can be important especially if the displacing drug also reduces the elimination of the object drug
C. Metabolism of 1 drug can be enhanced by an “enzyme-inducing” agent, e.g., Phenobarbital
D. Many commonly prescribed meds interfere with or are metabolized by the hepatic cytochrome P450 enzyme system. The CyP450 system refers to a collection of iso-enzymes that are responsible for the oxidative metabolism of many endogenous and exogenous compounds
E. Altered renal excretion can be caused by reduced excretion or change in urinary pH
F. Pharmacodynamic interaction occurs when drugs with either additive or antagonistic properties are given concomitantly

II. SELECTED CLINICALLY RELEVANT DRUG INTERACTIONS
The following table is not comprehensive. Drugs in parentheses are important examples of that class of drug

<table>
<thead>
<tr>
<th>Object Drug</th>
<th>Precipitant Drug</th>
<th>Effect/Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors, ARBs Absorbers</td>
<td>K⁺-sparking diuretics (Amiloride, Spironolactone), K⁺ supplements</td>
<td>↑ Serum K⁺, especially in the presence of significant renal impairment. Monitor serum K⁺</td>
</tr>
<tr>
<td>NSAIDs, ARBs</td>
<td>NSAID plus diuretic</td>
<td>↑ Anti-inflammatory plasma levels. Monitor patient carefully if used concurrently</td>
</tr>
<tr>
<td>Antihypertensives, Type 1C: Enalapril, Lisinopril, Quinapril</td>
<td>Enzyme inhibitors: Cimetidine, Quinidine, SSRI (Fluoxetine, Paroxetine)</td>
<td>↑ Antiarrhythmics plasma levels. Monitor patient carefully if used concurrently</td>
</tr>
<tr>
<td>Antiarrhythmics, Type 1C: Encainide, Mexiletine, Propafenone</td>
<td>Enzyme inhibitors: Cimetidine, Quinidine, SSRI (Fluoxetine, Paroxetine)</td>
<td>↑ Antiarrhythmics plasma levels. Monitor patient carefully if used concurrently</td>
</tr>
<tr>
<td>Antihyperglycemics: Insulin, Sulfonylureas</td>
<td>ß-blockers, e.g. Nadolol, Propranolol, Timolol</td>
<td>Alternation of glycemic control and/or masking of some signs of hypoglycemia (e.g. tachycardia, tremor)</td>
</tr>
<tr>
<td>Antiarrhythmics: Itraconazole, Ketoconazole</td>
<td>Enzyme inhibitors: Ketoconazole, Itraconazole, Nelfinavir</td>
<td>↑ Benzodiazepine levels, may lead to unexpected CNS impairment or other toxic effect. Contraindication</td>
</tr>
<tr>
<td>Antiarrhythmics: Apixaban, Rivaroxaban</td>
<td>Enzyme inhibitors: Ketoconazole, Itraconazole, Nelfinavir</td>
<td>↑ Benzodiazepine levels, may lead to unexpected CNS impairment or other toxic effect. Contraindication</td>
</tr>
<tr>
<td>ß-blockers, non-selective: Nadolol, Propranolol, Timolol</td>
<td>Epinephrine</td>
<td>↑ Risk of bradycardia and AV block. Avoid combination</td>
</tr>
<tr>
<td>Carbamazepine (CBZ)</td>
<td>Enzyme inhibitors: Cimetidine, Erythromycin, Diltiazem, Fluoxetine, INH, Propoxyphene, Verapamil</td>
<td>↑ Serum CBZ levels significantly within 2–3 days. Monitor serum CBZ levels and signs of CBZ toxicity (e.g. drowsiness, ataxia, nystagmus, blurred vision, nausea)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Enzyme inhibitors: Cimetidine, Erythromycin, Diltiazem, Fluoxetine, INH, Propoxyphene, Verapamil</td>
<td>↑ Serum levels. Antidromic atrioventricular block, and accelerated junctional rhythm may occur. Consider reducing Digoxin dosage</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Renal and non-renal clearance: Antiarrhythmics (Amiodarone, Propafenone, Quinidine), Ca-channel blockers (Verapamil)</td>
<td>↑ Digoxin levels. Amiodarone and Quinidine can cause a ~2-fold increase in Digoxin levels. Effects of Propafenone and Verapamil may be less. Patients starting on these drugs should have Digoxin levels reduced by 30%. Additional dosage adjustment may be necessary. Monitor Digoxin concentrations and signs of toxicity (e.g. GI upset, CNS disturbances, arrhythmias)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>K⁺-wasting diuretics (Furosemide, HCTZ)</td>
<td>↑ Serum Digoxin levels. Monitor serum K⁺ and risk of TdP</td>
</tr>
<tr>
<td>Dofetilide (Tikosyn)</td>
<td>Renal clearance: Cimetidine, Trimethoprime (alone or TMP/SMZ), Ketoconazole (Nizoral), Megestrol (Megaject), Prochlorperazine (Compazine)</td>
<td>↑ Risk of TdP. Monitor K⁺ level and risk of TdP</td>
</tr>
<tr>
<td>Dofetilide (Tikosyn)</td>
<td>Drugs that prolong QTc interval (e.g., Sotalol, Amiodarone, TCAs, Phenothiazine, Macrolides)</td>
<td>↑ Risk of TdP. Monitor K⁺ and Mg²⁺ closely</td>
</tr>
</tbody>
</table>

(Chart continued on next page)
### Selected Clinically Relevant Drug Interactions (continued)

<table>
<thead>
<tr>
<th>Object Drug</th>
<th>Precipitant Drug</th>
<th>Effect/Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG CoA reductase inhibitors (not Pravastatin) esp. Simvastatin</td>
<td>Azoles (Itraconazole, Ketocconazole, Cyclosporine, Diltiazem, Verapamil, Erythromycin, Fenofibrate (Tricor), Gemfibrozil (Lopid), Niacin</td>
<td>Myopathy, ↑ risk of rhabdomyolysis. Close monitoring is required</td>
</tr>
<tr>
<td>Lithium</td>
<td>Cold/cough medicines (Dexmethorphan, Sympathomimetics), Meperidine, SSRI's (e.g. Fluoxetine, Paroxetine, Sertraline), Food rich in tyramine (e.g. cheese, red wine, smoked fish)</td>
<td>Severe reactions (shivering, seizures, agitation, delirium, and death). Avoid combination</td>
</tr>
<tr>
<td>MAO inhibitors</td>
<td>Cold/cough medicines (Dexmethorphan, Sympathomimetics), Meperidine, SSRI's (e.g. Fluoxetine, Paroxetine, Sertraline), Food rich in tyramine (e.g. cheese, red wine, smoked fish)</td>
<td>↑ Serum Li+ levels within days. Monitor serum Li+ levels and signs of toxicity (e.g. ataxia, nyctagmus, mental impairment)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Enzyme inducers: Carbamazepine, Phenobarbital, Phenytoin, Primidone, Rifampin, L enterohepatic recycling: Ampicillins, Tetracycline, Griesediecklin</td>
<td>↓ Efficacy of oral contraceptives, resulting in breakthrough bleeding or pregnancy. Use another method of contraception</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Enzyme inhibitors: Amiodarone, Cinclididine, Fluconazole, Fluoxetine, Isoniazid, Omeprazole</td>
<td>↑ Serum Phenytoin levels. Monitor serum Phenytoin levels and signs of toxicity (e.g. ataxia, nyctagmus, mental impairment)</td>
</tr>
<tr>
<td>Protease inhibitors: Ritonavir (Norvir), Indinavir (Crixivan), Saquinavir (Invirase), Nelfinavir (Viracept)</td>
<td>See chapter 120, Ambulatory HIV/AIDS Management, for further information</td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>Enzyme inducers: Phenobarbital, Phenytoin, Rifampin</td>
<td>↓ Serum Quinidine levels. Adjust Quinidine dose as needed when initiating or discontinuing enzyme inducers</td>
</tr>
<tr>
<td>Quinolones (e.g., Cipro, Floxin)</td>
<td>Chelating effect: Antacids, iron salts, Sucraltate</td>
<td>↑ Bioavailability of Quinolones. The antibiotic should be given 2 hrs before or 4 hrs after a dose of antacid</td>
</tr>
<tr>
<td>Quinolones: Gatifloxacin (Tequin), Moxifloxacin (Avelox), Sparfloxacin (Zagam)</td>
<td>Antiarhythmic agents Class IA and III (e.g., Dicyclomamide, Procainamide, Quinidine, Sotalol)</td>
<td>↑ Risk of TdP. Concomitant use of Sparfloxacin with class IA and III agents is contraindicated</td>
</tr>
<tr>
<td>Phosphodiesteerase Type 5 inhibitors, Anrafalt (Viagra), Tadafalt (Cialis), Vardenalt (Levitra)</td>
<td>Nitrates</td>
<td>Sildenafil potentiates the vasodilatory effect of circulating nitric oxide, resulting in a significant and potentially fatal fall in BP. Concomitant use is contraindicated</td>
</tr>
<tr>
<td>SSRIs, SNRIs</td>
<td>Triplans (e.g., Naratriptan (Amerge), Rizatriptan (Maxalt), Sumatriptan (Imitrex), Zolmitriptan (Zomig), Tricyclic antidepressants, Tramadol)</td>
<td>Serotonin syndrome (agitation, confusion, diarrhea, fever, and sweating)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Enzyme inhibitors: Cinclididine, Ciprofloxacin, Erythromycin, Fluoxamine, Tacrine, Tricyclics, Verapamil, Zileuton (Zyflo)</td>
<td>↑ Serum Theophylline concentrations, leading to toxicity within 2-3 days. Theophylline dose may need to be adjusted by 30-50%. Monitor serum Theophylline levels and signs of toxicity (e.g. tachycardia, nausea, tremor)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Enzyme inducers: Carbamazepine, Phenobarbital, Phenytoin, Primidone, Rifampin</td>
<td>↑ Serum Theophylline concentrations gradually over 1-2 weeks. Monitor serum Theophylline levels and adjust dose as needed</td>
</tr>
<tr>
<td>Tramadol (Ultram)</td>
<td>Carbamazepine (Tegretol)</td>
<td>↓ Analgesic effect of Tramadol. Seizure risk associated with Tramadol. Avoid combination</td>
</tr>
<tr>
<td>Tramadol (Ultram)</td>
<td>CNS depressants (e.g. alcohol, sedatives)</td>
<td>↓ Risk of respiratory depression. Reduce dose of Tramadol</td>
</tr>
<tr>
<td>Tramadol (Ultram)</td>
<td>CYP2D6 enzyme inhibitors: Quinidine, Fluoxetine, Paroxetine, Amitryptilne</td>
<td>↑ Serum Tramadol levels and ↑ risk of seizures</td>
</tr>
<tr>
<td>Tramadol (Ultram)</td>
<td>MAO inhibitors, SSRIs, TCAs, other Opioids, Neuripreps</td>
<td>↑ Risk of seizure. Also ↑ risk of Serotonin syndrome when use concomitantly with SSRIs or MAO inhibitors</td>
</tr>
<tr>
<td>Tricyclic antidepressants: Amiprilyme, Imipramine, Noriprozine</td>
<td>Enzyme inhibitors: Cinclididine, Fluconazole, Propoxyphene, Quinidine, SSRIs (Fluoxetine, Paroxetine)</td>
<td>↑ Tricyclic antidepressant serum concentrations possibly leading to toxicity. Monitor closely</td>
</tr>
</tbody>
</table>

(Chart continued on next page)
### Selected Clinically Relevant Drug Interactions (continued)

<table>
<thead>
<tr>
<th>Object Drug</th>
<th>Precipitant Drug</th>
<th>Effect/Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (Coumadin)</td>
<td>Acetaminophen (Tylenol)</td>
<td>Inhibits Warfarin metabolism. ↑ INR monitoring in patients taking &gt; 2 g/day regularly</td>
</tr>
<tr>
<td>Warfarin (Coumadin)</td>
<td>Enzyme inhibitors: Amiodarone, Antimicrobials (Quinolones, Erythromycin, Fluconazole, Itraconazole, Ketoconazole, Metronidazole, Rifampin, Sulfonamides), Cimetidine, Cisapride, Diclofenac, Fosfomycin, Furosemide, Hypoglycemic agents, Monoclonal antibodies, Omeprazole, Propafenone, Zafirlukast (Accolate), Zileuton (Zyflo), inhibitors of platelet function: NSAIDs, Salicylates</td>
<td>Unknown mechanism: Androgens, Clofibrate, Gemfibrozil (Lopid), thyroid hormones. ▲ Hypoprothrombinemic response of Warfarin and ↑ risk of bleeding. Concurrent use of Clofibrate should be avoided if possible due to the difficulty in the management of these interactions. Amiodarone may produce a large increase in INR over a period of weeks. When Amiodarone is added to therapy, a 50% reduction in Warfarin dose may be needed. NSAIDs also increase the risk of GI bleeding in anticoagulated patients. Use conservative Warfarin dosing, monitor INR more frequently, and monitor for clinical sign of bleeding. It may take 7-10 days to reach new steady state anticoagulant response.</td>
</tr>
<tr>
<td>Warfarin (Coumadin)</td>
<td>GI absorption: Bile acid Sequestrants (Cholestyramine, Colestipol)</td>
<td>↓ Hypoprothrombinemic response of Warfarin. Monitor INR more frequently and watch for excessive anticoagulant effect when the inducer is discontinued. Avoid use of Rifampin with Warfarin if possible due to the difficulty in the management of these interactions.</td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td>Antimicrobials Class 1A and III, Mesoridazine, Thiorthidazine, Chlorpromazine, Droperidol, Pimozide, Sparfloxacin, Gatifloxacin, Moxifloxacin, Halofantrine, Mefloquine, Pentamidine, Arsenic trioxide, Levomepromazine, Dolasetron, or Tacrolimus</td>
<td>↑ Risk of TdP. Concomitant use of these drugs with Dofetilide is contraindicated.</td>
</tr>
</tbody>
</table>

#### III. PREVENTING MEDICATION PRESCRIBING ERRORS

A. Confirm that patient’s weight is correct for weight-based dosages. Write patient’s weight on the prescription
B. Identify drug allergies in patients and reconfirm each time writing a prescription
C. Give patient oral and written instructions without using abbreviations
D. Specify exact dosage strength. When writing for narcotics specify quantity in numerals and written out, e.g., #20 (twenty)
E. Avoid use of a terminal zero to the right of the decimal point (e.g., use 5 rather than 5.0) to minimize 10-fold dosing errors
F. Use a zero to the left of a dose less than 1 (e.g., use 0.1 rather than .1) to avoid 10-fold dosing errors
G. Spell out dosage units rather than using abbreviations
H. Ensure that prescriptions and signatures are legible

(Chart on next page)
### Selected Drugs that Cause QT Prolongation and Torsade de Pointes

<table>
<thead>
<tr>
<th>Drug Name (Brand)</th>
<th>↑ QTc</th>
<th>TdP</th>
<th>Warning in Label</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiarrhythmics:</strong> very probable TdP risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone (Cordarone)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>TdP risk is regarded as low</td>
</tr>
<tr>
<td>Disopyramide (Norpace)</td>
<td>X</td>
<td></td>
<td></td>
<td>Case reports</td>
</tr>
<tr>
<td>Dofetilide (Tikosyn)</td>
<td>X</td>
<td></td>
<td></td>
<td>TdP risk is highest within first few days of therapy and at high doses</td>
</tr>
<tr>
<td>Flecainide (Tambocor)</td>
<td>X</td>
<td></td>
<td></td>
<td>Case reports (rare), possible TdP risk</td>
</tr>
<tr>
<td>Ibutilide (Corvert)</td>
<td>X</td>
<td></td>
<td></td>
<td>Black box warning</td>
</tr>
<tr>
<td>Procainamide (Pronestyl)</td>
<td>X</td>
<td></td>
<td></td>
<td>Risk is higher when the drug is given IV</td>
</tr>
<tr>
<td>Quinidine (Quinidex)</td>
<td>X</td>
<td></td>
<td></td>
<td>Higher risk when the drug is given IV</td>
</tr>
<tr>
<td>Sotalol (Betapace)</td>
<td>X</td>
<td></td>
<td></td>
<td>TdP risk is highest within first few days of therapy and at high doses</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesoridazine (Serentil)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Black box warning</td>
</tr>
<tr>
<td>Thioridazine (Mellaril)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Black box warning; very probable TdP risk</td>
</tr>
<tr>
<td>Pimozide (Orap)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Probable TdP risk</td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td>X</td>
<td></td>
<td></td>
<td>Probable TdP risk</td>
</tr>
<tr>
<td>Chlorpromazine (Thorazine)</td>
<td>X</td>
<td></td>
<td></td>
<td>Possible TdP risk in high risk patients</td>
</tr>
<tr>
<td>Haloperidol (Haldol)</td>
<td>X</td>
<td></td>
<td></td>
<td>Possible TdP risk in high risk patients</td>
</tr>
<tr>
<td>Hesperidone (Hisparal)</td>
<td>X</td>
<td></td>
<td></td>
<td>Possible TdP risk in high risk patients</td>
</tr>
<tr>
<td><strong>Antiemetics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Droperidol (Inapsine)</td>
<td>X</td>
<td></td>
<td></td>
<td>Black box warning</td>
</tr>
<tr>
<td>Dolasetron (Anzemet)</td>
<td>X</td>
<td></td>
<td>Related to blood levels of active metabolite</td>
<td></td>
</tr>
<tr>
<td>Ondansetron (Zofran)</td>
<td>X</td>
<td></td>
<td>Limited documentation</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium Channel Blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bepridil (Vascor)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Black box warning</td>
</tr>
<tr>
<td>Isradipine (DynaCirc)</td>
<td>X</td>
<td></td>
<td>Case reports of slight QT prolongation</td>
<td></td>
</tr>
<tr>
<td>Nicardipine (Cardene)</td>
<td>X</td>
<td></td>
<td>Case reports of slight QT prolongation</td>
<td></td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin (Biaxin)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Possible TdP risk in high risk patients</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Possible TdP risk in high risk patients</td>
</tr>
<tr>
<td><strong>Quinolines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemifloxacin (Factive)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Possible TdP risk in high risk patients</td>
</tr>
<tr>
<td>Moxifloxacin (Avelox)</td>
<td>X</td>
<td>X</td>
<td>Case reports of QT prolongation</td>
<td></td>
</tr>
<tr>
<td><strong>Other Anti-infectives</strong></td>
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<tr>
<td>Halofantrine (Halfan)</td>
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<td>X</td>
<td>Black box warning</td>
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<tr>
<td>Pentamidine (Pentam)</td>
<td>X</td>
<td></td>
<td>Case reports, possible TdP risk in high risk patients</td>
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<tr>
<td><strong>Opioids</strong></td>
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<tr>
<td>Levomethadyl (Orfam)</td>
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<td>X</td>
<td>Black box warning</td>
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<tr>
<td>Methadone (Dolophine)</td>
<td>X</td>
<td>X</td>
<td>Case reports of TdP in patients taking high doses</td>
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<tr>
<td><strong>Antidepressants</strong></td>
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<td>SSRI: Citalopram (Celexa), Fluoxetine (Prozac), Paroxetine (Paxil), Sertraline (Zoloft)</td>
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<td>X</td>
<td>(Celexa)</td>
<td>Case reports (very rare), TdP risk unlikely</td>
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<tr>
<td>TCAs: Amitriptyline (Elavil), Desipramine (Norpramin), Imipramine (Tofranil)</td>
<td>X</td>
<td></td>
<td></td>
<td>Can affect cardiac conduction; case reports of increased QTc; TdP risk possible in high risk patients</td>
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<tr>
<td>Venlafaxine (Effexor)</td>
<td>X</td>
<td>X</td>
<td>Case reports (rare), TdP risk possible in high risk patients</td>
<td></td>
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</tbody>
</table>
IV. EXAMPLES OF DRUGS THAT MAY CAUSE RENAL TOXICITY
A. NSAIDs: decrease renal perfusion, may cause interstitial nephritis and nephrotic syndrome
B. ACE inhibitors, ARBS, Aliskiren: cause renal failure in patients with bilateral renal artery stenosis
C. Aminoglycosides: direct tubular injury occurring 7–10 days after initiation of treatment
D. Amphotericin B: direct tubular injury
E. Cyclosporine: Prerenal, thrombotic thrombocytopenic purpura—hemolytic uremic syndrome, or chronic renal failure
F. Radiographic contrast dye: Prerenal and acute tubular necrosis
G. Foscarnet, Ganciclovir, Pentamidine

V. EXAMPLES OF DRUGS THAT MAY CAUSE HEPATIC TOXICITY
A. Acetaminophen: Direct toxic reactions
B. Alcohol: Cirrhosis
C. Amiodarone: Fatty liver and alcoholic hepatitis
D. Estradiol: Cholestatic reactions
E. Isoniazid: Idiosyncratic reactions
F. HMG CoA reductase inhibitors: Mild elevations in AST/ACT, cholestatic injury
G. Phenytoin: Allergic hepatitis
H. Sustained-release nicotinic acid: Ischemic damage
I. Vitamin A: Indolent cirrhosis

VI. GRAPEFRUIT-DRUG INTERACTIONS: Grapefruit juice can inhibit intestinal CYP 3A4 and increase plasma concentration of the following drugs:
A. Antiarrhythmics
B. Calcium channel blockers
C. Statins
D. Immunosuppressants (Cyclosporine)
E. Protease inhibitors (Saquinavir)

CLINICAL PEARLS
• Always be alert for potential drug interactions with drugs that have narrow therapeutic indexes. E.g., antiarrhythmics, anticonvulsants, Cisapride, Lithium, MAOIs, nonsedating antihistamines, Theophylline, and Warfarin
• If the patient is stabilized on the object drug, it may be necessary to adjust the dose when starting, stopping or altering the dose of the precipitant drug
• Monitoring of serum drug concentrations may be useful in adjusting drug dosage
• Educate patient regarding early signs of a possible drug interaction and monitor carefully the clinical response of the patient
• The onset of drug interactions may vary, depending on the time required to reach the steady-state concentration of the precipitant drug
• Alcohol may potentiate the CNS effects of antidepressants, antihistamines, antipsychotics, benzodiazepines, narcotics, and sedatives. Alcohol can cause a disulfiram-like reaction (flushing, palpitations, tachycardia, nausea etc.) when it is taken concurrently with Metronidazole or Chlorpropanide

References
85. Medication Adherence

Michael B. Weinstock, MD

I. STATISTICS
A. Approximately 20% of patients do not fill their prescriptions and approximately 50% of patients do not take their meds as prescribed. Common reasons given are:
1. Think their meds are unnecessary
2. Do not think the meds will work
3. Worried about side effects
4. Cost
5. Poor understanding of the disease
B. Up to 5–10% of hospital admissions of the elderly may be associated with med non-adherence

II. FACTORS WHICH INCREASE THE RISK OF NON-ADHERENCE
A. Lives alone
B. Uses more than 1 pharmacy or more than 1 provider
C. Multiple daily doses
D. Frequently changed regimen
E. Large number of drugs
F. Lack of understanding of the diagnosis and the role of meds
G. Poor cognition, vision or dexterity
H. Low literacy
I. Multiple chronic diseases
J. Depression

III. HINTS TO IMPROVE MEDICATION ADHERENCE
A. Minimize the number of meds patients are taking
B. Explain to patients what their meds do and why they need to take them
C. Prescribe meds with minimal side effects
D. Inform patients about potential side effects and how to best manage them
E. Review patients’ meds at each visit to ensure the meds they are taking (or not taking) are the same meds you think they are taking (or not taking)
F. Identify patients at high risk for med non-adherence (illiterate, decreased mobility, ignorant, rebellious (teenagers), and patients on multiple meds). Spend extra time with these patients and/or enlist the help of ancillary medical personnel (nurses, pharmacists, social workers, home health workers) to help with adherence
G. Minimize the number of times per day that a patient needs to take meds. If a patient is on a TID med, when possible, prescribe another TID med instead of a Q 6hr med
H. Instruct, then observe patient taking metered dose inhalers. Use a spacer to increase delivery of the med
I. Be aware of cost of meds. Often prescriptions will not even be filled when the pharmacist tells patient the cost. A brilliant diagnosis dims when a patient does not take the meds
J. Refill only enough meds to get the patient to the next appointment
K. Ask patients how many times per week they take the meds. Ask in a non-judgmental, non-threatening way such as: “Many patients feel it is difficult to take all of their medications every day. How many times per week do you take (or do you miss) your medications?”

CLINICAL PEARLS
• Be alert for med toxicity in patients recently admitted to a hospital or extra-care facility. A clinician may have increased the dose of a patient’s med because it was thought that the med was not working at a lower dose when, in fact, the patient was not taking the med. When the patient is admitted and receives prescribed dose, toxic
levels are achieved. Admission equals compliance!
• In women who begin hormone replacement therapy (HRT), 33% will have stopped taking the meds at 6 months and 75% will have stopped at 3 years

References

Dawn Prall, MD

86. CHRONIC NON-CANCER PAIN MANAGEMENT

I. WHAT IS CURRENT PAIN?—DEFINITIONS
A. Acute pain is a symptom of an underlying problem. Examples include broken bones, kidney stones, post-op pain, etc. Pain management strategies tend to be aggressive towards pain relief
B. Chronic non-cancer pain (the focus of this chapter) is a complex disease process characterized by persistence of pain beyond normal expected healing time, often complicated by environmental, psychosocial and behavioral factors
C. Chronic cancer pain—Pain caused by an underlying cancer-related disease
D. Terminal illness is disease that is irreversible. Comfort measures are paramount for management as risk of death already present

II. HOW TO APPROACH TREATMENT OF CHRONIC PAIN
A. Goal of treatment is improving quality of life (functional, psychosocially, emotional) as opposed to simple pain relief. Pain management is part of the treatment plan but pain relief is not the expected outcome
1. Evaluate risks and benefits of all treatments and interventions
2. Ongoing monitoring is required to balance effectiveness recommendations and treatments with their unintended side effects
B. Team approach to pain management is best
1. Requires active participation from the patient and skilled guidance from the provider
2. Refer to the “Ten Steps” outlined in the American Chronic Pain Association website: http://www.theacpa.org/Ten-Steps
   a. This website is a great resource for patients
   b. Involve others, including friends and family, counseling/psychologist, dietician/nutritionist, acupuncturist, chiropractor, physical therapy, occupational therapy, nurse, recreational therapy, vocational counselor, pharmacist
C. Set realistic goals early. Use functional, objective assessments initially and to evaluate the progress of the treatment plan over time (i.e., at every visit). Offer hope—patients may never have complete pain relief but they can have a good quality of life
D. Diagnose and treat mental illness (See Sec. X. Care of Patients with Psychiatric Disorders)
   1. Approach discussions about this in a non-confrontational manner. These diseases are very common
   2. Lack of timely diagnosis with treatment will decrease the patient’s quality of life and hinder pain management
E. Employ relaxation and stress management strategies
F. Consider non-medication management and lifestyle change first
   1. Diet, exercise, hydration
   2. Good sleep hygiene
   3. Stress management
   4. Topical ice, heat
   5. Counseling/biofeedback
   6. Alternative therapies/modalities
      a. Massage
      b. Chiropractic care
      c. Acupuncture
      d. Medication
      e. Yoga

G. If medications are needed, consider risks and benefits before initiating the medications
   1. Non-controlled substance options preferred though controlled substances can be used
   2. Screen for addiction prior to using any controlled substances. See this SBIRT reference for more details: http://www.healthyohioprogram.org/ed/~/media/FD00387E09FF494E81DE74239BD776E0.ashx
      a. Alternately, ask basic screening questions, such as:
         i. Do you smoke?
         ii. Do you drink alcohol? If so, how much and how often?
         iii. Do you use any illicit substances (including alcohol)?
         iv. Consider asking about pain pill misuse/diversion as well
   3. If controlled substances are initiated, screening for risk AND ongoing monitoring is imperative. If opioid therapy does not result in a significant increase in the person’s level of functioning, reduction/elimination of pain complaints, or has problems with side effects, then stop the opioids
      a. 4 A’s of monitoring controlled substances
         • Analgesia –Use a pain scale, usually 10 point
         • Activities of daily living (physical, psychological, social)
         • Adverse side effects
         • Aberrant or abnormal drug-related behavior
      b. ABCDE signs of addiction. If present, consider more comprehensive evaluation by addiction specialist
         • Inability to consistently ABSTAIN
         • Impairment in BEHAVIORAL control
         • CRAVING or increased hunger for drugs or rewarding experiences
         • DIMINISHED recognition of significant problems with one’s behaviors and interpersonal relationships
         • A dysfunctional EMOTIONAL response
   3. Adjuncts to controlled substance therapy
      a. Use pain agreements when initiating controlled substances
         i. There are many examples. One is referenced here:
            http://www.healthyohioprogram.org/ed/guidelines
      b. Use Prescription Monitoring Programs often. Check your local laws regarding requirements for usage. Many states require you to check the database if you prescribe controlled substances
      c. Drug screens, while helpful, have limitations. Know the limitations. Use them often in high risk patients
         i. Make this a part of your pain agreement
         ii. Do not give the patient more than 48–72 hours warning that you are requesting a drug screen

III. DEPENDENCE, ADDICTION, DIVERSION
A. Definitions
   1. Dependence: Can be physical, psychological or both. Dependence is characterized by tolerance that results in withdrawal symptoms if drug is removed. Can be present without addiction
   2. Addiction: “compulsive use of a substance, despite its negative or dangerous effects”
3. Pseudoaddiction: Term is falling out of favor but is still is a helpful concept to many providers. It is characterized by addiction-like behaviors that resolve with appropriate pain management therapy.

4. Diversion: “Illegal distribution, abuse or unintended use of prescription drugs”

B. Why is it important to know the difference?
   1. Because approach to treatment is very different based on disease or behavior

IV. STATISTICS ABOUT CHRONIC PAIN AND CONTROLLED SUBSTANCES
A. It is estimated that chronic pain affects about 116 million Americans
   1. Total US adult population: approximately 250 million
B. Accidental drug overdose death is now the #1 cause of accidental death nationwide (since 2009). Motor vehicle accidents—which have been the #1 cause for several decades—are now the #2 cause of accidental death nationwide.
   1. Those tiny little pills are more dangerous than cars!
   2. Prescription pain medication now causes more deaths than heroin and cocaine combined
C. Use caution with prescribing opiates. Death rates directly correlate with availability of opiates in circulation. Monitor use closely when you do prescribe them
D. 1 person dies every 14 minutes in the US from accidental drug overdose. The most common cause of death is prescription opiates
E. For every person who dies from prescription pain medication, there are 10 treatment admissions for abuse, 32 emergency department visits for misuse, 130 people who abuse or are dependent and 825 non-medical users

CLINICAL PEARLS
- Develop your strategy for managing chronic pain early. Establish guidelines up front with patients and set expectations early
- Use written pain agreements if you are writing controlled substances
- Use objective quality of life evaluations
- Be a partner with your patient, not simply the leader. Your role is to be an educated guide for the patient. Engage the patient in this process!
- Evaluate for mental illness and addiction. Refer early
- Do not use controlled substances for someone who has untreated mental illness and/or addiction. Once stabilized in treatment, use controlled substances cautiously
- Treat the whole patient and manage chronic pain from multiple aspects—physical, psychological, emotional, spiritual. Patients need balance in their treatment plans
- The goal of chronic pain management is improving quality of life, not getting rid of disease
  1. Chronic pain should be viewed as a chronic disease process. It will often be life-long
  2. Patients can often live healthy, happy, productive lives with chronic pain.
      This is the goal of chronic pain management

References
VII. Musculoskeletal/Sports Medicine

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87. COMMON FRACTURES/DESCRIBING FRACTURES

INTRODUCTION: The ability to describe fractures and dislocations is essential to all physicians for accurate documentation and for communication with other health providers.

I. FRACTURES: Each fracture can be described using an organized system based on what is seen radiographically. Fracture nomenclature includes location, fracture type, the relationship of fragments to one another, and the relationship to surrounding tissues.

A. Anatomic location: Name bone involved and anatomic location
   1. Location along the bone (diaphysis, metaphysis, epiphysis, or intraarticular)
   2. Fractures in children may also involve the growth plate (physis)
   3. Long bones are generally divided into thirds (proximal, middle, distal)
   4. Special location may be used (e.g., intertrochanteric femur fracture)

B. Fracture type: May include fracture line, fragments, and forces involved
   1. Fracture line describes direction of fracture
      a. Transverse: Fracture runs 90° to the long axis of the bone
      b. Oblique: Fracture runs less than 90° to the long axis of the bone
      c. Spiral: Torsion results in curved fracture around the bone
      d. Greenstick: Incomplete fracture in children, disrupted periosteum opposite the fracture
   2. Fragmented fractures
      a. Comminuted: More than 2 fracture fragments
      b. Segmental: Type of comminuted with large well-defined fragments
   3. Fracture forces
      a. Impacted: Force down the shaft, forcing 1 fragment into another
      b. Avulsion: Muscle contraction pulls a fragment off from its attachment site
      c. Compression: Usually seen in cancellous flat bones (vertebral bodies)
      d. Torus or buckle: Seen in children, similar forces to an impact fracture
      e. Stress fracture: Skeletal breaks resulting from overuse

C. Relationship of fragments
   1. Alignment: Describes direction and angle of distal fragment relative to proximal fragment, e.g., distal femur fragment is angulated 15° laterally
   2. Displacement: Shifting of fragments in relation to one another. Usually described in terms of percentage of subluxation. Fracture with 100% displacement and shortening is referred to as a bayonette fracture

D. Relationship to surrounding tissues
   1. Open: Skin broken by either outside forces or fracture fragment
   2. Closed: Skin intact

Fracture Line Orientation


II. DISLOCATION AND SUBLUXATION

A. Dislocation: Complete disruption of joint so that articular surfaces are no longer in contact.
1. Description based on the position of distal bone relative to proximal bone, e.g., posterior elbow dislocation/displacement of ulnar olecranon, posterior relative to the humerus
2. May be associated with fractures
3. Bones often lie side-by-side, locked in that position until dislocation reduced

B. Subluxation: Incomplete disruption of a joint where articular surfaces are in contact but not perfectly aligned

III. TERMINOLOGY: Orthopedics has unique language to describe bony structures and relationships
A. Salter classification: Refers to physeal fractures in children
   1. I-Fracture through the physis
   2. II-Fracture through the physis with continuation towards the metaphysis
   3. III-Fracture through the physis with continuation towards the epiphysis
   4. IV-Fracture through the physis with continuation towards both the epiphysis and metaphysis
   5. V-Crush injury to the physis

   ![Epiphyseal fractures based on Salter-Harris classification](source)


B. Long bone locations
   1. Diaphysis: Shaft of long bones
   2. Metaphysis: Widened “neck” portion of bone adjacent to epiphysis
   3. Epiphysis: Ossification center at the end of long bones, separated from the metaphysis by the physis in children
   4. Physis: Cartilaginous growth plate

C. Other terminology
   1. Ankylosis: Restricted motion in a joint
   2. Apophysis: Ossification center at the insertion of a tendon
   3. Arthrodesis: Surgical stiffening/fusion of a joint
   4. Kyphosis: Curvature of the spine with posterior convexity
   5. Lordosis: Curvature of the spine with anterior convexity
   6. Spondylolisthesis: Slippage of 1 vertebra on another
   7. Spondylolysis: Fracture of the pars interarticularis
   8. Valgus: Distal part away from midline
   9. Varus: Distal part toward midline
   10. Volar: Towards palmar surface of hand

D. Unique fracture names
   1. Boxer’s Fracture: Fracture of the fifth metacarpal neck with volar displacement of the metacarpal head
   2. Colles’ Fracture: Distal radius fracture with dorsal displacement
   3. Smith’s Fracture: Distal radius with volar displacement
   4. Jones’ Fracture: Diaphyseal fracture of base of fifth metatarsal
   5. Maisonneuve’s Fracture: Proximal fibula fracture with syndesmosis rupture and associated medial malleolar fracture or deltoid ligament rupture
   6. Monteggia’s Fracture: Fracture of proximal third of ulnar shaft with radial head dislocation
   7. Nightstick Fracture: Isolated fracture of ulna due to direct trauma
   8. Rolando’s Fracture: Y shaped intra-articular fracture of base of first metacarpal

References
I. INTRODUCTION: Although most ankle injuries are simple sprains of the lateral ligaments, a variety of other structures near the ankle may also be injured. Included in the differential diagnosis should be medial ankle sprains, trauma to the Achilles and peroneal tendons, tarsal tunnel syndrome, fractures, syndesmotic sprains and synovial impingement.

II. ANATOMY

A. Ligaments of the lateral ankle
1. Anterior talofibular ligament
   a. Prevents forward subluxation of the talus/prevents inversion in plantar flexion
   b. Most frequently injured ligament with inversion injury
2. Posterior talofibular ligament—strongest lateral ligament and rarely injured
3. Calcaneofibular ligament—prevents inversion in neutral position

B. Ligament of the medial ankle: Deltoid ligament
1. Broad ligament with superficial and deep fibers
2. Prevents eversion

C. Tibiofibular joint/syndesmosis: The following ligaments connect the tibia and fibula. They form a fibrous joint between the distal tibia and fibula called the syndesmosis (see syndesmosis squeeze test below)
1. Anterior tibiofibular ligament
2. Posterior tibiofibular ligament
3. Interosseous membrane

D. Superficial posterior compartment of the leg: All of the following muscles insert at the calcaneus through the Achilles tendon
1. Gastrocnemius muscle
2. Soleus muscle
3. Plantaris muscle

III. HISTORY

A. General: Swelling, ecchymosis, abrasions, lacerations, paresthesias, pain at proximal tibia/fibula

B. Mechanism of injury
1. Was a “pop” felt or heard at the time of injury
2. Ability to bear weight immediately following injury
3. Mechanism of injury (amount of force; inversion, eversion, etc.)
4. Location of pain
5. Swelling or ecchymosis, abrasions or lacerations

C. Previous injury to either ankle

D. Type of employment and level of athlete

IV. PHYSICAL: Patients with acute ankle injuries will most likely have loss of range of motion (ROM) and decreased strength secondary to swelling and pain which may compromise the exam (drawer tests, etc.). It may be helpful to reexamine after the swelling has decreased

A. Inspection for swelling and ecchymosis to help localize the site of the injury. Inspect the unaffected side for comparison. Ecchymosis extending proximately from the ankle to the leg may indicate a syndesmotic injury

B. Palpation: Gently palpate to find areas of greatest tenderness—start with examining the areas of least suspected tenderness. Particularly observe for tenderness of the malleoli, navicular, cuboid, proximal 5th metatarsal, anterior process of the calcaneus, deltoid ligament, anterior talofibular ligament/calcaneofibular ligament, Achilles tendon, peroneal tendons, and tibialis anterior tendon. Also palpate the proximal fibula to evaluate for a possible Maisonneuve fracture

C. Range of motion: Normal is 13–16° of dorsiflexion and 31–44° plantar flexion

D. Pulses: Dorsal pedis and posterior tibial

E. Neurologic: Check sensation (L4: medial lower leg and medial foot; L5: dorsum of foot; S1: lateral foot)
F. Ankle stress testing: To assess ankle instability. Exam after acute injury may be limited by pain and swelling. Always compare exam to contralateral side

1. Anterior drawer test: To test for laxity or disruption of the anterior talofibular ligament
   a. Method: Have patient sit or lie flat with the legs unweighted. Grasp lower leg with one hand and the heel with the other hand and then, with the ankle in slight plantar flexion, apply anterior force to the calcaneus to displace the talus forward
   b. Results: Displacement of 8–10mm is noted with division of the anterior talofibular ligament, and 10–15mm displacement is noted with tearing of anterior and posterior talofibular ligament and calcaneo-fibular ligament

2. Talar tilt (inversion test): To test for laxity or disruption of the calcaneo-fibular ligament
   a. Method: Have patient sit or lie flat with the legs unweighted. Place inversion stress on the ankle
   b. Results: Indicative of anterior talofibular ligament disruption if 10–20° of inversion is noted. If talar tilt greater than 20° then calcaneo-fibular ligament may also be torn

3. Syndesmosis squeeze
   a. Method: 10cm above the lateral malleolus, compress the proximal fibula against the tibia
   b. Results: If the patient reports localized pain at the distal tibia and fibula during the syndesmosis squeeze, this may be indicative of a fibular fracture, interosseous membrane disruption or distal tibiofibular syndesmosis damage

4. Thompson test
   a. Method: Have the patient lie prone with feet off the edge of the table. Compress the mid-calf and observe for plantar flexion
   b. Results: A positive test (no plantar flexion) helps to confirm the diagnosis of an Achilles tendon rupture

V. EVALUATION

A. Plain x-ray: Not all ankle injuries necessitate obtaining radiographic films. The Ottawa ankle rules apply to patients 18 or older and suggest that films be obtained:
   1. If the patient is unable to bear weight initially and when examined
   2. Bone tenderness at the posterior edge of the lower 6 cm of the distal tibia or fibula, proximal 5th metatarsal, or over the navicular bone

B. CT: To localize osteochondritis dissecans, loose bodies and subchondral cysts
C. MRI: To evaluate for stress fractures; osteochondral lesions such as osteochondritis
dissecans and talar dome fractures; visualization of Achilles, peroneal and posterior tibial tendons

D. Technetium bone scan: To evaluate for stress fractures, infections or degenerative arthritis

VI. MANAGEMENT OF ANKLE SPRAINS

A. Incidence: 85% are lateral sprains, typically involving the anterior talofibular ligament, 10% are syndesmotic sprains, and 5% are medial sprains involving the deltoid ligament

B. Grade severity of ankle sprain

<table>
<thead>
<tr>
<th>Severity</th>
<th>Pathophysiology</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Weight-bearing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Minimal tearing of fibers</td>
<td>Minimal pain or instability</td>
<td>Slight edema</td>
<td>Unimpaired or instability Anterior drawer and talar tilt test negative</td>
</tr>
<tr>
<td>Grade II</td>
<td>Incomplete rupture of ligament</td>
<td>Moderate pain and disability</td>
<td>Moderate edema and ecchymosis</td>
<td>Difficult</td>
</tr>
<tr>
<td>Grade III</td>
<td>Complete rupture of ligament</td>
<td>Severe pain with loss of function</td>
<td>Severe edema and ecchymosis Anterior drawer and talar tilt tests positive Possible avulsion fracture</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from table 2—Ankle sprain grading system from Reisdorff, EJ. The injured ankle: New twists to a familiar problem. Emergency Medicine Reports 1995;16(5).

C. Management of Grade I and II sprains

1. Support to prevent eversion and inversion and provide early mobilization
   a. Aircast/Airsplint
   b. Gelsplint
   c. Early range of motion (ankle pumps, drawing alphabet)
   d. Physical therapy
2. RICE and meds (see below)

D. Management of Grade III sprains

1. Non-weight bearing initially
2. Immobilization
   a. Plaster posterior splint
   b. Sugar-tong splint
3. Orthopedic evaluation
4. RICE: See E. below
5. Meds: See F. below

E. RICE

1. Rest: Encourage weight bearing as tolerated; use crutches if needed
2. Ice: 20 minutes Q2–3hrs × 48hrs or until edema and inflammation have subsided
3. Compression: Elastic wrap from distal foot to mid calf will support ankle and decrease edema
4. Elevation: Elevate foot to 15–25 cm above level of heart

F. Meds

1. NSAIDs: Ibuprofen 600–800mg PO TID-QID, other NSAIDs should be equally efficacious
2. Acetaminophen: 650–1000mg PO Q 4–6hrs, max 4g daily. May be combined with low dose NSAIDs to enhance analgesic effect
3. Narcotics if necessary
   a. Hydrocodone/Acetaminophen (Vicodin): 1–2 tabs Q4–6hrs PRN #12–20
   b. Oxycodone/Acetaminophen (Percocet): 5mg–1–2 tabs Q4–6hrs PRN #12–20
4. Nonnarcotic analogesics: Tramadol/Acetaminophen (Ultracet) 1–2 PO Q4–6hrs PRN

G. Rehabilitation

1. Range of Motion
   a. Achilles tendon stretching
   b. Alphabet exercises: Moving the ankle in multiple planes by drawing the letters of the alphabet
2. Muscle Strengthening Exercises: Start once full ROM obtained
   a. Start with isometric exercises and progress to dynamic exercises
   b. Perform in all 4 directions of ankle movement
3. Proprioception: Start once the patient can bear weight without pain. May involve toe raises with eyes closed or the use of devices such a wobble boards
4. Activity Specific Training: Graded progression to full activities which should be supervised by a therapist or trainer. The use of lace-up ankle brace or athletic tape is useful early in the return to activities

VII. DIFFERENTIAL DIAGNOSIS OF THE NON-HEALING ANKLE INJURY
A. Incomplete rehabilitation
B. Chronic instability
C. Reflex sympathetic dystrophy (RSD)
D. Peroneal tendon pathology
E. Fractures (talar dome, 5th metatarsal, navicular, growth plate)
F. Anterior impingement
G. Neuroma
H. Accessory navicular bone
I. Osteochondritis dissecans (OCD)
J. Lisfrance injury (tarsso-metatarsal articulation of the foot)

CLINICAL PEARLS
- Prolonged immobilization may lead to slowed return to normal function
- If an ankle injury is not allowed to adequately heal and the ligaments are not allowed to adequately tighten, patients may be left with a “loose ankle”, predisposing them to future ankle strains
- The typical mechanism of injury of a lateral ankle sprain is by inversion, which frequently occurs with some degree of plantar flexion
- Ecchymosis extending proximally from the ankle to the lower leg may indicate a tibiofibular syndesmotic injury. Syndesmotic sprains tend to require a more prolonged recovery time
- Tibiofibular syndesmosis is a commonly associated injury with injury to deltoid ligament
- Osteochondral fractures of the talar dome are typically diagnosed 4–6 weeks after an ankle “sprain” that does not heal
- In studies of patients with ankle sprains, no difference was found in the number of patient complaints or residual ankle stability between those who were casted and those who were not

References
I. ANATOMY

A. Bursae: Provide lubrication between dynamic components

B. Cruciate ligaments
   1. Anterior cruciate ligament (ACL): Stabilizes knee to prevent anterior motion of the tibia
   2. Posterior cruciate ligament (PCL): Stabilizes knee to prevent posterior motion of the tibia

C. External tendons and ligaments
   1. Quadriceps tendon
   2. Patellar tendon
   3. Medial collateral ligament (MCL): Stabilizes knee to prevent excess valgus motion
   4. Lateral collateral ligament (LCL): Stabilized knee to prevent excess varus motion

D. Muscles
   1. Knee flexors: Hamstrings and gastrocnemius
   2. Knee extensors: Quadriceps

E. Articulations
   1. Lateral and medial tibiofemoral articulations
   2. Patellofemoral articulation

II. HISTORY

A. Acute trauma: Pain which began suddenly during a certain activity. Position of the knee when injured (flexed, extended, etc.), or as a result of a direct blow

B. Chronic trauma: Activities

C. Swelling
   1. Immediate swelling after the injury suggests fracture, ACL injury or patellar dislocation
   2. Delayed swelling suggests meniscal injury or OCD

D. Locking/Buckling of the knee: Catching suggests meniscal injury

E. Aggravating and relieving factors (stairs, sitting, etc.)

F. History of patellar dislocation

G. Problems elsewhere in the lower extremity: One joint above and one joint below. Hip or foot problems, new shoes, etc.

H. Systemic illness: Polyarthralgia, fever, morning stiffness, history of gout, hyperuricemia, rheumatoid arthritis, or pseudogout

I. Past history: Knee injury, past surgeries of the knee

III. PHYSICAL: Compare to uninjured side

A. Visually inspect knee for effusion or soft tissue swelling, evidence of past surgeries/ injuries, abrasions, contusions, ecchymosis, erythema, patellar location. Visually inspect leg muscles for atrophy, leg length discrepancy, etc.

B. Range of motion, crepitus, gait, patellar grind, strength, reflexes

C. Patella
   1. Palpate for effusion
      a. Inspection: With the patient seated and both knees flexed 90°, observe for a bulge on either side of the patellar ligament in the symptomatic knee
      b. Ballottement: The patient lies supine with knee extended and the examiner's first hand compresses from above and also on both sides of the patella then the examiner's other hand compresses the patella to see if it is ballotable
      c. Carlin maneuver: With patient supine, milk or squeeze the suprapatellar area and with the other hand place fingers on either side of the patellar tendon palpate for fluid redistribution or bulging of accumulated fluid
   2. Evaluate for hypermobility of the patella by attempting to sublux the patella laterally
   3. Apprehension sign: Pain and involuntary contraction of the quadriceps with deviation of the patella laterally
D. Lachman test: Test for ACL injury
1. Method: Have the patient supine and the leg in slight external rotation and the knee in 15° of flexion (often the foot is slightly off the edge of the table). Example for left knee: With the examiner on the patient’s right, grasp the lateral aspect of the distal thigh with the left hand and the medial aspect of the proximal lower leg with the right hand and pull anteriorly on the lower leg (with the right hand)
2. Results: The test is positive if there is anterior laxity. This is the most sensitive test for ACL injury

E. Drawer tests: Test for ACL or PCL injury
1. Method: Anterior and posterior drawer tests—patient is supine with the hip flexed 45° and the knee flexed 90° and the plantar aspect of the foot resting on the table. The examiner sits on the patient’s foot and then grasps the proximal aspect of the lower leg with both hands and attempts to anteriorly or posteriorly displace the tibia on the femur
2. Results: Anterior subluxation of the tibia on the femur suggests injury to the ACL and posterior subluxation suggests injury to the PCL

F. Tibial sag test: Test for PCL injury
1. Method: Place patient in the supine position with hips flexed to 45° and both knees flexed to 90°
2. Results: Affected tibia sags on the femur suggesting PCL injury

G. Varus-valgus stress test: MCL or LCL injury
1. Method: Patient is supine with knee flexed about 20° and a varus or valgus stress is placed on the knee with the examiner’s hand
2. Results: Laxity with valgus stress suggests injury to the MCL, and laxity with varus stress suggests injury to the LCL

H. McMurray test: Test for meniscus injury
1. Method: With the patient supine and the knee flexed at 90°, externally rotate the foot and then extend the knee. Repeat with the foot internally rotated, and then extend the knee
2. Results: A test is positive with pain and/or a palpable click at the medial or lateral joint lines

I. Apley grind test: Test for meniscus injury
1. Method: With the patient prone and the knee flexed at 90°, push straight down on the foot and then rotate the foot (compresses the meniscus). Repeat by pulling up on the foot and then rotating the foot
2. Results: If there is pain when the foot is pushed down, but no pain when the foot is pulled up, then consider a meniscus injury

IV. RADIOGRAPHY/SPECIAL TESTS
A. Radiography: Evaluate for fracture, osteochondritis dissecans, dislocation, Osgood-Schlatter’s disease, etc.
B. MRI: Meniscus injury/internal derangement, occult fracture or bone bruise
C. Aspiration of knee effusion: Aspirate to evaluate for hemarthrosis, infection (septic joint), fat globules (fracture), and for relief of symptoms

V. DIFFERENTIAL DIAGNOSIS AND MANAGEMENT OF COMMON KNEE PROBLEMS
A. Fracture: Obtain x-ray with appropriate suspicion (mechanism, swelling, deformity, joint tenderness etc.) and orthopedic referral if positive

B. Meniscus injury
1. History
   a. Twisting, flexion injury
   b. Inability to flex knee
   c. Difficulty in bearing weight
   d. Clicking or locking of the knee
   e. If chronic, may see intermittent effusions, locking, and possibly quadriceps wasting
2. Physical
   a. Knee effusion
   b. Tenderness over joint line (medial with medial meniscus injury, lateral with lateral meniscus injury)
   c. McMurray test and Apley test: See above for method
3. Acute management: Rigid knee immobilizer (short term), crutches, ice, rest
4. Refer to orthopedist if still symptomatic after 14 days of conservative management

C. Ligament injuries
1. History
   a. Pain immediately at time of injury (mechanism of injury)
   b. Knee stiffness and tenderness
   c. Knee swelling (occasionally)
   d. Decreased ability to ambulate
2. Physical
   a. Tenderness to palpation of ligament (MCL, LCL)
   b. Lachman test: Positive with ACL injury (see above)
   c. Drawer tests (test for ACL, PCL injury) and tibial sag test (PCL injury)
   d. Tests for lateral instability (MCL, LCL)
3. Classification
   a. Grade I—Stretching of fibers without significant damage
   b. Grade II—Partial tear of fibers
   c. Grade III—Complete tear of fibers
4. Management
   a. Ice, elevation, rest
   b. Rigid knee immobilizer or posterior splint
   c. Crutches for grade II and III injuries
   d. Orthopedic/sports medicine referral/surgery
   e. Physical therapy

D. Patellofemoral syndrome
1. Etiology
   a. Lateral subluxation (Hypermobility of the patella)
      i. May be caused by increased angle between the quadriceps and patellar tendon
         (Q angle). This is called patella alta. Normal Q angle is up to 20° (women)
      ii. Patella alta can be identified on a lateral knee x-ray where the length of the
          patellar tendon exceeds the length of the patella by more than 1cm
      iii. Other causes include variation in hip anatomy that results in compensatory
           tibial torsion
   b. Chondromalacia: Damage to soft cartilage on posterior patella causing crepitus
      and pain
2. History
   a. Pain worsened by walking or running up or down hills, climbing stairs or kneeling
   b. Pain often disappears during activity and returns just after activity is completed
3. Physical
   a. Patella alta
   b. Hypermobility of the patella
   c. Pain or crepitus with patellofemoral movement
   d. Apprehension sign: Pain and involuntary contraction of the quadriceps with
      deviation of the patella laterally
   e. Patellar grind test
   f. Possible knee effusion
4. Testing
   a. Typically a clinical diagnosis
   b. If x-rays are obtained, include lateral (to evaluate for patella alta or DJD) and
      sunrise view (to evaluate for lateral subluxation or DJD)
5. Management
   a. Rest, ICE
   b. NSAIDs
   c. Physical therapy (quadriceps strengthening, hip rotator strengthening)
   d. Orthotics if needed for foot over-pronation
   e. Surgical consideration if conservative therapy fails

E. Osgood-Schlatter’s Disease (Apophysitis of the tibial tubercle)
1. General
   a. Common cause of knee pain in males age 11–15; females age 8–13
   b. Secondary to traction of the patellar tendon where it inserts into the growth plate
of the tibial tubercle
  c. Pain is at the insertion of the patellar tendon on the tibial tubercle
2. History
  a. Pain with activity (especially with running, jumping, kneeling)
  b. Recent growth spurt
  c. Often bilateral
3. Physical exam
  a. Prominence over the tibial tubercle
  b. Tenderness at the tibial tubercle
  c. Tightness of quadriceps and hamstring muscles
  d. May have pain with resisted knee extension
4. Management
  a. Avoid activities that involve knee extension (running, climbing, jumping, kicking) until symptoms have subsided ~6–8 weeks
  b. Range of motion and stretching: Physical therapy
  c. Oral analgesics, ice after activity
  d. Surgical management if pain persists after ossification is complete

F. Osteochondritis dissecans (OCD): Occurs secondary to ischemia
1. General
  a. Loss of blood supply (avascular necrosis) to an area next to a joint surface
  b. The ischemic/dead bone and overlying cartilage gradually loosen and cause pain
  c. This osteochondral fragment may break loose into the joint and cause locking, sharp pain and effusion
  d. Rule out OCD in contralateral joint; 20–30% of cases are bilateral
2. History: Gradual onset of swelling and vague pain. Worse with activity. Insidious onset may be over several months
3. Physical: Often pain with palpation of the medial femoral condyle (most common site is the lateral portion of the medial condyle). Quadriceps wasting. Decreased ROM of the knee
  a. Radiologic diagnosis with plain films
  b. MRI needed to stage the lesion
  c. Orthopedic referral
G. Other: Prepatellar bursitis, retropatellar bursitis, patellar tendonitis, fat pad syndrome, pes anserinus bursitis, neoplasm, loose bodies

H. Arthritis: See Chapters 73–77

CLINICAL PEARLS
• Acetaminophen and NSAIDs are equally effective in osteoarthritis of the knee
• Tears of the medial meniscus are 10 times as common as tears of the lateral meniscus
• MRI is 90% sensitive for meniscus injury
• Following meniscectomy, patients may have joint space narrowing and arthritic changes
• Knee has highest prevalence of benign and malignant tumors than any other joint
• Osgood-Schlatter’s disease occurs most commonly from age 11–15 and affects males more than females
• Osteochondritis dissecans predisposes to degenerative arthritis

References
I. SHOULDER ANATOMY AND BIOMECHANICS

A. Introduction: Normal shoulder function is a combination of the anatomic arrangement and the complex action of many muscles. The shoulder is the joint with the largest range of motion, but this allows for more instability. A single small injury to the shoulder may lead to functional deficit which potentiates damage to other structures.

B. Anatomy
1. Sternoclavicular joint (synovial joint)
2. Acromioclavicular joint
3. Glenohumeral joint (golf ball on a tee)
4. Humeral head
5. Glenoid fossa
6. Glenohumeral ligaments
7. Rotator cuff (SITS: Supraspinatus, infraspinatus, teres minor, subscapularis)
8. Scapula rotators (trapezius, rhomboids, levator scapulae, serratus anterior)

C. History: See history under each specific diagnosis

D. Physical exam
1. Inspect for asymmetry and deformity of shoulder girdle
2. Palpate for tenderness and crepitus
3. Range of motion
4. Neck and elbow exam (to exclude referred pain)
5. Neurovascular exam of bilateral upper extremities
6. Apprehension test: Most sensitive finding with shoulder instability
   a. Method: With patient in supine position apply anterior force to the humerus with external rotation
   b. Result: Pain (apprehension) of impending subluxation suggests anterior instability
7. Relocation test
   a. Method: With patient in supine position apply posterior force to the humerus with external rotation
   b. Result: Relief of pain or apprehension suggests anterior instability
8. Sulcus sign
   a. Method: With patient in sitting position, apply downward traction to the humerus
   b. Result: Development of a sulcus between the greater tuberosity of the humerus and acromion suggests posterior instability
9. Apley scratch test
   a. Method: Patient attempts to touch the superior and inferior aspects of the opposite scapula
   b. Result: Loss of range of motion suggests rotator cuff disease
10. Supraspinatus test
    a. Method: Patient’s arms are abducted 90° and internally rotated. Downward force is applied while patient attempts to maintain position against resistance
    b. Result: Inability to maintain the position against resistance suggests rotator cuff disease
11. Drop arm test
    a. Method: Arms are passively abducted and patient slowly lowers arm to waist
    b. Result: If arm drops to side, suggests rotator cuff disease
12. Neer’s sign
    a. Method: The arm is forcibly forward flexed
    b. Results: If pain is invoked, suggests impingement
13. Impingement test
    a. Method: 10cc of 1% Lidocaine is injected into the subacromial space and Neer’s sign maneuver is repeated
    b. Results: Relief of pain after injection suggests impingement

II. SHOULDER INSTABILITY
A. Introduction: Shoulder instability (symptomatic abnormal glenohumeral translation) is a common problem, especially in overhead athletes. Anterior instability is the most common and can range from subluxation to complete dislocation. Instability can also result from repetitive microtrauma as the ligaments are stretched.

B. History
1. Anterior: Shoulder is usually abducted and externally rotated. Force is applied to arm causing more external rotation and extension. This event is very painful and athlete may feel shoulder slide out of place. Athlete may have associated symptoms of a “dead arm” for seconds to minutes following the event.
2. Posterior: Shoulder is usually in flexed, adducted, and internally rotated position and a force applied to hand causes posterior dislocation. Happens with falls and in offensive linemen in football.
3. Multidirectional or recurrent: Pain is usual complaint that brings patients to see doctor. These injuries can masquerade as many other injuries because of disrupted biomechanics of shoulder.

C. Physical exam
1. Positive apprehension test and sulcus sign
2. With recurrent injuries check for signs of nerve palsies. Also there may be a loss of internal rotation (10°) and crepitus with ROM. Think of impingement as a sign of instability (injection test).

D. Radiography
1. Plain films
2. MRI: Most useful with recurrent instability and determining associated complications (labral tears, chondral defects).

E. Management
1. Shoulder dislocation
   a. Multiple techniques including modified hippocratic (traction-countertraction), Rowe maneuver (touch opposite ear), Stimson (prone with traction weights).
   b. Post-reduction repeat plain films and immobilize 2–6 weeks. Rehabilitation will include early isometrics.
2. Chronic instability
   a. Protect shoulder from provocative movements, and regain ROM and normal shoulder function with physical therapy. Gradual return to sport specific exercise and play. Plan 3–6 months of therapy.
   b. Surgical indications: Irreducible acutely, displaced tuberosity fracture, unstable glenoid rim fracture, absolute stabilization needed prior to return to sport, and loss of time not an option.

F. Clinical Pearls
1. Need good on-field exam before reduction
2. Shoulder pain is the most common symptom of shoulder instability
3. When you think of impingement, think of chronic instability.
4. Asymptomatic laxity can be a normal variant, but may lead to chronic instability.

III. ROTATOR CUFF DISEASE
A. History: Symptoms can range from minimal to marked pain limiting function and decreased range of motion. Special attention should be given to throwing athletes because they are prone to overuse injuries. Chronic tendinitis may present with night pain.

B. Physical
1. Tenderness over the greater tuberosity of humerus and painful abduction of arm. Positive drop arm test, supraspinator test, and impingement sign
2. Weakness or pain with internal or external rotation

C. Radiography
1. Plain films: AP and lateral films
2. MRI may be used in either the acute or chronic tear if rehabilitation has failed. MRI is 89–96% sensitive and 49–100% specific for rotator cuff tear.

D. Management
1. Acute tears: Begin with conservative treatment (rest, ice, and NSAIDs). Rehabilitation program to be started in 1–2 weeks. If not improved, consider MRI.
2. Chronic tears: Begin with a stretching and strengthening program, avoiding overhead activities. Consider ice, heat, massage and ionophoresis. Consider NSAIDs and/or corticosteroid injection. If patient improves, slowly work in overhead activities and then sport specific activities. With continued pain consider MRI and surgical referral.

E. Clinical Pearls
1. Rehabilitation (physical therapy) is the most important part of treatment
2. A partial thickness tear may easily progress to full thickness tear
3. Age is one of the great dividers in this injury

IV. IMPINGEMENT
A. Introduction: There are 2 reasons for impingement: Increase in volume of the structures in the space (muscle hypertrophy, inflammation, trauma) and decreased available space (fibrosis, osteophyte, convex acromion)
B. History: Patients present with a toothache-like pain in shoulder. Worse with overhead movements. Inquire about past history of any injuries to the shoulder (subluxations or rotator cuff) and any medical problems (inflammatory diseases). Night pain is common
C. Physical exam: Findings are consistent with early rotator cuff disease. Patient should not have any weakness of the cuff muscles. Positive impingement sign and Neer’s sign
D. Radiology: May indicate anatomic variations in acromions predisposed to impingement
E. Management: Relative rest with avoidance of overhead (greater than 90°) movements. Physical therapy for stretching and rehab of muscles. NSAIDs followed by injection of steroids in 2–4 weeks. Surgery may be needed in cases that do not improve or those that have osteophytes as the primary problem

V. ADHESIVE CAPSULITIS (FROZEN SHOULDER)
A. Introduction: Capsular thickening and contraction of shoulder joint that results in pain and limited mobility. More common in middle age women and diabetics. Number one predisposing factor is a prolonged period of inactivity
B. History: Patient almost always has some history of prolonged immobilization of shoulder. This may have been in the remote past but the patient has a new job or demand on the shoulder. Other symptoms include nocturnal pain and pain with movement
C. Physical exam: Stiffness and limited active and passive ROM in all directions, especially abduction. In abduction, patient will rely on scapulothoracic movement to abduct arm. Patient may have tenderness around capsule and a thickened capsule to palpation, and muscle spasm
D. Radiology: A decrease volume of the glenohumeral joint will be present in most cases
E. Management: NSAIDs and ROM exercises. Patient should rest arm in between exercises and sometimes a sling is used. Frozen shoulder may resolve spontaneously but in most cases prolonged treatment is needed. Steroid injections are used commonly but do not always help. In difficult cases manipulation under anesthesia is used. Rarely surgical intervention is needed but it does not have a high success rate

CLINICAL PEARLS
• MRI is 89–96% sensitive and 49–100% specific for rotator cuff tear

References
91. Elbow Injuries

I. ANATOMY
A. Olecranon humeral joint is a hinge joint
B. Radius articulates with capitulum and the ulna with trochlea
C. Lateral joint space is supported by radial and ulnar collateral ligament complexes
D. Upper extremity is innervated by 5 nerve branches that originate at brachial plexus (axillary, radial, musculocutaneous, ulnar and median nerves). Ulnar nerve is found easily by palpation in groove behind medial epicondyle

II. PATHOPHYSIOLOGY
A. In adults most injuries occur to ligaments, tendons, or bone itself
B. In children, the weakest links are the growth plates, apophysis and epiphysis
C. Tendon damage often occurs secondary to overuse and microrupture
D. Repetitive strains may lead to ligament damage, chondromalacia, osteophytes, tendonosis, neuritis, loose bodies, or osteochondritis dissecans
E. Overhead throwing can lead to medial tension overload, lateral compression, and posterior olecranon impaction

III. ELBOW PAIN BY ANATOMIC LOCATION
A. Lateral elbow pain
1. Lateral epicondylitis (Tennis elbow): Overload of forearm extensors, mainly extensor carpi radialis brevis causing microscopic ruptures and inflammation at the insertion to the bone
   a. History: Patient complains of pain, especially with combing hair, playing tennis or golf, shaking hands
   b. Physical exam: Pain over the tendon about 1–2 cm distal to the lateral epicondyle. Pain is exacerbated by active extension of the wrist or passive flexion
   c. Management: Conservative therapy with ice, NSAIDs, and physical therapy is usually successful. If not better after 1–2 weeks consider steroid injection (see Chapter 94, Corticosteroid Injection of Joints). Other important therapies are enforced proper technique, decreased string tension on racquet, applying a cushioned grip, and use of counter force bracing. Strengthening of the muscle may be accomplished by extending the fingers with an elastic band stretched over them or by reverse wrist curls. If not better after 12–16 weeks, consider surgery
2. Radial nerve entrapment
   a. History: Patient complains of local pain, paresthesias, dull ache
   b. Physical exam: Pain in forearm often with radiation proximal and distal. Pain exacerbated by supination and resisted extension of middle finger with wrist in neutral position. Tenderness often 2–3 cm distal to lateral epicondyle. May be aggravated by counter bracing
   c. Management: Rest, NSAIDs, and rehabilitation. Surgical release for resistant cases
3. Radiocapitellar Overload Syndrome
   a. History: Pain with overhead throwing
   b. Caused by radial head impaction on the capitellum during valgus stress of the elbow accompanied by medial instability. May consist of radiocapitellar chondromalacia, radiocapitellar degeneration, osteochondral fracture, or loose bodies
   c. Physical exam: Patient will have lateral pain and occasionally locking of the elbow
B. Medial elbow pain
1. Medial epicondylitis (Golfer’s elbow)
   a. History: Sharp pain, trouble lifting objects
   b. Physical: Pain at the common flexor origin. Sometimes affects pronator teres and
C. Posterior elbow pain

1. Triceps tendonitis
   a. History and physical: Pain over triceps tendon exacerbated by resisted elbow extension
   b. Management: Initial management with ice, NSAIDs, physical therapy. Rupture is rare and treated by direct surgical repair

2. Valgus extension overload syndrome
   a. Insidious onset of pain with full extension exacerbated by valgus stress. Caused by impingement of the olecranon allowed by ulnar collateral instability and repetitive valgus stress
   b. Physical exam: May find tenderness at the tip of the olecranon with the elbow in 45° of flexion
   c. X-ray: May reveal osteophytes of the olecranon
   d. Management: Conservative measures preferred, but if osteophytes present, surgery is required

3. Stress fracture of the olecranon
   a. Pain over olecranon with throwing. Due to the repetitive sudden snap at full extension. May need bone scan or CT to diagnose if not seen on x-ray
   b. Management: Rest if the fracture is stable. Surgery if conservative measures fail

4. Triceps apophysitis
   a. Seen in children and is similar to Osgood-Schlatter’s disease of the knee. Patient has pain with resisted extension and is tender over the olecranon
   b. Management: Internal fixation with bone grafting

5. Olecranon bursitis
   a. Presents with a distended soft posterior elbow
   b. Management: Ice and compression. May aspirate the bursa if elbow has decreased range of motion. Send for fluid analysis to ensure not infectious. Can inject with steroids

D. Anterior elbow pain

1. Anterior capsule stretch or tear: Can occur secondary to fall on extended elbow, resisted flexion, forceful supination, hyperextension, or direct trauma. Conservative measures are recommended

2. Pronator teres syndrome: Radiating forearm pain with numbness and tingling in distribution of median nerve. Physical exam reveals pain with active pronation and resisted long finger extension

3. Distal biceps tendon rupture
   a. Most often occurs when the elbow is flexed to 90° and the contraction is overcome by a sudden extension force
b. Physical exam will reveal a palpable deformity, balling of the biceps muscle, decreased strength in elbow flexion and supination, and ecchymosis in the antecubital fossa.

c. Acute surgical anatomic repair is treatment of choice.

E. Subluxation of the radial head (nursemaid’s elbow)

1. Definition and mechanism of injury
   a. Subluxation of radial head is common among preschool children. After age 7 radial head is larger than radial neck and subluxation is not common.
   b. Mechanism of injury is sudden traction on the hand with the elbow extended and the forearm pronated. Forceful traction fibers, which encircle the radial neck, slip and become trapped between the radial head and capitellum.

2. History
   a. Important to elicit a history of traction on the child’s hand; the act may have been unrecognized by the parent or the history withheld because of a feeling of guilt.
   b. About 50% of the radial head subluxations present with an atypical history.

3. Physical exam
   a. Child may present irritable, playful or comfortably in parents’ lap. Common symptom is unwillingness to use the extremity.
   b. Any child not using an arm that is flexed and pronated and without signs of trauma should be considered to have a radial head subluxation, unless history strongly suggests another diagnosis.

4. Evaluation: Radiographs are not necessary, unless another diagnosis is being considered or if reduction is not accomplished.

5. Management
   a. Reduction is carried out by firmly placing the thumb over the radial head while the other hand is placed on the wrist. Forearm is fully supinated. If a “click” is not felt, elbow is flexed. Maneuver may be repeated if initial attempt does not reduce subluxation.
   b. If a second attempt is not successful, then x-ray elbow.
   c. Reduction as evidenced by a “click” is highly predictive and will result in relief from pain and, shortly thereafter, use of the affected arm.
   d. After first subluxation, no immobilization is required. For recurrent subluxations, patient’s arm should be immobilized in a sling. Should be referred for orthopedic consultation.

CLINICAL PEARLS

- “Little League Elbow” is actually a constellation of diseases seen in skeletally immature athletes including medial epicondylar apophysitis, osteochondrosis of the radial head, osteochondrosis of the capitellum, and non-union of a stress fracture of the olecranon epiphysis. Due to overuse of overhead throwing.
- If triceps tendonitis doesn’t heal, consider an olecranon stress fracture.
- Encourage proper sporting technique, stretching, strengthening, and proper fitting equipment.

References
I. DEFINITION: Syndrome caused by compression of the median nerve as it passes through the carpal tunnel. Increased pressure in the carpal tunnel presumably leading to intraneural ischemia. The most common entrapment neuropathy of the upper extremity

II. SIGNS AND SYMPTOMS
A. The classic pattern includes pain and paresthesias in the distribution of the medial nerve (but may include the entire hand). Symptoms may often affect the fourth and fifth digits (ulnar nerve) and the wrist with or without proximal radiation. Pain and paresthesias may radiate to the forearm, elbow, and shoulder.
B. Symptoms often occur with activity but are often worse at night and are relieved by “flicking” the wrist.
C. Tinel’s sign: Paresthesias (tingling) in fingers when the volar aspect of wrist is tapped by examiner’s fingers.
D. Phalen’s sign: Symptoms reproduced by full flexion of the wrist for 60 seconds.
E. Direct median nerve compression test: Symptoms reproduced with direct pressure over the carpal tunnel for 60 seconds.
F. Weakness of thumb abduction.
G. Atrophy of thenar eminence (late finding).
H. Diminished 2-point discrimination and vibratory sensation of the index finger relative to the little finger (late finding).

III. ETIOLOGY
A. Repetitive motion injury (flexor tenosynovitis).
B. Trauma, Colles’ fracture, degenerative joint disease, rheumatoid arthritis, ganglion cyst.
C. Hyperparathyroidism, hypocalcemia, associated with diabetes, hypothyroidism, pregnancy, amyloidosis, acromegaly, use of corticosteroids and estrogens.
D. Poor work ergonomics.

IV. DIAGNOSIS
A. Clinical diagnosis: A history which correlates with physical exam (see signs and symptoms above). Most highly predictive findings are:
   1. Symptom location that fits with median nerve distribution.
   2. Hypoalgesia (diminished sensitivity to pain along the palmar aspect of the index finger).
   3. Weak thumb abduction.
B. Electromyography: Diagnostic standard for carpal tunnel syndrome. Obtain when diagnosis is in doubt. May have up to a 20% false negative rate. Will show prolonged distal latency of the stimulated nerve with reduced sensory nerve action potential.
C. MRI: Imaging is reserved for special concerns including anomalous muscle bellies, severe synovitis, or nerve tumors.

V. MANAGEMENT
A. Non-operative: Reassess efficacy in 4–6 weeks.
   1. Wrist splint (cock-up splint) in the neutral position—usually worn at night but wearing during daily activities has additional benefits. Splints alleviate symptoms in up to 80% of patients.
   2. NSAIDs: No more effective than placebo.
   3. Oral corticosteroids: More effective than placebo/NSAIDs. Dose used in studies is Prednisone 20mg PO QD for 2 weeks then 10mg PO QD for 2 weeks.
4. Intermittent Icing: 20 minutes TID
5. Corticosteroid injection: See chapter 94, Corticosteroid Injection of Joints. Long term efficacy is questionable but works well to relieve local ischemia and reduce synovial swelling in the carpal tunnel. Many patients relapse despite initial improvement

B. Operative: Recommended after failure of non-operative measures or if axonal loss is suspected (constant numbness, symptoms > 12 months, thenar muscle atrophy or weakness)
1. Open or endoscopically
2. Provides relief in >95% of patients
3. Progress to full utilization in 4–6 weeks

C. Prevention
1. Hourly breaks while performing repetitive work
2. Padded gloves to protect the carpal tunnel from vibration and trauma
3. Ergonomic changes

References
Katz JN, Simmons, BP. Carpal tunnel syndrome. NEJM 2002;346:1807–12.

93. Low Back Pain

I. INTRODUCTION
A. Low back pain (LBP) is one of the most common ambulatory complaints, with a 60–70% lifetime incidence
B. LBP is the second most common cause of repeat office visits and the most common cause of disability in patients <45
C. Red flags include: Age >65, previous cancer history, unexplained weight loss, fever, chronic infection, failure to improve after 1 month of therapy or duration of pain > 1 month, nighttime pain, history of intravenous drug use (IVDU), trauma, history of peripheral vascular disease
D. For such a common problem, there are relatively few randomized, controlled trials to guide management. Most patients improve with conservative management and do not require diagnostic studies

II. HISTORY AND PHYSICAL EXAMINATION
Goals are to exclude systemic disease, characterize neurologic deficits, determine the etiology of LBP, differentiate mechanical vs. non-mechanical pain, and evaluate for social or psychological distress which may amplify or prolong the pain

A. History
1. Determine mechanism of injury, onset, and duration
2. Location and character of pain
3. Constancy (intermittent, constant, or waxing and waning)
4. Distribution (focal, extended, or radiating)
5. Aggravating and relieving factors (position, etc.)
6. Presence (or absence) of radicular pain
7. Bowel or bladder dysfunction
8. Fever, weight loss, trauma, morning stiffness
9. Previous drug and therapeutic treatments (and their success or failure)
10. Life stressors
11. History of cancer, IVDU

B. Physical examination
1. Begin with observation of posture and gait, pain behavior
2. Motor examination includes hip flexion (L2), knee extension (L3), ankle dorsiflexion (L4), great toe dorsiflexion (L5), and ankle plantarflexion (S1)

**GRADING OF MUSCLE STRENGTH**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No movement</td>
</tr>
<tr>
<td>1</td>
<td>Trace movement without joint motion</td>
</tr>
<tr>
<td>2</td>
<td>Partially or fully moves body part with gravity eliminated</td>
</tr>
<tr>
<td>3</td>
<td>Completely moves body part against gravity</td>
</tr>
<tr>
<td>4</td>
<td>Moves body part against moderate resistance through full range of motion</td>
</tr>
<tr>
<td>5</td>
<td>Normal</td>
</tr>
</tbody>
</table>

3. Reflex examination includes patella or knee jerk (L4), medial hamstring (L5) and Achilles or ankle (S1)
4. Because the sensory exam can be quite time consuming, instruct the patient to point out areas of sensory deprivation and compare to a dermatomal map
5. Limitation of lumbosacral range of motion should be noted in extension, flexion, side-bending, and rotation; palpation of the low back and buttocks can help localize pain and detect tender or “trigger points”
6. Straight leg raise test: Passive elevation of the lower extremity on the symptomatic side to less than 60° while the patient is supine; the test is positive with resulting radicular pain. Sensitivity is 95%, specificity is 40%
7. Abdominal exam for organomegaly, pulsatile abdominal mass
8. Look for Waddell signs (at least 3 indicate a psychologic or non-organic component of the pain)
   a. Inappropriate or widespread tenderness
   b. Pain on simulated physical maneuvers
   c. Inconsistent exam while patient is distracted
   d. Regional non-anatomic distribution of pain or weakness
   e. Overreaction to exam (excess moaning or grimacing)

III. DIAGNOSTIC STUDIES
A. Radiologic studies: Generally overused. *If a careful history and physical examination indicate acute musculoskeletal/radicular LBP in a patient age 20–50, radiologic imaging is unnecessary*
1. Indications for radiographs
   a. Trauma to exclude fracture
   b. Possible neurologic deficits, fever, unexplained weight loss, history of cancer, corticosteroid use or IVDU, or suspicion of serious underlying illness based on “red flags” (see I. C., above). Note: If any of these diagnoses are being evaluated, the sensitivity of plain x-rays is very poor and other diagnostic testing such as CBC, ESR, or MRI should be considered
2. Indications for MRI (note: see below for the incidence of false positive findings on MRI
   a. Suspicion of serious underlying cause of pain
   b. Progression of symptoms despite conservative management
   c. Prior to evaluation for surgery or epidural steroid injections
   d. MRI and clinical symptoms do not always correlate. Studies on asymptomatic volunteers < 60 show that 22–54% have herniated or bulging disc and the prevalence in patients > 60 is 36–79%
3. Bone scan: Indicated to evaluate osteomyelitis, neoplasm or occult fracture

B. Electrodiagnostic studies (EMG) assess the neurophysiologic status of the nerve fibers but do have some limitations and are not helpful for acute back pain
C. Laboratory: As indicated to screen for serious underlying illness (see I. C., above)

<table>
<thead>
<tr>
<th>STUDY</th>
<th>SUBJECTS</th>
<th>ANATOMICAL FINDINGS</th>
<th>prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>STUDY SUBJECTS</td>
<td>Herniated Disk</td>
<td>Bulging Disk</td>
</tr>
<tr>
<td>Boden et al.</td>
<td>Volunteers &lt;60 yr old</td>
<td>22</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Volunteers &gt;60 yr old</td>
<td>36</td>
<td>79</td>
</tr>
<tr>
<td>Jensen et al.</td>
<td>Volunteers (mean age, 35 yr)</td>
<td>28</td>
<td>52</td>
</tr>
<tr>
<td>Weishaupt et al.</td>
<td>Volunteers (mean age, 35 yr)</td>
<td>40</td>
<td>24</td>
</tr>
<tr>
<td>Stadnik et al.</td>
<td>Patients referred for head or neck imaging (median age, 42 yr)</td>
<td>33</td>
<td>81</td>
</tr>
</tbody>
</table>

*NR denotes not reported. References omitted.


IV. DIFFERENTIAL DIAGNOSIS OF LOWER BACK PAIN

<table>
<thead>
<tr>
<th>Disease or condition</th>
<th>Patient age (years)</th>
<th>Location of pain</th>
<th>Quality of pain</th>
<th>Aggravating or relieving factors</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back strain</td>
<td>20 to 40</td>
<td>Low back, buttock, posterior thigh</td>
<td>Ache, spasm</td>
<td>Increased with activity or bending</td>
<td>Local tenderness, limited spinal motion</td>
</tr>
<tr>
<td>Acute disc herniation</td>
<td>30 to 50</td>
<td>Low back to lower leg</td>
<td>Sharp, shooting or burning pain, paresthesia in leg</td>
<td>Decreased with standing; increased with bending or sitting</td>
<td>Positive straight leg raise test, weakness, asymmetric reflexes</td>
</tr>
<tr>
<td>Osteoarthritis or spinal stenosis</td>
<td>&gt;50</td>
<td>Low back to lower leg; often bilateral</td>
<td>Ache, shooting pain, <em>pins and needles</em> sensation</td>
<td>Increased with walking, especially up an incline; decreased with sitting</td>
<td>Mid decrease in extension of spine; may have weakness or asymmetric reflexes</td>
</tr>
<tr>
<td>Spondylolisthesis</td>
<td>Any age</td>
<td>Back, posterior thigh</td>
<td>Ache</td>
<td>Increased with activity or bending</td>
<td>Exaggeration of the lumbar curve, palpable &quot;step off&quot; (defect between spinous processes), tight hamstrings</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>15 to 40</td>
<td>Sacroiliac joints, lumbar spine</td>
<td>Ache</td>
<td>Morning stiffness</td>
<td>Decreased back motion, tenderness over sacroiliac joints</td>
</tr>
<tr>
<td>Infection</td>
<td>Any age</td>
<td>Lumbar spine, sacrum</td>
<td>Sharp pain, ache</td>
<td>Varies</td>
<td>Fever, percussive tenderness; may have neurologic abnormalities or decreased motion</td>
</tr>
<tr>
<td>Malignancy</td>
<td>&gt;50</td>
<td>Affected bone(s)</td>
<td>Dull ache, throbbing pain, slowly progressive</td>
<td>Increased with recumbency or cough</td>
<td>May have localized tenderness, neurologic signs or fever</td>
</tr>
</tbody>
</table>


V. TWO CATEGORIES OF LBP

A. Mechanical/discogenic
   1. Acute undetermined soft tissue injury (LUMBOSACRAL SPRAIN): May present with lumbosacral pain following a traumatic injury or possibly accompanied by a tearing sensation while lifting
      a. History and physical examination reveal no evidence of radiculopathy
      b. The natural history of nonspecific LBP (often referred to as lumbosacral strain)
is that ½ are substantially better at 1 week and ¾ at 7 weeks. Reoccurrences are common.

Treatment

i. NSAIDs, muscle relaxants and analgesics
ii. Physical therapy emphasizes stretching hamstrings, gluteals, hip flexors, and tensor fascia lata
iii. Instruction on strengthening of extensor muscles (walking, jogging, swimming) and proper lifting techniques

2. Acute discogenic LBP (HERNIATED DISC): Caused by either disruption of the annular fibers of the disc or herniation of the disc with resulting nerve root impingement (radiculopathy)

a. Radiculopathy almost always involves the L5 or S1 nerve root
b. The peak age for herniated disc disease is 30–55

c. History: Usually includes a previous episode of similar LBP that resolved spontaneously in 3–5 days; patients often complain that pain is worse in a seated position; occurs after lifting or trauma
d. The natural history of herniated disc is that ½ have partial or complete resolution at 6 months

e. Treatment

i. In patients without progressive neuro deficit or cauda equina syndrome, use conservative management for at least 1 month
ii. Bed rest for no more than 2–3 days if patient is unable to ambulate
iii. A steroid taper or NSAIDs to decrease inflammation and provide relief
iv. Pain control
v. Physical therapy
vi. Epidural steroid injections or surgery for patients who fail to improve with conservative treatment

3. Chronic LBP: Most episodes of acute LBP respond by 10–12 weeks. Pain beyond this time frame should result in the following actions

a. Review the diagnosis to exclude systemic disease
b. Determine patient compliance with activity modifications and meds
c. Review the type of treatment patient is receiving in physical therapy
d. Screen for an underlying depression (see Chapter 109, Depression) or myofascial pain/fibromyalgia

B. Non-mechanical

1. Cancer: Multiple myeloma, metastatic disease to bone from lung, prostate, kidney, or breast
2. Gynecologic
3. Renal: UTI/pyelonephritis, renal colic, renal artery occlusion
4. Rheumatoid arthritis: Morning stiffness > 1 hr, improvement with exercise, gradual onset of symptoms, and pain duration > 3 months
5. Gastrointestinal: PUD, pancreatitis
6. Osteoporosis/compression fractures: See Chapter 115, Compression Fractures
7. Vascular: Abdominal aortic aneurysm (AAA)

VI. MANAGEMENT

A. Meds: NSAIDs, muscle relaxants and analgesics (narcotic or non-narcotic) may be effective (see Chapter 106, Pain Management)

B. Physical therapy: May be used in the acute phase and may include superficial heat, deep heat, ultrasound, cold packs, massage, instruction in stretching, lifting techniques and exercise

C. Chiropractic: Studies have suggested that chiropractic intervention may be useful

D. Psychologic: Most useful reliable predictor of return to work after a back injury is prior job satisfaction. Patients with depression or substance abuse may have difficulties with pain resolution. Pending litigation may affect return to work

E. Physical therapy: Communication

F. Surgery Note: There is no evidence from trials that surgery is effective unless patients have radicular pain, pseudoocludication, or spondylolisthesis
Indications for Surgical Referral Among Patients with Low Back Pain

### Sciatica and Probable Herniated Disks
- The cauda equina syndrome (surgical emergency): characterized by bowel or bladder dysfunction (usually urinary retention), numbness in the perineum and medial thighs (i.e., in a saddle distribution), bilateral leg pain, weakness, and numbness
- Progressive or severe neurologic deficit
- Persistent neuromotor deficit after 4-6 weeks for nonoperative therapy
- Persistent sciatica (not low back pain alone) for 4-6 weeks, with consistent clinical and neurologic findings (in this circumstance, and for persistent neuromotor deficit, surgery is elective, and patients should be involved in decision making)

### Spinal Stenosis
- Progressive or severe neurologic deficit, as for herniated disks
- Back and leg pain that is persistent and disabling, improves with spine flexion, and is associated with spinal stenosis on imaging tests; surgery is elective, and patients should be involved in decision making

### Spondylolisthesis
- Progressive or severe neurologic deficit, as for herniated disks
- Spinal stenosis with referral indications as above
- Severe back pain or sciatica with severe functional impairment that persists for a year or longer


**CLINICAL PEARLS**

- In patients with spinal stenosis, 70% are stable at 4 years, 15% improved, and 15% worsen.
- Low back pain in a patient taking long-term corticosteroids is a compression fracture until proven otherwise.
- 98% of clinically significant lumbar disc herniations occur at either the L4-5 or L5-S1 level.
- The single most reliable predictor of return to work is job satisfaction.
- Scoliosis is 80% idiopathic. The presence of concurrent back pain is a red flag to look for other causes (cerebral palsy, muscular dystrophy, spina bifida, neurofibromatosis, tumor).
- For back pain in pregnancy: Can use Acetaminophen, maternity back supports, or physical therapy (except ultrasound).

**References**


94. Corticosteroid Injection of Joints

I. INTRODUCTION: Joint aspiration and injection can be a part of any primary care office. Aspiration can give symptomatic relief and a quick diagnosis with fluid analysis. Joint injection can be part of a diagnostic exam of a painful joint (Lidocaine) or part of a treatment plan (steroids)

II. GENERAL LIST OF CONDITIONS IMPROVED WITH STEROID INJECTION

A. Articular conditions: Rheumatoid arthritis, ankylosing spondylitis, arthritis associated with inflammatory bowel disease, psoriasis, Reiter’s syndrome, gout, pseudogout, osteoarthritis

B. Nonarticular disorders: Fibrositis, bursitis, adhesive capsulitis, tenosynovitis/tendonitis, tennis elbow, golfer’s elbow, plantar fasciitis, carpal tunnel syndrome, tarsal tunnel syndrome, costochondritis, Tietze’s syndrome

III. CONTRAINDICATIONS TO JOINT INJECTION/ASPIRATION

A. Cellulitis or broken skin over the entry site
B. Coagulopathy or uncontrolled anticoagulation
C. Prostheses
D. Septic effusion, unstable joints, lack of response to previous injections (steroids)
E. Allergy to injected med

IV. SIDE EFFECTS

A. Steroid arthropathy
B. Tendon rupture
C. Skin atrophy, depigmentation
D. Iatrogenic infectious arthritis
E. Acceleration of cartilage attrition
F. Lipodystrophy
G. Transient hyperglycemia (most important for diabetics)

V. TECHNIQUE: Follow standard sterile procedure for any procedure where skin barrier is broken. Locate your landmarks and mark entry point with thumbnail or pen. Prep area and aspirate the joint. Use hemostat to hold needle in place if syringes are switched to inject joint. Never inject directly into a nerve or tendon

A. Knee: Place the knee in a slightly flexed position by placing a towel under the popliteal space. A lateral or medial approach may be used. Find the superior lateral (medial) border of the patella. Mark a point perpendicular to the border at a level just posterior to the patella. Insert needle at that point keeping the needle perpendicular to the axis of the knee and guide the needle under the patella. There should be no resistance

B. Subacromial bursa: Locate the lateral edge of the acromion just posterior to the AC joint. There is usually a soft spot just superior to the humeral head. Insert the needle through the deltoid muscle and under the acromion. Needle should move freely in the space

C. Plantar fascia: Medial approach is done by locating the most tender point of the fascia’s insertion. From the medial side of the foot insert the needle perpendicular to the bottom of the heel and superior to the heel fat pad

D. Greater trochanter: Insert needle over the point of maximum tenderness making sure that the needle remains perpendicular to the femur. Patient will usually have pain when the needle enters the bursa

E. Olecranon bursa: Place the elbow at 90° of flexion and insert the needle into the area of most fluid. Tensing the bursa in your opposite hand may help you to localize the best insertion site
94. Corticosteroid Injection of Joints  
Musculoskeletal/Sports Medicine

F. Carpal tunnel: Dorsiflex the wrist to 30° and locate the palmaris longus tendon. Insert the needle proximal to the carpal tunnel and radial to the palmaris longus. Advance the needle downward at a 45° angle toward the middle finger. Advance the needle 1–2 cm until there is no resistance. If there is any discomfort in the fingers pull back the needle and redirect.

G. Acromioclavicular joint: With patient seated and arms relaxed to sides, the joint sulcus is identified. A superior approach is used to guide needle into posterior portion of joint. Need to fan out the medication in this space.

H. DeQuervain’s Tenosynovitis: Tendon identified by placing thumb in the hitchhiking position. With thumb relaxed, insert needle into the tendon sheath. Movement of thumb will identify if needle has been placed in tendon. Do not inject tendon directly. Injection will meet little resistance if needle is in proper position.

I. Glenohumeral joint: A posterior approach is used. Location for needle insertion is approximately 2 cm medial to posterior lateral corner of the acromion. Needle is inserted into joint while aiming at the coracoid process. Med should flow freely.

VI. GENERAL GUIDELINES FOR EQUIPMENT AND STEROID DOSING

A. Technique
1. Mark the injection site
2. Clean with povidone iodine and then clean with alcohol prep
3. Consider anesthetizing site with ethyl chloride spray

B. Meds
1. Steroid: Kenalog, Decadron, Depo-Medrol, Celestone
   a. Kenalog 40mg/mL (K-40)
   b. Kenalog 10mg/mL (K-10)
   c. Depo-Medrol 80mg/mL (D-80)
   d. Depo-Medrol 40mg/mL (D-40)

2. Anesthetic: Lidocaine (Xylocaine), Bupivacaine, (Sensorcaine)
   a. Lidocaine 1% without Epinephrine (L)
   b. Sensorcaine 0.25% (S)

C. Materials: Size of needle, type and amount of steroid and anesthetic
1. AC joint
   a. 22 gauge, 1½” needle
   b. 1mL (K-40) + 1–2mL (L)
2. Shoulder (subacromial bursa; joint)
   a. 22–27 gauge, 1/8”–1½” needle
   b. 1mL (K-40) + 5mL (L) or 1mL (D-40) + 1mL (K-40) or (K-10) + 3mL (L)
3. Elbow (olecranon bursa; joint)
   a. 22 gauge, 1”–1⅛” needle
   b. ½–1mL (K-40) + 1–2mL (L)
4. Elbow (lateral epicondyte)
   a. 25 gauge, ¼” needle
   b. ½mL (D-80) + 1mL (L)
5. Wrist (joint)
   a. 25 gauge, ¼” needle
   b. ½mL (D-80) + ½mL (L)
6. Wrist (carpal tunnel)
   a. 25 gauge, ⅛”–⅜” needle
   b. ½mL (D-40) only
7. Hip (pointer)
   a. 18–22 gauge, 1⅜” needle
   b. 2mL (K-40) + 10mL (L)
8. Hip (femoral trochanter bursa)
   a. 22 gauge, 1” needle
   b. 1mL (D-40) + 1mL (K-40 or K-10) + 3mL (L)
9. Knee
   a. 22 gauge, 1¼” needle
   b. 1mL (K-40) + 2–5mL (L)
10. Ankle
   a. 20–22 gauge, 1½" needle
   b. 1mL (D-40) + 1mL (L)
11. Heel (spur)
   a. 18–25 gauge, ½"–1½" needle
   b. 1mL (K-40) + 2–3mL (L)
12. Muscle (general trigger pain)
   a. 25 gauge, ½" needle
   b. 1mL (D-40) + 2–3mL (L)

References

Timothy P. Graham, MD

95. OCCUPATIONAL MEDICINE

I. INTRODUCTION—Occupational medicine is a multi-faceted discipline which includes
   the evaluation and management of industrial injuries, pre-employment physical examina-
   tions, Department of Transportation (DOT) evaluations, determinations of fitness to re-
   turn to work, disability evaluation and employee wellness. Many specifics of the legal
   aspects of the management of occupational injuries are variable dependent upon the
   specific State in which the care is provided

II. TERMINOLOGY
   A. Additional allowance: A condition not originally recognized in the claim which is
      requested to be added to the claim as an allowed condition
   B. Allowed condition: This is a medical condition that is recognized within an industrial
      claim as being related to the original injury either directly or indirectly. Only allowed
      conditions in a claim may be treated through the industrial claim
   C. Causation: The relationship of a presenting condition to an alleged industrial injury
   D. Cumulative trauma: A condition arising out of repeated exposure to a moderate or
      high-risk occupational situation
   E. Disallowed condition: A condition that has been requested to be part of an industrial
      claim which is determined to not be reasonably related to the injury either directly or
      indirectly. Disallowed conditions cannot be treated through an industrial claim
   F. Flow-through condition: A condition that did not occur at the time of the original
      injury but has been determined to be reasonably related to the conditions allowed in
      the claim. For example, a patient who underwent a shoulder surgery and subsequently
      developed cellulitis at the incision site
   G. Independent Medical Evaluation (IME): Evaluation requested when there is a dis-
      agreement with the allowance of a claim, a condition, or a requested service in an
      industrial claim. The independent medical examiner is a physician who provides an
      expert opinion on the appropriateness of a claim. The IME physician does not estab-
      lish a doctor-patient relationship with the injured worker and does not provide medi-
      cal care for the injury
   H. Maximum Medical Improvement (MMI): This refers to the point where a specific
      condition has had all reasonably appropriate and necessary treatment that the injured
      worker is agreeable to, and no further improvement can be expected. MMI does not
      mean that the injured worker cannot receive ongoing maintenance care, but it can
      affect compensation if they are unable to continue to work
   I. Physician of record: This term refers to the primary physician who is managing the
      injured worker’s care. The injured worker can only have one physician of record,
although they can be referred to other specialists as necessary. Whether the patient can choose their physician of record is dependent upon the State regulations.

J. Statute of limitations: The amount of time that a claim can still be filed after the original injury or that a claim can remain open without ongoing activity. This varies from State to State.

K. Substantial aggravation: A condition that pre-existed an industrial injury is objectively demonstrated to be worsened by the injury.

L. Unallowed/unrecognized condition: These terms refer to conditions that have not been requested to be part of an industrial claim. These conditions cannot be treated through the claim without being approved as additional allowances.

III. INITIAL EVALUATION OF ALLEGED WORK-RELATED INJURIES

A. General—Occupational medicine is different from traditional primary care, in that the only conditions that can be addressed in the visit are those related to the industrial injury. The initial evaluation of an industrial injury is extremely important, as it is the best opportunity to obtain the details necessary for determination of causation. When opening a new claim for a patient presenting for the first evaluation of an alleged occupational injury, the provider will be asked for an opinion regarding whether or not the presenting conditions are related to the injury as described by the injured worker.

B. History

1. A description of the injury itself: This should include specifics about posture, body part position, weight/force (when applicable), amount of time engaged in the activity described, length of employment, and any extraneous factors that may have contributed to the injury (e.g., a broken/malfunctioning piece of equipment).
2. Past medical history: History of prior injuries to the same body part(s), prior surgeries or potentially confounding medical conditions (pre-existing osteoarthritis, etc.).
3. Treatment: What has the worker done for the injury thus far? Been seen elsewhere? Go to the Emergency Department? Used over-the-counter anti-inflammatories/analgesics?

C. Physical exam

1. If musculoskeletal, include inspection, palpation, range of motion testing, strength testing, sensory testing and special testing when appropriate.
2. Evaluation of the joint above and below the injured joint.
3. Progression: Document specific parameters (e.g., range of motion and grip strength) to monitor over time.

IV. INJURY MANAGEMENT—Only conditions related to the original injury and allowed in the industrial claim may be treated. This requires the establishment of causality as related to the injury as either work-related or non work-related.

A. Establishing causation: Often the most challenging part of the treatment. The treating physician must gather and synthesize information, physical exam findings and diagnostics to determine whether or not the presenting condition is or is not likely related to the alleged injury.

B. Opening a claim: Once causation has been determined, the physician of record will help the injured worker open a claim. The process of doing this varies from state to state. Most forms ask for an expert opinion from the treating physician as to whether or not the conditions being treated are or are not related to the injury.

C. Initial management: Workers compensation is driven by protocols and evidence-based injury management guidelines. Several well-established resources are available to assist with determining the appropriate course of treatment, including guidelines from the Work Loss Data Institute and the Official Disability Guidelines (ODG). Following these guidelines makes it more likely that any services being requested will be approved. All services necessary for treatment of the injury generally need to be approved by the workers compensation authority or a third-party administrator before they can be scheduled.

D. Designation of Maximum Medical Improvement (MMI): After all therapies have been attempted and there is no further expectation of improvement, the injured worker is designated to have reached a point of maximum medical improvement.
E. **Closing a claim**: A claim may close after a period of inactivity, and will eventually become a "dead claim," which is a legal determination that may vary from State to State.

V. **DEPARTMENT OF TRANSPORTATION (DOT) EXAMINATIONS/COMMERCIAL DRIVERS LICENSE (CDL) EXAMINATIONS**

A. **DOT Examinations**: The Department of Transportation is a federal governing body that regulates drivers engaged in commercial transport (trucking, aviation, railway or waterway).

B. **Specific physical requirements for drivers—potential contraindications**
1. Diabetes mellitus requiring insulin
2. Uncontrolled hypertension
3. Narcolepsy
4. Seizures
5. The use of schedule I medications
6. Alcoholism
7. Vision impairment (worse than 20/40)

C. **Maximum clearance is 2 years—may be a shorter period if hypertension is uncontrolled, etc.**

D. **Medical providers will be required to complete a medical examiner training program**

References
www.fmcsa.dot.gov
www.odg-twc.com
VIII. Dermatology

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96. DESCRIBING DERMATOLOGIC LESIONS

I. TYPE OF LESION (see illustrations on next page)

A. Macule: A circumscribed area of skin in which the color is different from the surrounding skin. (Can differentiate from papule by oblique lighting). A macule is flat and may measure up to 1cm

B. Patch: A flat area of color change > 1cm in size (basically a macule >1cm)

C. Papule: A solid lesion, generally < 0.5cm in diameter, that is elevated above the plane of the surrounding skin. Confluence of papules leads to plaque formation

D. Nodule: A palpable, solid, round or ellipsoidal lesion that is deeper than a papule and is in the dermis or subcutaneous tissue (basically a large papule). These result from infiltrates, neoplasms or metabolic deposits and are often indicators of systemic disease

E. Vesicle: A circumscribed, elevated fluid-containing lesion (blister) < 0.5cm, often translucent

F. Bulla: A blister measuring greater than 0.5cm. Both bulla and vesicles are formed from a cleavage at various levels of the skin, i.e., epidermal layers or dermal-epidermal interface

G. Pustule: Blister filled with pus

H. Plaque: An elevation above the skin surface that occupies a relatively large area in comparison with its height above the skin

I. Wheal: An edematous pink papule or plaque that is characteristically evanescent, disappearing within hours

J. Crusts: Dried serum, blood or exudate on the surface of the skin
   1. Honey-colored: Impetigo
   2. Thick and adherent over entire epidermis: Ecthyma

K. Erosion: A break in the surface epithelium

L. Ulcer: A skin defect in which there has been loss of the epidermis and dermis. Describe the location, borders, base, discharge and any topographic features

M. Comedone: A plugged pilosebaceous opening, open (blackhead) vs. closed (whitehead)

N. Burrow: A linear trail produced by parasites

O. Atrophy: Loss of substance in the epidermis, dermis, and/or subcutaneous tissue

P. Telangiectasia: A superficial dilatation of blood vessels

Q. Purpura: Non-blanching red or violaceous lesions

R. Cyst: A cavity with a lining containing liquid or semisolid material

S. Scale: Superficial dead epidermal cells cast off from the skin

T. Fissure: Skin split extending into the dermis

U. Excoriation: Superficial skin erosion caused by scratching

V. Lichenification: Skin markings and thickening with induration secondary to chronic inflammation caused by irritation (such as scratching or pressure point)
II. COLOR: Of either the skin (if diffuse involvement) or the lesion
   A. White
      1. Hypopigmented
      2. Depigmented (no pigment)
   B. Erythema
      1. Pink
      2. Violaceous
   C. Brown
      1. Hypermelanosia
      2. Hemosiderin
   D. Black, blue, gray, orange, yellow

III. PALPATION
   A. Soft, firm, hard, fluctuant, board-like
   B. Temperature difference
   C. Mobility of lesion
   D. Tenderness
   E. Depth

IV. SHAPE
   A. Round
   B. Oval
   C. Polygonal
   D. Polycyclic
   E. Annular
   F. Iris
   G. Serpiginous

Source: Goldstein BG, Goldstein AO, eds. Practical Dermatology, 2nd ed. St. Louis: Mosby, 1997; Tables 1–1, 1–2. With permission from Elsevier, Inc.
97. Contact Dermatitis

I. DEFINITION: Acute, subacute or chronic inflammation of the epidermis and dermis caused by external agents, toxicity or an allergic reaction and characterized by pruritus or burning

II. TYPES
A. Allergic contact dermatitis: Cell-mediated type IV hypersensitivity reaction
B. Irritant contact: Due to inflammation from a local toxic effect of a chemical on the skin
C. Contact photodermatitis: A type of allergic contact dermatitis triggered by ultraviolet light
D. Contact urticaria: Wheal and flare reaction—may be allergic (IgE) or nonallergic

III. HISTORY
A. Family history of atopy
B. Exposure history: Inquire about new exposures to common irritants (listed below)
   1. Nickel: Cheap jewelry, metal clothing fasteners, coins
   2. Potassium Dichromate: Cement, paper, leather, metal paint, detergent
   3. Paraphenylenediamine: Hair dyes, ink, fur dyes, radiographic fluid
   4. Chrome
   5. Formaldehydes: Permanent press fabrics, shampoos, smoke
   6. Rhus plants: Poison ivy, oak and sumac
C. Duration of lesions and previous successful or unsuccessful therapy

IV. PHYSICAL EXAM

CLINICAL PEARLS
- Persistent and unidentifiable nodules should be biopsied and a portion ground and cultured for fungi and bacteria
- If a wheal remains longer than 72hrs, consider biopsy as this can be caused by urticarial vasculitis

Ryan Hanson, MD
John Rockwood, PA-C
97. Contact Dermatitis

A. Acute contact dermatitis: Vesicles and/or bullae filled with clear fluid or erythematous, edematous skin
B. Subacute contact dermatitis: Erythema, minimal edema, multiple papules
C. Chronic contact dermatitis: Lichenified plaques with minimal erythema, minimal edema, possible scales
D. Rhus dermatitis (poison ivy dermatitis—see below)
E. Attempt to correlate the location of the eruption with exposure (e.g., dermatitis due to nickel in cheap earrings is present on the earlobes)
F. Evaluate for secondary infection

V. PATCH TESTING
A. Patch testing may be performed in patients who are suspected of having contact allergy but no allergen can be elicited by history. This should be done after the episode of dermatitis has resolved
B. Apply patch test to skin on back and occlude for 48hrs
C. Interpret in 72hrs
D. Positive test with the development of erythema, papules, vesicles

VI. MANAGEMENT
A. Identify and eliminate the offending agent, i.e., remove exposure
B. Wet compresses for oozing and vesiculation
C. Wash BID with soap and water
D. Burrow's solution: Aluminum Acetate tablets in water (1:40) for wet compresses, then apply steroid cream to suppress inflammation
E. Topical steroid cream: Use a stronger cream for areas of thick skin (back of arms, palms, etc.) (see Chapter 100, Topical Steroids, for a listing of different steroid creams.) Do not use fluorinated steroid creams on face as it may result in depigmentation of skin
F. Systemic (oral) corticosteroids for extensive dermatitis. Begin with Prednisone 1–2mg/kg/day (40–60mg max) given QD or as a divided dose and taper over 2–3 weeks. An easy taper is to give: Prednisone 10mg. Give #30. Use 4 pills per day for 3 days, 3 pills per day for 3 days, 2 pills per day for 3 days and 1 pill for 3 days. Shorter courses may result in a rebound phenomenon
G. Symptomatic meds
1. Adults
   a. Hydroxyzine (Atarax): 25mg PO TID–QID
   b. Diphenhydramine (Benadryl): 25–50mg PO TID–QID
2. Children
   a. Younger than 6yrs: Hydroxyzine (10mg/5cc), 25–50mg/day PO in divided doses,
      ≥ 6yrs: 50–100mg/day divided TID
   b. Benadryl: 12.5mg/5mL, used in children > 20lb; 2–6yrs: 6.25mg Q 4hrs, not to exceed 25mg/24hrs; 6–12yrs: 12.5–25mg Q 4–6hrs

VII. RHUS DERMATITIS: POISON IVY, POISON SUMAC, ETC.
A. Hypersensitivity reaction from exposure to rhus plants either directly (by contact with a plant) or indirectly (by contact with something which has been exposed to the plant and carries its oils—clothing, gloves, pets, shoelaces, etc.)
B. Exanthem develops over 48–72hrs and consists of linear vesicles (with direct exposure) or grouped vesicles (with indirect exposure) which may be weeping. The fluid inside the vesicles is not contagious as it does not contain the plant oils
C. Complications: Infection
D. Management
1. Wash lesions BID with soap and water
2. Cold washcloth or shower will help decrease itching
3. Symptomatic meds: See VI. G. above
4. Topical steroid cream: See VI. E. above
5. Oral steroids: Indicated for most rhus rashes unless small area (topical) or asymptomatic or contraindicated. See VI. F. above
6. Cut fingernails short in children
7. Patients (especially children) should be educated in identification of plants
CLINICAL PEARLS

• A rash from poison ivy that seems to be spreading may be caused by repeated exposure to the plant, exposure to clothes/pets which bear the oils, or different sensitivities of the skin which has been exposed (arm vs. face).

• Contact dermatitis is one of the most common reasons for worker’s compensation claims for skin disease.

References

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Miriam Chan, PharmD
Michael B. Weinstein, MD
Daniel M. Neides, MD

98. ACNE & ROSACEA

I. DEFINITION

A. Acne vulgaris: Chronic inflammation of the pilosebaceous units, caused by increased sebum production, abnormal follicles, propionibacterium, and hormonal and immunological factors.

B. Rosacea: Chronic acneform inflammation of the pilosebaceous units of the face coupled with an increased reactivity of the capillaries to heat, leading to flushing and telangiectasias.

C. Special forms of acne include:
   1. Acne conglobata: Severe cystic acne with coalescing nodules, cysts and abscesses.
   2. Acne fulminans: Acute, severe suppurative cystic acne with fever and generalized arthritis.

— PART ONE: ACNE VULGARIS —

II. ETIOLOGY

A. Caused by Propionibacterium

B. Endocrine
   1. Premenstrual and androgenic disorders such as polycystic ovary, or Cushing’s syndrome.
   3. Hirsutism.

C. Environment
   1. Humidity.
   2. Excessive sweating.
   3. Working in an environment with aerosolized fats (i.e., fast-foods).

D. Mechanical
   1. Pressure.
   2. Constant rubbing of clothes.
   3. Picking/squeezing: May lead to scarring and worsening.
   4. Washing with harsh soaps, excessive scrubbing.

E. Cosmetics

F. Meds: Steroids, ACTH, androgens, Dilantin, barbiturates, Lithium, Isoniazid, Cyclosporine, iodides and bromides, oral contraceptives with strong androgens and/or anti-estrogenic activity.
III. HISTORY
A. Duration and previous successful and unsuccessful therapies
B. Relation to menses
C. Presence of hirsutism
D. Cleansing habits (vigorous scrubbing, etc.), cosmetics
E. Mechanical factors: Tight clothing, constant rubbing of clothes, picking and squeezing
F. Meds: Listed above
G. Seasonal prevalence: Often worse in fall and winter
H. Diet: No firm studies link diet to acne, but patients may notice worsening of acne after eating certain foods

IV. PHYSICAL
A. Comedones: Sebum clogged sebaceous follicles, open (blackheads) or closed (whiteheads)
B. Pustules: Erupting follicular contents
C. Papules: Inflammatory raised lesions in dermis
D. Cysts: Deep, intense inflammatory papule progressing to fluctuant, painful area
E. Seborrhea may also be seen
F. Inspect face, back, chest and buttocks for lesions and scarring
G. Severity: To guide treatment
   1. Type 1: Mild—Inflammatory acne: Comedonal, less than 10 lesions, face only, no scarring
   2. Type 2: Mild—Papular acne: Less than 25 lesions, face and trunk, mild scarring
   3. Type 3: Moderate—Pustular acne: More than 25 lesions with moderate scarring
   4. Type 4: Severe—Cystic acne: Nodulocystic with extensive scarring

V. LABS: Indicated in young women who don’t respond to therapy
A. Hormone testing: Androgens, plasma testosterone, dihydroepiandrosterone, partial 11- or 12-hydroxylase block
B. Genetics: Severe acne in XYY
VI. MANAGEMENT: Listed by type of acne. For doses of meds see below

- **Mild (Comedones)**
  - Start with Retinoid
  - Adapts in 4-8 wks
  - Consider adding topical antibiotics

- **Mild (Papules/pustules +/- Nodules 0)**
  - Start with Retinoid or topical antibacterials or start with both

- **Moderate (Papules/pustules ++/++++ Nodules +/++)**
  - Use as combination therapy initially or add later

- **Severe (Papules/pustules +++/+++++ Nodules ++/++++)**
  - Minimal scarring: try conventional topical and oral Rx before Accutane
  - Scarring, long history of acne, treatment, failed other Rx, depressed with appearance

- **Minimal scarring:**
  - Try conventional topical and oral Rx before Accutane

- **Scarring, long history of acne treatment, failed other Rx, depressed with appearance:**
  - Retinoid or topical antibiotics

- **Maximum effect at 8 weeks then add retinoid if acne is not controlled**

- **Rx fails Accutane:**
  - Use as combination therapy initially or add later
  - Oral antibiotic (3 month trial)

- **Women:**
  - Rx fails
  - Not a candidate for Accutane
  - Relapse after second course of Accutane
  - Determine endocrine status

Source: Habif TP, Clinical Dermatology, 5th ed. Fig. 7-4. Copyright © Elsevier, Inc. 2010. Used with permission.

**A. General**

1. Wash with mild soap (e.g., Dial, Ivory, Phisoderm, Panoxyl, Neutrogena)
2. If any of the above factors (listed in etiology) are contributing to a worsening of acne, then modify as needed. Avoid foods noted to cause flare-ups, avoid mechanical pressure, vigorous cleansing, etc.

**B. Medications—Topical (Table 1)**

1. **Salicylic acid:** Available in OTC as cream, gel, and cleansers for mild acne. It can be used in combination with other topical agents
2. **Benzoyl Peroxide** Most useful for treatment of mild to moderate acne. Apply to clean, dry skin QHS or BID. Available in OTC and prescription preparations and in a variety of concentrations and formulations. Common preparations are 5% and 10% as gel, cream, lotion, and liquid. The liquid and cream are less irritating and gel is better for oily skin. It is often used in combination with topical or oral antibiotics, or with a retinoid. Skin irritation and bleaching can occur
3. **Topical retinoids:** Tretinoin, Adapalene, Tazarotene
   a. Retinoids normalize keratinization and have anti-inflammatory effects. They are effective for all types and severity of acne
   b. Apply a pea-size amount to cover the entire face once daily at bedtime. Available in a variety of formulations. Use cream for dry skin. Side effects include burning, stinging, dryness, and scaling. These can be reduced by starting therapy with the lowest strength. Avoid sun exposure
   c. **Tretinoin (Retin-A, generic):** Simultaneous application of Tretinoin and Benzoyl Peroxide can cause oxidation of Tretinoin and decrease its effectiveness. In combination therapy, apply Benzoyl Peroxide in the morning and Tretinoin in the evening. Pregnancy category C
   d. **Adapalene (Differin):** Photostable and can be used with Benzoyl Peroxide in a
4. Topical antibiotics
   a. Topical Clindamycin and Erythromycin are commonly used to treat mild to moderate acne. They are not recommended as monotherapy because of slow onset of action and emergence of antibiotic resistance. If topical antibiotic treatment is used for more than a few weeks, Benzoyl Peroxide should be added. Fixed-combination products containing Benzoyl Peroxide are available.
   b. Dapsone is an antimicrobial drug. Studies showed that topical Dapsone is most effective against inflammatory acnes. Application of both topical Dapsone and Benzoyl Peroxide at the same time can cause temporary yellow or orange discoloration of the skin. Pregnancy category C

C. Medication: Oral (Table 2)

1. Oral antibiotics are appropriate for moderate-to-severe inflammatory acne vulgaris. Avoid antibiotic monotherapy. Use in combination with a topical regimen that includes Benzoyl Peroxide. Discontinue or taper antibiotic within 1 to 2 months once new inflammatory acne lesions have stopped emerging. Incorporate a topical Retinoid or combination Retinoid/Benzoyl Peroxide product into the regimen when discontinuing oral antibiotic with goal of maintaining control with topical program. If retreatment is needed, use the same oral antibiotic. Educate patients on side effects of the antibiotic.
   a. Tetracycline, Doxycycline, and Minocycline should not be used in pregnant women and children aged < 8 years.
   b. Erythromycin: High prevalence of antibiotic-resistant P. acnes.
   c. Trimethoprim/Sulfamethoxazole (Bactrim): Not generally recommended for use as first or second line agent. Use judiciously in selected refractory cases. Side effects include toxic epidermal necrolysis, Stevens-Johnson syndrome, bone marrow suppression, hypersensitivity reactions, rash. Obtain CBC at baseline and periodically thereafter.

2. Oral Isotretinoin
   a. Isotretinoin targets all pathophysiologic factors involved in acne. It is very effective for severe nodulocystic acne. It reduces sebum production.
   b. Start the dose at 0.5 mg/kg/day given BID for 4 weeks, then increase to the full dosage of 1 mg/kg/day. Treatment usually lasts 4–5 months.
   c. Many adverse reactions including dermatologic, CNS, endocrine, GI, and musculoskeletal side effects (Table 2).
   d. The major adverse effect is its teratogenic potential.
      i. The FDA implemented a computer-based risk management program (iPLEDGE) which registers all Isotretinoin patients, physicians, pharmacies, and manufacturers.
      ii. The prescriber must register each patient in iPLEDGE. In addition, the prescriber must confirm patient counseling. For female of childbearing potential, the prescriber must enter the 2 contraception methods and pregnancy test results on a monthly basis. Isotretinoin must only be dispensed by a pharmacy registered and activated with iPLEDGE, and must only be dispensed to patients who are registered and meet all the requirements of iPLEDGE.
      iii. Oral Isotretinoin should only be prescribed by physicians with experience in the use of this very potent drug.

3. Systemic hormonal therapy
   a. Combination oral contraceptives (COCs) block the effects of androgens on the sebaceous gland.
   b. Use COCs with low estrogen dose. Products approved by the FDA for the treatment of moderate acne in women are Estrostep for aged ≥15 y, Ortho Tri Cyclen for aged ≥15 y, YAZ and Beyaz for ≥14 y.
   c. Obtain a family history of thrombotic events and ask if the patient smokes before OCs are prescribed.
d. COCs may be useful as second-line therapy in pubertal females with moderate-to-severe acne. Because of concerns about growth and bone density, many experts recommend withholding COC for acne unassociated with endocrinologic pathology until 1 year after onset of menstruation.

e. Spironolactone is a synthetic steroidal androgen receptor blocker. It is used off-label to treat acne in women. Dosages of 50–200mg have been used. Side effects include hyperkalemia, orthostatic hypotension, menstrual irregularity, breast tenderness, and reduced libido. Pregnancy category C

D. Phototherapy—Blue light, infrared lasers, photodynamic therapy and other light-based therapies have been used for the treatment of acne. Their long-term efficacy and how they compare to conventional drugs are unclear.

E. Treatment failure: If treatment fails, consider dermatology referral due to the serious side effects of the latter therapies and the risk of scarring.

<table>
<thead>
<tr>
<th>TABLE 1: SOME COMMONLY USED TOPICAL PREPARATIONS FOR ACNE</th>
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<tbody>
<tr>
<td><strong>Rx</strong></td>
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<td><strong>Keratolytic Agents</strong></td>
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</table>

Cr = cream; Gel = solution. *FDA approved for rosacea only.

*Estimated cost is expressed as a range of prices from the lowest strength and smallest size to the highest strength and largest size of that product. Cost is estimated by using prices listed at Lexicomp 2014.
### TABLE 2: SYSTEMIC AGENTS FOR ACNE VULGARIS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Side Effects</th>
<th>Pregnancy Category</th>
<th>Dosage Forms/Estimated Cost*</th>
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<tr>
<td><strong>Antibiotics</strong></td>
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<tr>
<td>Erythromycin (generic)</td>
<td>250-500 mg QD-BID</td>
<td>Dyspepsia, yeast infection, antibiotic resistance, drug interactions</td>
<td>B Tab: 250, 500 mg ($120/30s)</td>
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<tr>
<td>Doxycycline (generic)</td>
<td>50-100 mg QD-BID or 150 mg QD</td>
<td>Dyspepsia, yeast infection, antibiotic resistance, photosensitivity, and pseudotumor cerebri</td>
<td>D Cap: 50, 100 mg ($36/30s)</td>
<td></td>
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<tr>
<td>Minocycline (generic) ER tab (Solodyn)</td>
<td>50-100 mg QD</td>
<td>Same as doxycycline, vestibular toxicity, lupus-like reaction, and hypersensitivity</td>
<td>D Cap: 50, 100 mg ($51-60/30s) Solodyn ($1136/30s)</td>
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<tr>
<td>Tetracycline (generic)</td>
<td>500 mg BID</td>
<td>Dyspepsia, yeast infection, antibiotic resistance, photosensitivity, and pseudotumor cerebri</td>
<td>D Cap: 250, 500 mg ($150/30s)</td>
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<tr>
<td><strong>Oral Contraceptives</strong></td>
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<tr>
<td>EE 20, 30, 35 mcg/ Norethindrone 1 mg (Estrostep)</td>
<td>1 tab QD per tablet dispenser</td>
<td>Nausea, vomiting, GI symptoms, weight gain, bloating, breast tenderness, melasma, depression, mood swings, headaches, thromboembolism, stroke, hypertension, gallbladder disease, and potential effect on bone density</td>
<td>X $38/28s</td>
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<tr>
<td>EE 35 mcg/0.18, 0.215, 0.25 mg Norgestimate (Ortho Tri-Cyclen, Trisprinten, Trisprinten)</td>
<td>1 active tab QD x 21d followed by 1 placebo tab QD x 7 d, then repeat cycle</td>
<td>X $422/28s (Ortho Tri-Cyclen) $39/28s (Tri-sprinten)</td>
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<tr>
<td>EE 20 mcg/drospirenone 3 mg (YAZ), + levomefolate (Beyaz)</td>
<td>1 active tab QD x 24 d followed by 1 placebo tab QD x 4 d, then repeat cycle</td>
<td>X $93/28s</td>
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<tr>
<td><strong>Retinoids</strong></td>
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<tr>
<td>Isotretinoin (Accutane, Claravis, Absorica, Myorisan, Zenatane)</td>
<td>0.5-1 mg/kg/day given in 2 doses x 15-20 wk</td>
<td>Isotretinoin embryopathy, dry skin, chapped lips, eczema, photosensitivity, dry eyes, roseoleeds, hair shedding, myalgias, arthralgias, hypertylagic acid, acute pancreatitis, hepatotoxicity, pseudotumor cerebri, depression and suicidal thoughts, headaches, leukopenia</td>
<td>X Cap: 10, 20, 40 mg ($492-677/30s Claravis) Special prescribing requirements via iPLEDGE*</td>
<td></td>
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</table>

*EE = Ethinyl Estradiol

**Cost is estimated using average wholesale price, rounded to the nearest dollar, obtained from Lexicomp 2014.

*To prescribe isotretinoin, the prescriber must be registered and activated with iPLEDGE by visiting www.ipledgeprogram.com or calling 1-866-495-0654.

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### PART TWO: ROSACEA

#### I. HISTORY
- Usually ages 30–50
- Females > Males
- Celtic/Northern Europeans much more than pigmented races
- Hot liquids/heat may stimulate or worsen, alcohol increases flushing
- Emotional stress may be a factor
- Rosacea has now been associated with *H. pylori*. Treatment of *H. pylori* disease has improved co-existing rosacea

#### II. PHYSICAL
- Flushing
- Papular and papulopustular lesions
- Telangiectasias
- Nodules
- Absence of comedones
- Usually present on the face only: cheeks, chin, forehead, nose and rarely neck
- Associated rhinophyma
- Blepharitis, episcleritis and conjunctivitis may occur

#### III. DIFFERENTIAL DIAGNOSIS:
- Ethanol use, pheochromocytoma, mastocytosis, carcinoid tumor, Marfan’s syndrome, homocystinuria

#### IV. MANAGEMENT
- Decrease alcohol and hot beverage intake
- Topical
  1. Metronidazole 0.75% (MetroGel, MetroCream)—Apply BID to clean, dry skin; or 1% gel (MetroGel), 1% cream (Noritate)—Apply once daily. May take 4–8 weeks
  2. Azelaic Acid: Only 15% gel (Finacea) is approved for rosacea; 20% cream (Azelaic)
1. **INDICATIONS**

A. Lesions suspected of being malignant or pre-malignant (i.e., actinic keratosis)
B. A persistent rash, unresponsive to topical meds
C. Lesions that are difficult to diagnose by clinical exam
D. Ballooning dermatitis: Send for immunofluorescence
E. Cosmetic purposes

2. **INFECTED CONSENT**: Patient should understand risk of scarring, bleeding, the indications and alternatives, general risks and that further treatment may be necessary

3. **SITE**

A. Choose well-developed lesions
B. If a lesion is ulcerated, then biopsy the border
C. Lesions to avoid (consider referral)
   a. Hypertrophic scarring areas like upper chest and deltoid region
   b. Excoriated lesions

**CLINICAL PEARLS**

- About 50% of patients with rosacea have ocular involvement with irritation, blepharitis can often be cleared with simple lid scrubs with baby shampoo and PO Tetracycline

**REFERENCES**

3. Secondarily infected areas
4. High-infection areas: axilla and groin
5. Lesions overlying vital structures (nerves, arteries, joints)

IV. ANESTHESIA

A. 1% Lidocaine (Xylocaine) is usually adequate. Use enough to make a good wheal under the skin

B. Lidocaine with Epinephrine: Useful if hemostasis is an issue or prolonged effect desired. Do not use on fingers, toes, nose, clitoris or penis

C. Adjuncts
1. Topical anesthetics, i.e., EMLA cream (2.5% Lidocaine, 2.5% Prilocaine): Applied thickly over area with occlusion for at least an hour. Not to be used on mucous membranes or broken skin
2. Cryotherapy

V. TYPES: Take care with handling so as not to crush sample, place immediately in formalin. Special studies such as immunofluorescence and electron microscopy require special handling and stains

A. Shave biopsy: If the blade is kept parallel to the skin, scarring should be slight
1. Indications: Removal of protruding portion of superficial raised papular or pedunculated lesions or superficial lesions on a convex surface (pinnae of the ear or nose) when full thickness specimens are not required (e.g., milia, warts, seborrheic keratosis, molluscum contagiosum, benign appearing nevi)
2. Should NOT be the technique of choice for any lesion suspicious for melanoma (need full thickness specimen for Breslow or Clark staging)
3. Technique
   a. Infuse local anesthetic intradermal to raise lesion
   b. Stretch skin on either side of the biopsy site
   c. Use a No. 15 scalpel or a No. 10 scalpel for larger lesions
   d. Keep blade parallel to skin with cutting edge upward to prevent penetration into dermis
   e. Hemostasis (see below)

B. Punch biopsy: Full thickness cylindric biopsies, 2–8mm in size
1. Indications: When full thickness specimen is required (e.g., sarcoidosis, granuloma annulare, sclerosing basal cell CA, psoriasis, erythema multiforme, connective tissue disorders, bullous skin diseases). Easy removal of small tumors or when multiple biopsies are needed. If suspicious of malignant melanoma, perform an excisional biopsy
2. Technique
   a. Determine the proper size instrument required to adequately obtain clear skin margins (will help to avoid repeat excision for atypical or dysplastic lesions)
   b. Stretching skin perpendicular to tension lines while performing biopsy will result in oval shaped skin defect which can more easily be closed with sutures
   c. While rotating the instrument in an alternating clockwise/counterclockwise fashion, apply perpendicular pressure until the subcutaneous tissue is reached
   d. Lift specimen with toothless Adson forceps (or 25 gauge needle) and cut the base
   e. Close biopsy sites > 4 mm (e.g., 4–0 or 5–0 Ethilon). If site is not sutured, then inform patient that there will be a scar—usually a 1–2 mm white depression at the site
   f. Sutures should be removed in 5 days if on face, 7 days on upper extremity, and 10–14 days on lower extremity

C. Excisional biopsy: Removal of the entire area of pathology
1. Indications: Removal of tumors of the skin for diagnosis and cure
2. Technique
   a. Elliptic excision oriented parallel to the skin tension lines (Langer’s lines)
   b. Length is 3 times the width
   c. If suspicious of melanoma, then refer to physician experienced in skin cancer
   d. Undermining the wound may allow for easier closure (blunt dissection under...
wound edges to create a plane under the skin to allow the wound edges to be more easily brought together with minimum tension.
e. Consider layered closure for large defects (absorbable suture such as Vicryl for deep and nylon or polypropylene sutures (4–0 to 5–0) for the skin edges)
f. Hemostasis (see below)

D. Incision biopsy: Elliptic specimen taken from within a lesion
1. Indications: For examination of subcutaneous tissues (fibrous tumors, panniculitis) and when necessary to view transition from normal to abnormal tissue. In pigmented lesions, use only if there are contraindications to excisional biopsy (cosmesis or functional considerations)
2. Technique: Similar to excisional biopsy
   a. Narrow elliptic incision
   b. Choose location of most raised or most pigmented area of the lesion
   c. Technique as above
   d. Hemostasis (see below)

VI. HEMOSTASIS
A. Pressure
B. Pinpoint electrodesiccation
C. Topical solutions
   1. Aluminum Chloride Hexahydrate (Drysol)
   2. Absorbable gelatin powder (Gelfoam)
   3. 30% Aluminum Chloride
   4. Monsel’s solution (Ferric Subsulfate): May leave raised pigmented lesion
   5. Silver Nitrate

CLINICAL PEARLS
• Because of possibility of malignant transformation of congenital nevi, it is recommended that all congenital nevi be considered for prophylactic excision
• Never use a shave biopsy for pigmented lesions
• Allergy to Procaine (Novocain) is not a contraindication to use of Lidocaine
• The incidence of melanoma has nearly tripled in the last 3 decades, faster than any other cancer. The poor prognosis makes speed and accuracy of diagnosis essential. The ABCDE’s of malignant melanoma are:
   A—asymmetry
   B—border irregularity
   C—color variegation
   D—diameter > 6mm
   E—enlargement, rapid growth over weeks to months

References
### Topical Steroids

**Classification of Topical Steroid Preparations by Potency**

<table>
<thead>
<tr>
<th>Group</th>
<th>Potency</th>
<th>Drug</th>
<th>Brand Name(s)</th>
<th>Strength/Formulation</th>
<th>Size</th>
<th>Cost</th>
<th>Dosing Frequency</th>
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<tbody>
<tr>
<td>I</td>
<td>Super High Potency</td>
<td>Betamethasone dipropionate, augmented</td>
<td>Diprolene, generic</td>
<td>0.05% O, G</td>
<td>15g</td>
<td>$$</td>
<td>qd-bid</td>
</tr>
<tr>
<td>I</td>
<td>Super High Potency</td>
<td>Clobetasol propionate</td>
<td>Clobex, Temovate, Olux, generic</td>
<td>0.05% O, C, S, F, Sh, Spa</td>
<td>C: 30, 60g, L: Spa, 59mL</td>
<td>F: 50g, S: 50mL</td>
<td>Sh: 118mL</td>
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<tr>
<td>I</td>
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<td>Flucinonide</td>
<td>Vanos</td>
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<td>30, 60g</td>
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<tr>
<td>I</td>
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<td>$</td>
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<tr>
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<tr>
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<td>Diprolene AF, generic</td>
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<td>15g</td>
<td>$</td>
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<tr>
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<tr>
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<td>C:30g, L: 60mL</td>
<td>$$$</td>
<td>bid-qid</td>
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<tr>
<td>II</td>
<td>High Potency</td>
<td>Fluticasone propionate</td>
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<td>0.005% O</td>
<td>30g</td>
<td>$</td>
<td>qd-bid</td>
</tr>
<tr>
<td>II</td>
<td>High Potency</td>
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<td>Trinex, generic</td>
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<td>15g</td>
<td>$</td>
<td>bid-tid</td>
</tr>
<tr>
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<td>0.1% C</td>
<td>15 - 28.4g</td>
<td>$</td>
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<tr>
<td>III</td>
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<td>C:30g, L: 60 mL</td>
<td>$$$</td>
<td>bid-tid</td>
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<td>III</td>
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<td>($$</td>
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</tr>
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<tr>
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<td>0.05% C, G, O</td>
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<td>30g</td>
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<td>Trinex, generic</td>
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<td>15g</td>
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</tr>
<tr>
<td>III</td>
<td>Medium-High Potency</td>
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<td>Trianex</td>
<td>0.1% O</td>
<td>15g</td>
<td>$</td>
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<tr>
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<td>Medium Potency</td>
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<td>Diprolene, generic</td>
<td>0.05% L</td>
<td>30, 60ml</td>
<td>$</td>
<td>bid-tid</td>
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<tr>
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<td>Medium Potency</td>
<td>Betamethasone valerate</td>
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<td>$</td>
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<tr>
<td>IV</td>
<td>Medium Potency</td>
<td>Desoximetasone</td>
<td>DesOwen, generic</td>
<td>0.01% O</td>
<td>15, 45g</td>
<td>$</td>
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</tr>
<tr>
<td>IV</td>
<td>Medium Potency</td>
<td>Fluocinolone</td>
<td>Synalar, generic</td>
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<td>15, 120g</td>
<td>$</td>
<td>bid-qid</td>
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<tr>
<td>IV</td>
<td>Medium Potency</td>
<td>Hydrocortisone butyrilate</td>
<td>Locoid, generic</td>
<td>0.1% O, C, S</td>
<td>O: C, 15g, L: 60 mL</td>
<td>$</td>
<td>bid-tid</td>
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<tr>
<td>IV</td>
<td>Medium Potency</td>
<td>Hydrocortisone valerate</td>
<td>Westcort, generic</td>
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<td>45g</td>
<td>$$$</td>
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<tr>
<td>IV</td>
<td>Medium Potency</td>
<td>Hydrocortisone</td>
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<td>0.5% C</td>
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<td>$</td>
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<td>0.05% C</td>
<td>15, 45g</td>
<td>O: 45g</td>
<td>$</td>
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<tr>
<td>V</td>
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<td>Betatrex, generic</td>
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<td>$</td>
<td>bid-tid</td>
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<tr>
<td>V</td>
<td>Medium-Low Potency</td>
<td>Desoximetasone</td>
<td>DesOwen, generic</td>
<td>0.1% Pump</td>
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<td>$</td>
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<td>V</td>
<td>Medium-Low Potency</td>
<td>Flacitadione</td>
<td>Synalar, generic</td>
<td>0.025% C, L, F</td>
<td>C: 15, 60g, L: 60 mL</td>
<td>$</td>
<td>bid-tid</td>
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<td>V</td>
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<td>Mometasone furoate</td>
<td>Triderm, generic</td>
<td>0.1% L</td>
<td>15g</td>
<td>$</td>
<td>bid-tid</td>
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<tr>
<td>V</td>
<td>Medium-Low Potency</td>
<td>Triamcinolone acetonide</td>
<td>Kenalog, generic</td>
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<td>60mL</td>
<td>$</td>
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<tr>
<td>VI</td>
<td>Low Potency</td>
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<td>Diprolene, generic</td>
<td>0.05% O</td>
<td>15, 30g</td>
<td></td>
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<td>VI</td>
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<td>Betatrex, generic</td>
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<td>Low Potency</td>
<td>Flucinonide</td>
<td>Synalar, generic</td>
<td>0.01% C, S</td>
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<td>VI</td>
<td>Low Potency</td>
<td>Triamcinolone acetonide</td>
<td>Triderm, generic</td>
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<td>C: 15g, L: 60 mL</td>
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<td>bid-tid</td>
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<tr>
<td>VII</td>
<td>Lowest Potency</td>
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<td>$</td>
<td>bid-tid</td>
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<tr>
<td>VII</td>
<td>Lowest Potency</td>
<td>Hydrocortisone</td>
<td>Cortizone, generic</td>
<td>0.5% C</td>
<td>28g</td>
<td>$</td>
<td>bid-tid</td>
</tr>
</tbody>
</table>

*Cost is based on price listed in Medical Letter Treatment Guideline Drugs for Allergic Disorders (05/2013). $=$1-$50; $$ ($51-$100; $$$= $101-$200; $$$$= >$201

*Max 50 g/wk, limit use to 2 week duration, not to use on the face or groin

**Ointment, Cream, Lotion, Solution, Grigel, Foam Shampoo**

**References:**
101. WARTS, SCABIES, LICE & SUPERFICIAL TINEA INFECTION MANAGEMENT

I. TREATMENT OF WARTS

A. Cryotherapy: Scar formation is minimized
   1. If the wart is large, then shave it first (e.g. #10 blade). Apply liquid nitrogen for 30–60 sec then thaw and refreeze again
   2. Plantar warts often require applications at weekly or biweekly intervals

B. Duct tape: Apply tape and remove it after 6 days. Wash and gently debride the wart. Repeat this cycle for 1 month if necessary. There is little documented evidence of its effectiveness

C. Other physical modalities: Excision, CO₂ laser photodynamic therapy with aminolevulinic

D. Pharmacotherapies
   1. Topical Salicylic Acid (15%–40%): Available OTC, often the drug of first choice
      a. Patients with neuropathies should not use these products because of their inability to judge the extent of therapy and/or poor healing
      b. 40% transdermal patch (Duofilm patch, MediPlast, Dr. Scholl’s): Reserved for thicker areas and used in plantar warts
         i. Shave the wart as closely as possible, then soak in warm water to moisten. Vaseline may be applied to areas surrounding the wart to prevent tissue injury
         ii. Apply patch with occlusive dressing and keep dry for 48–72 hrs. Remove patch and pare down the wart. Repeat up to 12 weeks
      c. 15% transdermal patch (Trans-Ver-Sal): No soaking necessary. Apply before bedtime and remove in morning. Use up to 12 weeks
      d. 17% solution (Duofilm, Compound W): Apply directly to each lesion. Work better if covered with occlusive dressing
   2. Intraleional Candida or Mumps skin antigen: likely to be beneficial for recalcitrant warts
      a. Pretest patient with 0.1mL intradermally in the forearm. If response occurs, inject 0.1 to 0.3mL into the largest wart or split between 2 warts; max amount is 0.3mL per treatment
      b. Treat every 3–4 weeks for up to 3 treatments
      c. Side effects include pruritus, pain, burning or peeling
   3. Imiquimod 5% cream (Aldara), an immunomodulator:
      a. Approved for treatment of genital warts but has been used in flat warts when scarring is a concern and is also used as an adjunct with cryotherapy and topical Salicylic Acid
      b. Apply QHS. Decrease frequency of application if excessive irritation. Treatment duration can take weeks. Very expensive, approximately $22 per application
   4. Topical Retinoids: Tretinoin (Retin-A 0.5%, 0.1% cream, 0.01% and 0.25% gel)
      a. Approved for acne treatment but has been used in flat warts
      b. Apply OD or BID × 4–6 weeks. Adjust frequency of application if fine scaling and mild erythema occur. Protect surrounding skin with Vaseline. Sun protection is important
   5. 5-Flourouracil 5% cream (Efudex)
      a. Approved for actinic keratosis and basal cell carcinomas, but has been used in flat warts
      b. Apply with a cotton-tipped applicator to individual lesions OD to BID × 3–5 weeks
      c. May cause persistent hyperpigmentation. Sun protection is important since it is
6. Genital warts
   a. Provider-administered regimens:
      i. Cryotherapy with liquid nitrogen or cryoprobe. Repeat applications every 1–2 weeks
      ii. Podophyllin resin 25% in a compound tincture of Benzoin (Podocon)
      iii. Trichloroacetic acid (TCA) 80%–90% once per week until resolved
      iv. Surgical removal either by tangential scissor excision, tangential shave excision, curettage, or electrosurgery
   b. Patient-applied:
      i. Podofilox 0.5% solution or gel (Condylox) BID × 3 days, then 4 days rest, repeat up to 4×
      ii. Imiquimod 5% cream (Aldara, generics) or 3.75% (Zyclara) once/d 3×/wk up to 16 weeks
      iii. Sinecatechins 15% ointment (Veregen)–apply a thin layer TID up to 16 weeks

II. TREATMENT OF SCABIES
   A. CDC Treatment Guidelines 2010
      1. Recommended regimens
         a. Permethrin 5% cream (Elimite): After baths or showers, apply cream (30g) to the entire body from the neck down. Rinse after 8–14 hrs. Pregnancy category B. May be used in infants >2 mo of age
         b. Oral Ivermectin (Stromectol): 200 µg/kg once and repeat in 2 weeks
      2. Alternative regimens
         a. Lindane 1% lotion (Kwell): Second-line agent due to its potential risks of neurotoxicity. Should not be used in children, adults <110 lb, pregnant women, malnourished, with underlying skin disease or seizure disease
            i. Apply a thin layer (1 oz) over all skin from the neck down. Apply only once. Wash off in 8–12 hrs. DO NOT RETREAT
         B. Crotamiton 10% cream/lotion (Eurax): FDA-approved for scabies and often used when OTC preparations failed. Apply and wash off after 24 hrs. Reapply for an additional 24 hrs
         C. Treat all intimate contacts and family members. Bed linens, clothing and towels should be washed

III. TREATMENT OF PEDICULOSIS (LICE)
   A. Head Lice
      1. Topical therapies
         a. OTC products
            i. Permethrin 1% (Nix Crème Rinse): Often the drug of first choice
            ii. Synergized Pyrethrin (RID, Pronto, A-200)
            iii. Apply to clean hair and scalp, then rinse off after 10 min. Use comb to remove nits and lice. May repeat treatment in 7–10 days
         b. Permethrin 5% cream (Elimite): Available by prescription. Applied and left on the hair overnight under a shower cap. It may not be more effective than the OTC preparations
         c. Malathion lotion 0.5% (Ovide): Available by prescription
            i. As an irreversible cholinesterase inhibitor, it is useful for head lice resistant to Permethrin and Pyrethrins
            ii. It is contraindicated in infants. Pregnancy category B
            iii. Applied and left on the hair for 8–12 hrs. May repeat treatment in 7–10 days
            iv. Skin and eye irritation may occur. Some patients may not tolerate treatment well due to its bad odor, flammability of its alcoholic vehicle and prolonged application time
            v. Pregnancy category B
            vi. ~$150/59mL bottle
         d. Benzyl alcohol 5% (Ulesfia): Available by prescription
            i. Kills lice by asphyxiation. Not neurotoxic
ii. For children aged ≥6 mo
   Then rinse off with water. Repeat application in 7 days
iv. Side effects: pruritus, erythema, pyoderma, ocular irritation
v. Pregnancy category B
vi. ~$65/240mL bottle
e. **Spinosad 0.9% suspension (Natroba):** Available by prescription
i. Has pediculocidal and ovicidal activity
ii. For children aged ≥4 yr
   Then rinse off with warm water
iv. Repeat treatment in 7 days if live lice are seen
v. Side effects: site redness and irritation, ocular erythema
vi. Pregnancy category B
vii. ~$220/120mL bottle
f. **Ivermectin lotion 0.5% (Sklice):** Available by prescription
i. Binds selectively to glutamate-gated chloride channels in invertebrate nerve
   and muscle cell, causing paralysis and death
ii. Approved for children aged ≥4 yr
iii. Apply a sufficient amount to dry hair and scalp and leave on for 10 min.
   Rinse off with water
iv. Side effects: conjunctivitis, ocular hyperemia, eye irritation, dandruff, dry
   skin, skin burning sensation
v. Pregnancy category C
vi. ~$300/117g tube
g. **Lindane 1% shampoo (generic):** Used as last resort due to its potential for neurotoxicity. Should not use in
   infants, children, adults <50 kg, and pregnant women
ii. Apply shampoo and leave on for no longer than 4 min. DO NOT RETREAT
2. Nit removal is essential to treatment success. Remove nits manually or use a special
   nit comb or a nit removal product (e.g., Clear Lice Egg Remover gel)
3. Household members should be examined and treated if infested
4. Oral treatments
   a. **Ivermectin (Stromectol 6mg tab):**
      i. An anthelmintic agent not approved for treatment of head lice, but is found
         to be effective in killing head lice. Used when all other therapies for head
         lice have failed
      ii. 200µg/kg PO once (typical adult dose is 12mg). Repeat in 10 days
      iii. Should not be used in children <15 kg because of potential adverse effect
           on neurotransmission
   b. **Trimethoprim/Sulfamethoxazole (Bactrim)** kills synergistic bacteria in lice. A
      prolonged course could promote development of resistance. It should be
      reserved for severe or resistant infestations

B. **Pubic Lice:** CDC Treatment Guidelines 2010
1. Recommended regimens: **Permethrin 1% cream rinse (NIX) or synergized Pyrethrin (RID)** applied and washed off after 10 min
2. Alternative regimens
   a. **Malathion lotion 0.5% (Ovide)** applied for 8–12 hrs and washed off
   b. **Oral Ivermectin (Stromectol)** 250 µg/kg repeated in 2 weeks

C. **Body Lice**
1. The patient should be bathed thoroughly. Infested clothing and bed linen should be
   heat washed, dry cleaned, or discarded
2. If nits are found on body hair, use permethrin preparations or lindane (second-line
   agent)

D. **Eyelash infestation:** Manually remove lice and nits or apply petroleum jelly (Vaseline)
   to eyelids TID-QID for 8–10 days. Do not use pediculicides to treat eyelash infestations

IV. **TREATMENT OF TINEA CAPITIS**
   A. Systemic antifungal therapy is required to penetrate the hair follicles
1. Oral Griseofulvin: The “gold standard” therapy, particularly in children
   a. Microsize (Fulvicin U/F, Grisactin) Tab (500mg), Suspension (125mg/5mL):
      Adults: 500mg qd × 6–8 wk. Children: 5mg/lb/d × 6–8 wk
   b. Ultramicrosize (Fulvicin P/G, Gris-PEG) Tab (125, 250):
      Adults: 375mg qd × 6–8 wk. Children: 3.3mg/lb/d × 6–8 wk
   c. Common side effects include GI disturbances, headache, urticaria, and photosensitivity
   d. Monitor LFTs
2. Itraconazole (Sporanox), Fluconazole (Diflucan), and Terbinafine (Lamisil) are all effective but are not FDA approved for this indication and are more expensive than Griseofulvin

B. Adjunctive topical therapy
1. Ketoconazole (Nizoral) 2% shampoo or Selenium Sulfide 1% shampoo (Selsun Blue) is used to decrease shedding of viable fungi and spores.
2. Shampoo should be applied for 5 minutes, 2–3 times a week

V. TREATMENT OF TINEA PEDIS, TINEA CRURIS, AND TINEA CORPORIS
A. For limited infection, any of the topical antifungal agents in Table 1 is appropriate
1. Tinea cruris: Topical Azoles are often used because they also have high activity against Candida. A low dose topical steroid (e.g., 2.5% hydrocortisone) may be used for the first few days to relieve pruritus
2. Tinea pedis: Topical Azoles have traditionally been used. However, terbinafine (Lamisil), an allylamine, has also become the preferred agent of choice
B. Widespread or refractory infection may need treatment with an oral antifungal agent
1. Itraconazole (Sporanox): 200mg BID × 1–2 weeks
2. Terbinafine (Lamisil): 250mg QD × 2–4 weeks
3. Fluconazole (Diflucan): 150mg once a week × 2–4 weeks

<p>| TABLE 1: SOME TOPICAL ANTIFUNGAL AGENTS FOR TINEA CORPORIS, TINEA CRURIS, AND TINEA PEDIS |
|---------------------------------|-----------------|-----------------|----------|----------|</p>
<table>
<thead>
<tr>
<th><strong>Antifungal Agent</strong></th>
<th><strong>Rx/otc</strong></th>
<th><strong>Dosage Form</strong></th>
<th><strong>Tinea corporis, Tinea cruris</strong></th>
<th><strong>Tinea pedis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allylamines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naftinile (Naftin)</td>
<td>Rx</td>
<td>2% C</td>
<td>qd × 4 wk</td>
<td>15, 30, 60g ($50, 66, 105)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2% G</td>
<td>bid × 4 wk</td>
<td>20, 40, 60g ($70, 99, 127)</td>
</tr>
<tr>
<td>Terbinafine (Lamisil AT)</td>
<td>otc</td>
<td>1% C, S</td>
<td>bid × 1-4 wk</td>
<td>bid × 1-4 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15, 30g ($9–15); 1 oz ($10)</td>
<td></td>
</tr>
<tr>
<td><strong>Benzylamines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butenafine (Mentax)</td>
<td>Rx</td>
<td>1% C</td>
<td>qd × 2 wk</td>
<td>qd × 4 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15, 30g ($46, 86)</td>
<td></td>
</tr>
<tr>
<td><strong>Imidazoles</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clotrimazole (Lotrimen)</td>
<td>otc</td>
<td>1% C, L</td>
<td>bid × 2-4 wk*</td>
<td>bid × 4 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15g ($7), 10mL ($7)</td>
<td></td>
</tr>
<tr>
<td>Econazole (Spectazole)</td>
<td>Rx</td>
<td>1% C</td>
<td>qd × 2 wk</td>
<td>qd × 4 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15, 30, 60g ($16, 27, 50)</td>
<td></td>
</tr>
<tr>
<td>Ketoconazole (Nizoral)</td>
<td>otc</td>
<td>2% C</td>
<td>qd × 2 wk</td>
<td>qd × 6 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30g ($30)</td>
<td></td>
</tr>
<tr>
<td>Miconazole (Micatin)</td>
<td>otc</td>
<td>2% P, Sp</td>
<td>bid × 2 wk</td>
<td>bid × 4 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 oz ($6)</td>
<td></td>
</tr>
<tr>
<td>Oxiconazole (Osixstat)</td>
<td>Rx</td>
<td>1% C, L</td>
<td>qd-bid × 2 wk</td>
<td>qd-bid × 4 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15, 30, 60g ($39, 63, 89), 30mL ($63)</td>
<td></td>
</tr>
<tr>
<td>Sertaconazole (Ertaczo)</td>
<td>Rx</td>
<td>2% C</td>
<td>Not indicated</td>
<td>bid × 4 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15, 30g ($73)</td>
<td></td>
</tr>
<tr>
<td>Sulconazole (Exelderm)</td>
<td>Rx</td>
<td>1% C, S</td>
<td>qd-bid × 3 wk</td>
<td>bid × 4 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15, 30, 60g ($18, 31, 53), 30, 60 mL ($37)</td>
<td></td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciclopirox (Loprox)</td>
<td>Rx</td>
<td>0.77% C, L</td>
<td>bid × 4 wk</td>
<td>bid × 4 wk</td>
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<td></td>
<td></td>
<td></td>
<td>15, 30, 90g ($25, 45, 110); 60mL ($45)</td>
<td></td>
</tr>
<tr>
<td>Tolnaftate (Tinactin)</td>
<td>otc</td>
<td>1% C, G, P, Sp</td>
<td>bid × 2-4 wk*</td>
<td>bid × 4 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30g ($10), 10mL ($6)</td>
<td></td>
</tr>
<tr>
<td>Undecylenic Acid (Crux, Desenex)</td>
<td>otc</td>
<td>20% C</td>
<td>bid × 2 wk (tinea cruris)</td>
<td>bid × 4 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15g ($8)</td>
<td></td>
</tr>
<tr>
<td><strong>Antifungal/Steroid Combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clotrimazole/Betamethasone Dipropionate (Lotrisone)</td>
<td>Rx</td>
<td>1%/0.005% C</td>
<td>bid × 2 wk</td>
<td>bid × 4 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15, 45g ($77)</td>
<td></td>
</tr>
</tbody>
</table>

*2 wk for tinea cruris, 4 wk for tinea corporis
#cost is based on price, rounded to the nearest dollar, listed at www.drugstore.com (6/10/08). Generic brands are used when available.
VI. TREATMENT OF TINEA VERSICOLOR
A. This infection is characterized by hypopigmentation which may persist despite treatment
B. Topical Agent: Preferred
   1. Ketoconazole 2% shampoo (Nizoral): apply and lather, then wash off after 5 min. Repeat QD × 2 weeks
   2. Selenium Sulfide 2.5% lotion (Selsun): apply and lather, then wash off after 10 min. Repeat QD × 1 week
C. Topical Agent: Alternative
   1. Butenafine (Mentax) 1% Cream: QD × 2 weeks
   2. Miconazole (Monistat-Derm) 2% Cream: QD × 2 weeks
   3. Terbinafine (Lamisil) 1% Cream: BID × 2 weeks
D. Oral antifungal agent: Used in patients with extensive disease and those who do not respond to topical treatment
   1. Ketoconazole (Nizoral): 400mg PO once; alternatively, 200mg PO × 5 days. Reserved as last resort due to risks of severe hepatotoxicity and QT prolongation
   2. Fluconazole (Diflucan): 300mg per week × 4 weeks, or 300mg once and repeat in 2 weeks
   3. Itraconazole (Sporanox): 200mg BID × 1 day, or 200mg QD × 5 days
   4. Sweating may improve transfer of Ketoconazole and Fluconazole to the skin surface and the patient should not bathe for at least 12hrs after treatment
   5. Oral Terbinafine (Lamisil) is not effective for this condition

VII. TREATMENT OF TINEA UNGUIUM
A. Oral antifungal agents, Itraconazole (Sporanox) and Terbinafine (Lamisil): Used first-line
   1. Fingernails
      a. Terbinafine (Lamisil): 250mg QD × 6 wks
      b. Itraconazole (Sporanox): pulse therapy 200mg po BID × 7 days, then off for 3 weeks and repeat × 1 cycle
   2. Toenails
      a. Terbinafine (Lamisil): 250mg QD × 12 wks; monitor LFTs
      b. Itraconazole (Sporanox): 200mg QD × 12 wks; monitor LFTs and drug interactions
B. Topical Ciclopirox 8% solution (Penlac nail lacquer)
   1. Used in immunocompetent patients with mild to moderate onychomycosis of fingernails and toenails without lunula involvement
   2. Apply the lacquer evenly on the entire nail once daily. Once a week, remove the Penlac with alcohol and then apply Penlac once daily. May take 6 months of therapy before initial improvement of symptoms is noticed. Up to 48 weeks of daily application to achieve a clear nail
C. Topical antifungal drugs do not penetrate the nail plate adequately to be effective. They are used after oral treatment to prevent nail re-infection
   1. Ciclopirox (Loprox) cream or lotion
   2. Terbinafine (Lamisil AT) cream

VIII. TREATMENT OF ORAL CANDIDIASIS
A. Nystatin (Mycostatin) suspension: 5mL PO QID swish and swallow × 5–7 days
B. Clotrimazole (Mycelex): 10mg troches, dissolve in mouth 5 x/day for 14 days
C. Fluconazole (Diflucan)
   1. Oropharyngeal candidiasis: 200mg PO on day 1, then 100mg PO QD × 2 weeks
   2. Esophageal candidiasis: 200mg PO on day 1, then 100mg PO QD for minimum of 3 weeks. Continue for 2 weeks after symptoms resolve
   3. Monitor renal and liver function
D. Other antifungal agents: Itraconazole, Posaconazole (Noxafil)

References
102. Hair Changes & Balding

I. GENERAL
A. Hair is a type of keratin generated by the hair matrix, which forms the shaft and surrounding structures. The scalp has 100–150,000 hairs

B. Types of hair
1. Lanugo: Soft silky hair that covers fetus in utero; mostly shed before birth
2. Vellus: Short, fine hairs that cover the entire body except for the palms and soles
3. Terminal: Long, coarse pigmented hair; before puberty found only on the scalp and in eyebrows and eyelashes. After puberty in the axilla, pubic area and on the chest and face in men

C. Growth Cycle: Hair growth and loss is continuous and random, not cyclical or seasonal and can be defined by 3 discrete stages
1. Anagen: Active growth phase—1cm/month which decreases with age; plucked hair in this phase has a 2–3mm white sheath at the end
2. Catagen: Active follicular regression that signals end of anagen; plucked hair has a small white tip at end
3. Telogen: Resting phase, all cellular activity stops; represents 10% of all hair. 25–100 telogen hairs are normally shed each day; shampooing may increase this number

II. APPROACH TO PATIENT WITH HAIR LOSS—Signs and symptoms
A. Generalized versus discrete areas of hair loss and location
B. Rapid versus gradual hair loss
C. Partial versus complete balding
D. Changes in hair texture or breakage
E. Scarring
F. Meds/chemotherapy
G. Family history

III. PATTERNS OF HAIR LOSS AND MANAGEMENT
A. Diffuse, rapid hair loss
1. Telogen effluvium: Telogen (resting) hair loss often seen 3 months after pregnancy, fever or severe illness, major surgery or change in diet and resolves spontaneously over 1–2 months. No more than 50% of hairs are affected. Scarring and inflammation are absent
2. Anagen effluvium: Abrupt insult to active growth. Usually due to chemo-therapeutics. Only telogenic hairs remain
3. Management: Await resolution after insult is over

B. Diffuse, gradual hair loss, often with thinning, restricted to top of scalp—Androgenic alopecia
1. Male pattern baldness: Frontal recession or loss over the temples or crown
2. Female pattern baldness: Gradual loss on the central scalp with preservation of the frontal hair line
3. Management
   a. Minoxidil (Rogaine): Available OTC as 2% solution and as 5% (extra strength) solution or foam to be applied topically BID. Ineffective for frontal hair loss. Can grow moderate to dense hair in 50% of patients. Effects may not be apparent for 6 months and new hair is lost when treatment stopped
b. Finasteride (Propecia): 1mg PO QD. Approved for men only (18–41yrs). Effective on hair loss in vertex and anterior mid-scalp. May result in hair gain but some feel primary benefit is prevention of further hair loss. New hair lost when treatment stopped

c. Surgical options include hair transplants, scalp reductions and flaps, and hair weaves

C. Diffuse, gradual hair loss, often with thinning, all over scalp
1. Diffuse alopecia areata: Alopecia areata is rapid hair loss in sharply defined, usually round, areas. It rarely occurs in more diffuse distributions with poorer potential for regrowth
2. Etiology: Thyroid/iron deficiency, meds (Warfarin, Heparin, Propanolol, Vitamin A), secondary syphilis, lupus, gradual hair loss with age
3. Management: Directed toward underlying disorder

D. Discrete balding areas without scarring or scalp inflammation
1. Alopecia areata: Most common cause in both children and adults. Etiology is unknown. Check for ! shaped hairs at edge of balding areas. These are short, broken-off hairs where broken end is thicker and darker than where hair emerges from scalp. May be associated with nail pitting and longitudinal striations
   a. Management: Generally resolves spontaneously but can also be treated with intralesional steroids
2. Trichotillomania: Caused by the irresistible urge to pull out longer hairs leaving very short, fine hairs. Often seen in children

E. Discrete balding areas with scarring or scalp inflammation
1. Infection: Tinea capitis, kerion, bacterial infection, herpes zoster
2. Traumatic: Burns, radiation
3. Neoplastic: Basal cell carcinoma, metastatic disease
4. Systemic: S.L.E., psoriasis, eczema, lichen planus, scleroderma

CLINICAL PEARLS
- In US $900 million dollars spent each year on hair loss
- Androgenic alopecia (male pattern baldness) occurs in approximately 2/3 of men

References
IX. Surgery

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103. EVALUATION OF ABDOMINAL PAIN

I. INTRODUCTION
A. Abdominal pain accounts for 4–8% of adult emergency department visits
B. Special considerations should be taken with the elderly, immunocompromised, patients on steroids, and women of childbearing age

II. HISTORY
A. Pain
1. Onset and duration: Abrupt (vascular, perforation, torsion, or colic) vs. gradual (inflammation, infection). Was patient awakened from sleep?
2. Location: Site of onset/site presently (have patient point to area of worst pain)
3. Quality/Character: Visceral pain (steady ache or vague discomfort or excruciating or colicky pain); parietal pain (more localized to specific site); referred pain (e.g., renal colic may refer pain to the testicles or labia, biliary pain may be referred to the right infrascapular region)
4. Severity
5. Constant vs. intermittent
6. Aggravating/relieving (movement/coughing/respiration/food/vomiting/meds/lying still/car ride)
7. Change of any variables over time (better/worse/same)
8. Previous similar symptoms
B. Associated symptoms
1. Fever: Young patients are better able to mount a fever response compared to the elderly. Rectal temperatures generally more reliable. Temperature may be low due to antipyretics and oral temperature may register low in mouth breathing patient
2. Vomiting: Relationship of abdominal pain and vomiting (e.g., pain usually precedes vomiting by 3–4 hrs in patients with appendicitis but is just the opposite in gastroenteritis). Frequency of vomiting along with character (including color and content, i.e., bilious, bloody, coffee ground, etc.)
3. Anorexia: Usually associated with acute abdominal pain: often precedes the onset of pain in appendicitis
4. Bowels: Constipation, diarrhea, and recent change in bowel habits. Watery diarrhea with crampy pain suggests gastroenteritis. Large amount of loose stool suggests cause in lower GI. Smaller amounts of loose stools upper GI. Failure to pass flatus with crampy pain and vomiting suggests mechanical obstruction. Bloody diarrhea (infectious), bright red blood (lower GI causes—diverticulosis, neoplasm, infection, IBD, AVM, hemorrhoids, fissures, fistulae, or prolapse), melanic stools (upper GI causes—peptic ulcer, gastritis, varices, Mallory-Weiss)
5. Urination: Dysuria, frequency, urgency, incontinence, hematuria, back pain
6. Vaginal: Discharge (PID), bleeding (ectopic, miscarriage)
7. Menstruation: Last menstrual period (exact dates), frequency, duration, the type of contraception and duration of use
C. Past medical and surgical history
1. Prior surgeries/hospitalizations
2. History of similar pain suggests recurrent disease
3. History of chronic diseases (diabetes, HIV, CNS disease, i.e., multiple sclerosis)
4. Recent or current meds (including NSAIDs, steroids, pain meds, ATBs)
5. Social history: tobacco, alcohol and other drugs of abuse, living circumstances, others with similar symptoms, occupation
6. Recent out of country travel or exposure to lake, well, or stream water
III. PHYSICAL EXAMINATION

A. General: Patient's appearance, ability to answer questions, position in bed, and degree of discomfort. Dehydration may be suggested by dry mucous membranes, sunken eyes, and by rapid and shallow respirations. A patient writhing on the bed or pacing the room may have kidney stones, while a patient lying still is more likely to have peritoneal irritation. Facial expression may indicate pain of a crampy or constant nature. Pallor suggests anemia.

B. Vital signs: Temperature, tachycardia, and hypotension may signify hypovolemia. A variant in blood pressure between the arms and legs may indicate aortic dissection. Increased respirations may signify metabolic acidosis, DKA, diaphragmatic irritation, or pain.

C. Inspection: Scars, hernias, masses, distention, peristaltic waves, rash (herpes zoster), signs of liver disease (jaundice, spider angiomas, palmar erythema, ascites), pancreatitis (Grey Turner's sign—purple/red flanks; Cullen’s sign—red umbilical).

D. Auscultation: Frequency and pitch of bowel sounds. High pitched bowel sounds may indicate obstruction. Presence or absence of abdominal bruits.

E. Percussion and palpation
   1. Have patient point "with one finger" to area of greatest pain
   2. Begin in the quadrant free of pain and perform lightly (Note voluntary and involuntary guarding, rigidity and rebound). Study the face
   3. Organomegaly, and other masses including the bladder, and hernias. Pulsatile mass (AAA)
   4. Costovertebral angle tenderness

F. Genitourinary
   1. Umbilical hernia (and inguinal hernia)
   2. Examine the testicles for swelling and/or retraction
   3. Penis for discharge

G. Pelvic examination
   1. Both speculum and bimanual examination
   2. GC/Chlamydia cultures, Wet prep/Trichomoniasis evaluation if indicated
   3. Cervical motion tenderness (GU vs. peritonitis), adnexal tenderness, masses, discharge, bleeding or FBs

H. Rectal examination
   1. Probe for perirectal mass, fecal impaction, prostate enlargement or irregularity
   2. Guaiac stool
   3. Rectal tenderness 40% in appendicitis but rarely confirms or excludes the diagnosis

I. Signs
   1. Psoas sign: Pain on passive extension of the right hip. Suggestive of appendicitis
   2. Obturator sign: Pain with passive flexion and internal rotation of the right hip. Suggestive of appendicitis
   3. Rovsing's sign: Referred pain in the RLQ when palpating the LLQ. Suggestive of appendicitis
   4. Murphy's sign: Inspiratory arrest with deep palpation of the RUQ. Suggestive of cholecystitis
   5. Carnett's sign: Increased tenderness to palpation when abdominal muscles are contracted. Suggestive of abdominal wall pain

IV. DIAGNOSTIC STUDIES

A. Plain abdominal radiograph: Usefulness is limited and markedly overutilized. Utility limited to evaluation of perforation, obstruction and foreign body, though sensitivity much better with CT
   1. Both a supine and upright film of the abdomen should be obtained, as well as a PA (+/- lateral) chest film to exclude intrathoracic causes of acute abdominal pain (e.g., lower lobe pneumonia or aortic dissection)
   2. Conditions which may be diagnosed with acute abdominal series:
      a. Perforated viscus: May see free air under the diaphragm
      b. Bowel obstruction: Look for colonic haustra in order to distinguish large
from small bowel
c. Retroperitoneal inflammation: Psoas shadow is obscured
d. Foreign body
e. Kidney stone (poor sensitivity and specificity)

B. Laboratory
1. Complete blood count (CBC). Can indicate an infectious process, but if normal does not exclude one. Is potentially misleading and falsely reassuring. Up to 60% of patients with surgically proven appendicitis will have an initially normal WBC
2. Electrolytes, BUN/creatinine
3. Urinalysis: Urinary tract infection, renal or ureteral calculi. Patients with AAA may have some hematuria
4. Serum amylase (sensitivity and specificity for acute pancreatitis is 80–90% and 75% respectively at 3 × upper limit of normal) and lipase (sensitivity and specificity for acute pancreatitis is 90% and 90% respectively at 2 × the upper limit of normal), ALT/AST, Alk Phos, β-HCG, lactic acid
5. PT/PTT, type and screen (prior to surgery)

C. Ultrasonography: Cholelithiasis, fluid-containing cavities, intraabdominal masses, intrauterine or extrauterine pregnancy, ovarian cyst, and testicular torsion

D. Intravenous pyelogram (IVP) has been the test of choice for diagnosing kidney stones but has largely been replaced by helical CT which does not require administration of dye and can image other abdominal structures (AAA)

E. CT Scan: Useful in diagnosis of small bowel obstruction, mass, appendicitis, diverticular abscess, kidney stones, pancreatic necrosis, free air, AAA, and many other conditions. For evaluation of appendicitis, the helical CT with triple contrast (PO, IV, rectal) is about 98% sensitive. If a patient has a clinical diagnosis of appendicitis, do not do a CT as it may be a false negative. These patients need urgent surgical evaluation

F. Nuclear medicine: Helpful in diagnosing cholecystitis and testicular torsion

V. CAUSES OF ABDOMINAL PAIN IN PATIENTS PRESENTING TO AN ED

<table>
<thead>
<tr>
<th>Final Diagnosis</th>
<th>≤ 50 years old</th>
<th>≥ 50 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary tract disease</td>
<td>6%</td>
<td>21%</td>
</tr>
<tr>
<td>Nonspecific abdominal pain</td>
<td>40%</td>
<td>16%</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>32%</td>
<td>15%</td>
</tr>
<tr>
<td>Bowel obstruction</td>
<td>2%</td>
<td>12%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>Diverticular disease</td>
<td>&lt;0.1%</td>
<td>6%</td>
</tr>
<tr>
<td>Cancer</td>
<td>&lt;0.1%</td>
<td>4%</td>
</tr>
<tr>
<td>Hernia</td>
<td>&lt;0.1%</td>
<td>3%</td>
</tr>
<tr>
<td>Vascular</td>
<td>&lt;0.1%</td>
<td>2%</td>
</tr>
<tr>
<td>Acute gynecologic disease</td>
<td>4%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Other</td>
<td>13%</td>
<td>13%</td>
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</table>

VI. PRESENTATION OF COMMON CONDITIONS LEADING TO AN ACUTE ABDOMEN

<table>
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<tr>
<th>DIAGNOSIS</th>
<th>PRESENTATION</th>
<th>EVALUATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritonitis</td>
<td>Diffuse, severe tenderness; guarding or rigidity; absent bowel sounds; rebound</td>
<td>Diagnosis is clinical; upright chest film may show free intraperitoneal air</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>Focal, lower right quadrant (McBurney’s point) tenderness, with rebound; anorexia</td>
<td>Diagnosis is clinical; ultrasound, CT, spiral CT or barium enema may aid in diagnosis</td>
</tr>
<tr>
<td>Acute Pancreatitis</td>
<td>Diffuse upper abdominal tenderness radiating to the back, mild rebound; ileus; Grey Turner’s sign (flank hematoma)</td>
<td>Serum amylase and Lipase; ultrasound or CT</td>
</tr>
<tr>
<td>Acute Cholecystitis</td>
<td>Right upper quadrant tenderness; muscle guarding; worse with inspiration</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>Left lower quadrant tenderness; rebound; guarding; fever; quiet bowel sounds</td>
<td>CT; barium enema (Gastrografin should be used if a perforation is a possibility)</td>
</tr>
<tr>
<td>Small bowel obstruction — Proximal</td>
<td>Nausea, vomiting; alkalosis; normal or quiet bowel sounds; NO distension</td>
<td>Abdominal film; upper GI series; endoscopy</td>
</tr>
<tr>
<td>Small bowel obstruction — Distal</td>
<td>Nausea, vomiting; tenderness, distension; hyperactive bowel sounds</td>
<td>Abdominal film; angiogram; serum amylase</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>Fever, jaundice; right upper quadrant pain</td>
<td>Ultrasound; ERCP; cholangiogram</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>Peritonitis, hypotension; anemia; shock</td>
<td>B-UCG; vaginal ultrasound</td>
</tr>
<tr>
<td>Ruptured Aortic Aneurysm</td>
<td>Upper abdominal tenderness; back pain; pulsatile mass; hypovolemic shock</td>
<td>Angiogram; ultrasound, CT</td>
</tr>
</tbody>
</table>

VII. NONSURGICAL CAUSES OF ABDOMINAL PAIN

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>DISEASE</th>
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<tbody>
<tr>
<td>Cardiac</td>
<td>Myocardial infarction, acute pericarditis</td>
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<tr>
<td>Pulmonary</td>
<td>Pneumonia, pulmonary infarction or embolus, pleural effusion</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Pancreatitis, gastroenteritis, hepatitis, inflammatory bowel disease (IBD), peptic ulcer disease (PUD), irritable bowel syndrome (IBS)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>DKA, acute adrenal insufficiency, Addisonian crisis</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Acute porphyria, familial Mediterranean fever</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Rectus muscle hematoma</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Nerve root compression, tabes dorsalis</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Pyelonephritis, acute salpingitis, ovarian cyst, prostatitis, nephrolithiasis, endometriosis, dysmenorrhea</td>
</tr>
<tr>
<td>Psychologic</td>
<td>Depression, anxiety, somatization</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Herpes zoster</td>
</tr>
</tbody>
</table>

CLINICAL PEARLS

- Pain that is out of proportion to findings on exam may suggest ischemic bowel
- Most common etiologies of small bowel obstruction are adhesions, hernia, and tumor
- Most common etiologies of colonic obstruction are tumor, volvulus, and diverticular disease
- If an abdominal exam is difficult because of increased pain, peritoneal irritation can be demonstrated by having the patient cough and then asking to point to the area of maximum tenderness
- White blood cell count can be helpful, but may also be misleading. One study (1,800 patients) showed that a WBC > 10,000–11,000 only doubled the odds of appendicitis
- History and physical are almost worthless in excluding an ectopic pregnancy in a pregnant patient with abdominal pain and/or vaginal bleeding. An ectopic pregnancy
cannot be absolutely excluded based on quantitative hCG. A low (or high) hCG should NOT be reassuring to the clinician. Perform vaginal ultrasound in pregnant patients with abdominal pain and/or vaginal bleeding.

References
5. Hypoactive bowel sounds
6. Rectal exam may demonstrate tenderness on the left side and may be heme positive
7. Guaiac positive stools (rarely gross hematochezia)
8. Constipation or diarrhea
9. Tenesmus
10. Urinary frequency (from irritation of the bladder or ureter)

C. Complications
1. Ruptured diverticula/perforation
2. Hemorrhage
3. Fistula between colon and bladder (pneumaturia, fecaluria)
4. Paralytic ileus
5. Small bowel obstruction (if loop of bowel becomes narrowed or kinked in the inflammatory mass)
6. Large bowel obstruction from stenosis

V. EVALUATION
A. Diverticulosis
1. If bleeding, then obtain barium enema, colonoscopy or angiography
2. Diverticulosis is often an incidental finding on colonoscopy, flexible sigmoidoscopy and barium enema

B. Diverticulitis
1. Laboratory
   a. WBC: Normal with diverticulosis, may be elevated with left shift in diverticulitis
   b. H/H: May be decreased with bleeding (chronic diverticulosis)
   c. Urinalysis: May include WBC or RBC with fistula formation
   d. Blood culture: May be positive
2. Other studies
   a. Acute abdominal series: Free air (perforation), mass, obstruction
   b. Barium enema: For diagnosis of diverticulosis
   c. Abdominal CT: Evaluate for abscess or fistula
   d. Colonoscopy
   e. Angiography: With bleeding

VI. DIFFERENTIAL DIAGNOSIS: Colon cancer, appendicitis, inflammatory bowel disease, ischemic colitis, urinary tract infection, incarcerated hernia, prostatitis, irritable bowel syndrome, ovarian pathology (torsion, cyst, mass), ectopic pregnancy

VII. MANAGEMENT
A. Asymptomatic diverticula
1. Low fat and high fiber vegetable diet
2. High fiber diet (Note: A high fiber diet has been associated with a lower risk of developing diverticular disease, but studies have not conclusively shown that high fiber diet helps with symptoms or prevents complications)
3. Avoiding seeds and nuts is controversial

B. Bleeding diverticulosis: Note—80% of bleeding will cease spontaneously
1. Bowel rest
2. Colonoscopy with cautery
3. Angiogram with vasoconstrictor injection
4. Surgery

C. Diverticulitis
1. Outpatient: Mild but with persistent or worsening symptoms
   a. Bowel rest: Liquid diet for 48hrs
   b. ATBs: Need aerobic and anaerobic coverage. Use 1 of the following ATBs:
      i. Quinolones—Levaquin 750mg PO QD or Ciprofloxacin 750mg PO BID, plus Metronidazole (Flagyl) 500mg Q 6h
      ii. TMP-SMX DS BID
      iii. Amoxicillin/Clavulanate ER (Augmentin XR) 2 tab (1,000/62.5mg) Q 12h
      iv. Moxifloxacin (Avelox) 400mg PO Q 24h
2. Hospitalization
   a. Indications
i. Systemic signs or symptoms of infection
ii. Peritonitis/acute abdominal signs
iii. Inability to take oral meds
iv. Questionable diagnosis
b. Bowel rest
c. Broad spectrum ATBs

CLINICAL PEARLS
• Irritable bowel syndrome is often diagnosed as diverticular disease
• Bleeding occurs in 5–15% of patients with diverticulosis. Stops spontaneously in 75–95%
• Between 7 and 28% of people treated medically have recurrent bouts of diverticulitis

References

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I. PRIMARY GOALS OF WOUND MANAGEMENT:
A. Adequate hemostasis
B. Avoid/Prevent infection
C. Cosmetically acceptable scar
D. Restore function

II. HISTORY
A. How, when, and where did the injury occur
B. Mechanism of injury
   1. Helps determine presence of foreign body
   2. Helps determine prognosis for development of infection and scarring
C. Determination of allergies to local anesthetics, antibiotics, or latex
D. Extent of the wound
E. Neurovascular or tendon injury
F. Status of tetanus immunization

III. PHYSICAL EXAM
A. Location, length, shape, depth and tension lines of the wound
B. Associated tissue injury, such as joint, tendon or ligament involvement
C. Contaminants and foreign bodies
D. Neurovascular integrity and function

IV. LABORATORY AND RADIOLOGICAL STUDIES
A. If wound appears clinically infected, consider aerobic and anaerobic cultures. The best way to obtain culture is with a quantitative tissue culture (tissue biopsy)
B. Radiograph may be needed for suspected radiopaque foreign objects or fracture
C. Consider x-ray for all lacerations secondary to broken glass as glass may remain in the wound even if it is not seen during exploration and is a leading cause of malpractice litigation.

V. INITIAL WOUND PREPARATION
A. Optimal length of time between injury and wound repair has not been adequately defined.
B. Wounds generally should not be closed after 12–18 hours, except for facial/head wounds which may be closed up to 24 hours from time of injury. (There is minimal risk of infection because of the rich vascular supply)
C. Anesthetize wound
D. Prep and drape the area—Betadine may interfere with wound healing. Use of normal saline or sterile water is recommended
E. Clean the wound
F. Explore the wound
G. Copious irrigation with normal saline or sterile water—most important means of decreasing incidence of wound infection
H. Adequate debridement
I. Hair removal is not necessary unless it interferes with wound closure or knot formation. Shaving hair can leave small particles in the wound and increase risk of infection
J. Consider short-term placement of a tourniquet for extremity wounds to obtain bloodless field.

VI. ANESTHESIA
A. Anesthetic agents
1. Topical agents
   a. LET gel—Lidocaine 4%, Epinephrine 0.05%, Tetracaine 0.5% (extemporaneous preparation, not commercially available), particularly for scalp and facial laceration
   b. EMLA cream—Lidocaine 2.5%, Prilocaine 2.5%
   c. Topical Lidocaine (5%)
2. Infiltrative
   a. Lidocaine (1% or 2%): onset  2 min; duration 1.5–2 hr; max dose 4 mg/kg (not to exceed 280 mg) or 28 mL (1%) or 14 mL (2%)
   b. Lidocaine with Epinephrine (1:100,000 or 1:200,000): onset  2 min; duration 2–6 hr; max dose 7 mg/kg (not to exceed 500 mg) or 50 mL (based on Lidocaine 1%) or 25 mL (based on Lidocaine 2%)
   c. Bupivacaine (Marcaine) 0.25%: onset 5 min; duration 2–4 hr; max dose 2.5 mg/kg (not to exceed 175 mg) or 50 mL
3. Lidocaine with Epinephrine should not be used:
   a. On the genitals, digits, nose, earlobes, or skin flaps because vasoconstriction of the end arteries of these structures may cause ischemia and necrosis
   b. In contaminated wounds as vasoconstriction may delay the immune response and allow more time for bacteria to multiply
4. Allergy to Lidocaine
   a. Lidocaine and Bupivacaine are amide local anesthetics. Allergy to amides is rare and cross-reactivity among amides is very low
   b. When allergy does occur, it is usually caused by the preservatives: methylparaben in multidose vials or sulfites in Epinephrine-containing preparations.
      Methylparaben is metabolized to PAABA, a known allergen. Sulfites are used to prevent biodegradation of Epinephrine
   c. Consider using a preservative free single-dose Lidocaine preparation
   d. In a true Lidocaine allergy, use another amide such as Bupivacaine
   e. Diphenhydramine solution 1% has been used as an alternative to infiltrative anesthesia, but it is less efficacious than Lidocaine and carries an increased risk of tissue necrosis
5. Nerve blocks: most commonly used for face, hands, and feet.
B. Techniques to reduce pain with infusion
1. Use needle ≥ 25 gauge
2. Inject slowly
3. Inject through wound (as opposed to intact skin)
4. Use a buffering agent: Mix 9cc of 1% Lidocaine with 1cc of Sodium Bicarbonate with a concentration of 44mEq/50mL. The acidity of an acute wound decreases the effectiveness of local non-buffered anesthesia
5. Warm anesthetic to 98.6° F
6. Use topical agents or sedation in children
7. Regional nerve blocks in highly contaminated wounds, digital blocks for fingers and toes

VII. WOUND CLOSURE MATERIAL

A. Sutures

<table>
<thead>
<tr>
<th>SITE OF LACERATION</th>
<th>SUTURE*</th>
<th>SIZE OF SUTURE</th>
<th>SUTURE REMOVAL</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyelid</td>
<td>Nonabsorbable suture: Prolene monofilament (Prolene) Nylon monofilament (Ethilon)</td>
<td>6-0, 7-0</td>
<td>3 days</td>
<td>Prolene has the least amount of tissue reactivity</td>
</tr>
<tr>
<td>Cheek</td>
<td>same</td>
<td>5-0, 6-0</td>
<td>3–5 days</td>
<td></td>
</tr>
<tr>
<td>Nose, forehead, neck</td>
<td>same</td>
<td>4-0, 5-0</td>
<td>5 days</td>
<td></td>
</tr>
<tr>
<td>Ear</td>
<td>same</td>
<td>4-0, 5-0</td>
<td>4–5 days</td>
<td></td>
</tr>
<tr>
<td>Scalp</td>
<td>same</td>
<td>3-0</td>
<td>5–7 days</td>
<td></td>
</tr>
<tr>
<td>Arm, hand</td>
<td>same</td>
<td>3-0, 4-0</td>
<td>7-10 days</td>
<td></td>
</tr>
<tr>
<td>Leg, foot, chest, back</td>
<td>same</td>
<td>3-0, 4-0</td>
<td>10–14 days</td>
<td></td>
</tr>
<tr>
<td>Tendons</td>
<td>Prolene</td>
<td>3-0, 4-0</td>
<td>10–14 days</td>
<td></td>
</tr>
<tr>
<td>Deep closure of wounds, intraoral</td>
<td>Absorbable suture: Vicryl/ Dexon/ PDS/ Chromic gut</td>
<td>3-0, 4-0, 5-0 (intra-oral)</td>
<td>10-14 days</td>
<td>Vicryl and Dexon lose 50% of their tensile strength in 14-20 days PDS loses 50% in 5 weeks Synthetic sutures: preferable to gut in acute wounds</td>
</tr>
</tbody>
</table>

*Despite its ease of tying, silk suture should generally not be used because of increased tissue reactivity and chance of infection

B. Staples
1. Advantage: Faster
2. Precautions: Never use on face
3. Potential indications: Consider use on scalp, trunk, upper and lower extremities

C. Topical tissue adhesive
1. Example: 2-octylcyanoacrylate (Dermabond)
2. Technique: Approximate wound edges and 3 ever larger concentric circles over wound edges
3. Use only with superficial wounds under low tensile stress

VIII. TYPE OF CLOSURE

A. Depends on the age of the injury, the mechanism of injury, and the degree of contamination
B. Signs of inflammation are an absolute contraindication to wound closure
C. May occur in 3 ways:
1. Primary closure—Wounds caused by clean, sharp objects that have little or no devitalized tissue
2. Secondary intention
   a. Healing by granulation from the “bottom up”
   b. Indicated for:
      i. Deep stab or puncture wounds that cannot be adequately irrigated
      ii. Abscess cavities
iii. Contaminated wound
iv. Small noncosmetic animal bites
v. Presentation after significant delay

3. Delayed primary closure
   a. Consider for uncomplicated wounds that present after the first 12–18 hrs for trunk or extremity wounds or after 24 hrs for head and neck wounds
   b. Involves initial cleaning and debridement of the wound followed by a 4 or 5 day waiting period which allows host defense system to lessen the bacterial load
   c. May administer antibiotics to decrease the risk of infection

IX. SUTURE TECHNIQUE
A. Always use good lighting and be comfortable (easier to sit than stand or bend)
B. Most common suture technique is simple interrupted
C. Sutures should be placed with equal depth and width for best results. Sutures should be placed to evert wound edges without gapping or pulling. Eversion may be accomplished by placing the needle through the skin at a 90° angle and not tangentially
D. Sutures should be used to approximate the wound edges and not to pull the wound together. For wounds with high tension, place deep sutures or mattress sutures
E. Simple sutures are placed closer together and with smaller bites on the face and neck to minimize scarring
F. When suturing lips, place first suture through vermilion border (junction of lip and skin)
G. Delayed primary closure is preferred in heavily contaminated wounds if no signs of infection are present after 3–5 days
H. Hints for special circumstances
   1. Topical tissue adhesive for superficial lacerations with little tension
   2. Staples for selected sites such as scalp
   3. Continuous sutures for longer lacerations of the face and scalp
   4. Deep sutures for high-tension wounds
   5. Vertical mattress sutures for medium deep lacerations
   6. Half buried mattress sutures for flap lacerations

X. BITE WOUNDS
A. Introduction
   1. Animal bites are common with annual incidence of 2–5 million
   2. Account for approximately 1% of all visits to ED and 1–2% will result in hospitalization
   3. Causes of bites: Dogs, 85–90%; cats, 5–10%; rodents, 2–3%; humans, 2–3%; others, 0–6%
   4. Approximately 10% of bite wounds will require suturing and follow-up care
   5. Dog and cat bites are the most likely to become infected
B. Initial evaluation
   1. Generally, bite wounds are primarily closed in very vascular areas and if cosmetically necessary
   2. Areas usually primarily sutured are face, scalp, and neck. Avoid deep sutures
   3. Consider closing wounds of trunk, arm and legs
   4. Avoid suturing any bite wounds of the hands and feet
C. Wound preparation: See above. Very important to use copious irrigation and debridement of devitalized tissue
D. High risk bite wounds
   1. Location: Hand, foot, wrists, joints. In infants: Scalp or face
   2. Type of wound: Crush injuries, puncture wounds, bites involving the hands, cat or human bites except those to the face, dog bite wounds with delayed presentation, and bite wounds in immunosuppressed hosts
   3. Patient: Age > 50, asplenic, alcoholic, immunocompromised, diabetic, peripheral vascular disease, chronic steroid use, prosthetic or diseased cardiac valve or joint
E. Human bites
   1. Most commonly located on the face, upper extremities, and trunk. Note: Be aware of closed fist injury (“fight bite”) in young patients with laceration over MCP
   2. Most common organisms include α-hemolytic Streptococcus, Staphylococcus
Eikenella corrodens, Corynebacterium, and Bacteroides

3. Carry the highest risk of infection on the hand (47% risk of infection)
4. If there is invasion of the MCP joint capsule (usually from injuries sustained during a fight), refer to a hand surgeon for possible debridement in the OR
5. Wound closure
   a. Human bites to the hand should not be closed
   b. Those in other areas may be closed if less than 6hrs old after adequate irrigation and debridement
6. ATB prophylaxis: Amoxicillin/Clavulanate (Augmentin) 875mg PO BID × 5 days

F. Dog bites
1. Majority of dog bites occur in children with the highest rate in boys between 5 and 9 years of age. Most common organisms include Strep viridans, Pasteurella multocida, S. aureus, E. corrodens, Bacteroides
2. Dog bites tend to be more of an open, tearing type of wound
3. Wound closure
   a. Dog bites to the hand should not be closed
   b. Those in other areas may be closed if less than 6hrs old after adequate irrigation and debridement
4. ATB prophylaxis—10 day course
   a. Only 5% of dog bites become infected
   b. Prophylaxis should be administered in high risk bite wounds (see above) and optional in other wounds
   c. Give prophylactic antibiotics as soon as possible.
   d. ATB prophylaxis: Amoxicillin/Clavulanate (Augmentin) 875mg PO BID × 3–5 days if indicated
   e. Alternative
      i. Adults: Clindamycin 300mg PO QID plus Fluoroquinolone (e.g., Cipro 500mg BID)
      ii. Children: Clindamycin plus Bactrim
   f. Give prophylactic antibiotics as soon as possible.
5. Follow-up: Daily follow-up, especially in dog bites involving the hands until it is clear that the infection is resolving and surgical intervention is not needed

G. Cat bites
1. 89% of cat bites are provoked
2. Occur more commonly in adults and females
3. Cat bites are usually deep puncture type wounds
4. Most common organisms include staph and strep species and Pasteurella multocida
   a. Pasteurella multocida infection develops within 24hrs
   b. P. multocida is resistant to Cephalexin, Dicloxacillin, Clindamycin; many strains resistant to Erythromycin
5. Wound closure: Leave all cat bites open to heal by secondary intention
6. ATB prophylaxis
   a. Risk of infection is ~ 50% without ATBs
   b. Recommended: Amoxicillin/Clavulanate (Augmentin) 875mg PO BID × 3–5 days
   c. Alternative: Cefuroxime (Ceftin) 500mg PO BID or Doxycycline 100mg PO BID
   d. Caution: Do not use Cephalexin (Keflex) or Dicloxacillin
7. ATB Tx: Use same drugs as for prophylaxis, but tx at least 10 days

H. Rabies prophylaxis
1. Indications for rabies immunization
   a. If the animal (dog or cat or ferret) is healthy and available for 10-day observation, use prophylaxis only if animal develops signs of rabies
   b. If the animal is rabid or suspected of being rabid, treat immediately with rabies vaccine and Rabies immune globulin (RIG)
   c. In unknown or escaped cases, consult public health officials
2. For patient not previously vaccinated:
   a. RIG 20 IU/kg as a single dose. The full dose should be infiltrated around the wounds and any remaining volume should be administered IM at an anatomical
105. Management of Wounds

site distant from vaccine administration
b. Rabies vaccine: 5-dose series—1.0mL dose given IM in the deltoid area on days 0, 3, 7, 14, and 28. There are 2 types of vaccines available: Human diploid cell vaccine (Imovax Rabies) and Purified chick embryo cell vaccine (RabAvert)
3. For previously vaccinated persons: 2 doses of vaccine (1mL each) given IM, one immediately and one 3 days later

XI. METHICILLIN RESISTANT STAPH AUREUS
A. General: Most common cause of skin infections. Earliest outbreaks occurred in jails and athletic teams but now prevalent in general community
B. Diagnosis: Patient often complains of a spider bite. Appearance of abscess with cellulitis. Clusters of folliculitis with satellite lesions. Severe cases with necrosis and local tissue damage
C. Treatment
1. Incision and drainage (I&D): As with other abscesses, definitive treatment is I&D. Antibiotics not required if there is no surrounding cellulitis (Note: Studies of I&D without antibiotics were done before emergence of MRSA)
2. Antibiotics
   a. Trimethoprim/Sulfamethoxazole (Bactrim) DS: 1–2 tab PO BID × 10 days
   b. Clindamycin (Cleocin): 300–450mg PO TID × 10 days
   c. Doxycycline: 100mg PO BID × 10 days
   d. Linezolid: 600mg PO BID
3. Duration of therapy: 5–10 days, individualized based on the patient’s clinical response
4. Decolonization: Nasal mupirocin, chlorhexidine body wash, hibiclens. If infections recur despite above measures, Rifampin may be added to an oral agent
   Note: Trimethoprim/Sulfamethoxazole active against staph but not strep. If β-hemolytic strep a possibility, then add Cephalexin (Keflex) 500mg PO QID to regimen

XII. AFTERCARE
A. General
   1. Topical ATBs
   2. Dressings (non-adherent or sterile gauze)
   3. Splint lacerations over joints
B. Wounds that should be rechecked in 24–48hrs
   1. Hand wounds
   2. Bite wounds
   3. Heavily contaminated wounds
C. Tetanus prophylaxis

<table>
<thead>
<tr>
<th>History of Adsorbed Tetanus Toxoid (Doses)</th>
<th>Nontetanus-Prone Wounds</th>
<th>Tetanus-Prone Wounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown or &lt;3</td>
<td>Tdap or Td²</td>
<td>TIG</td>
</tr>
<tr>
<td>≥ 3</td>
<td>No³</td>
<td>No</td>
</tr>
</tbody>
</table>

¹ Examples: wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite
² Tdap is preferred to Td for persons aged ≥11–64 years who have never received Tdap. Td is preferred to TT for those who received Tdap previously or when Tdap is not available
³ Yes, if ≥10 years since the last tetanus vaccine dose
⁴ Yes, if ≥5 years since the last tetanus vaccine dose
1. Tetanus immune globulin (TIG): 250U in a single dose given IM
2. Tetanus vaccine:
   a. Td (Tetanus and diphtheria toxoid adsorbed) for those aged ≥7 years
   b. Tdap (Tetanus, reduced diphtheria toxoid, and acellular pertussis)—2 vaccine products available: Boostrix for ages 10–18, Adacel for ages 11–64
3. Give TIG and tetanus vaccine (Td or Tdap) IM, using a separate syringe at different anatomical sites

CLINICAL PEARLS

- Lidocaine with Epinephrine should not be used in areas with poor blood supply (nose, fingers, toes, skin flaps, etc.)
- Wounds should generally not be closed after 6–8 hrs, but may be primarily closed up to 24 hrs in very vascular areas such as the face and scalp
- Subcutaneous suture in the hand and any silk suture is generally not used because of increased tissue reactivity and increased risk of infection
- Shaving the hair around a wound increases the chance of infection

References

CDC. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. MMWR 2006;55:25.

Michael B. Weinstock, MD

106. Pain Management in Adults & Children

I. GENERAL

A. Pain can be divided into 3 main origins:
1. Visceral pain: Poorly localized and usually either cramping, sharp or aching
2. Somatic pain: Well localized and usually sharp, achy, throbbing or pressure-like
3. Neuropathic pain: Radiating and usually burning or stabbing

B. General principles in treating chronic pain (pain from chronic conditions such as cancer)
1. Schedule dosing with PRN breakthrough doses of pain meds
2. One method is to use an initial dose scheduled at an appropriate frequency (generally Q3–4hrs) and provide a 1 hr PRN dose of 1/2 of the scheduled dose. If patient requires more than 2 breakthrough pain doses, adjust the scheduled dose by adding previous scheduled dose and previous breakthrough dose. Adjust new breakthrough dose of 1/2 of new scheduled doses. Continue with this method until pain is controlled
3. Anticipate side effects
   a. When prescribing opiates, consider concomitantly prescribing laxatives
   b. Anticipate nausea when initiating high doses of opiates
   c. Discuss sedation and ways to prevent falls (lighting, hand rails, slow movement, see Chapter 114, Falls in the Elderly)

C. Selection of oral pain medications: Multiple studies have shown that Tylenol #3 and Darvocet are no better than Acetaminophen (Tylenol) alone at treating pain, but they have many side effects including nausea and vomiting. If analgesia is desired, use a medication that decreases pain such as Oxycodeone or Hydrocodone or perhaps Tramadol (Ultram) with Acetaminophen
## PAIN MANAGEMENT IN ADULTS AND CHILDREN

<table>
<thead>
<tr>
<th>Medication</th>
<th>Equivalent analgesic dose PO*</th>
<th>Equivalent analgesic dose IM/SC</th>
<th>Duration of analgesia (hours)</th>
<th>Recommended dose in adults and children^ (start with the lowest dose for pain control and then increase dose as needed)</th>
</tr>
</thead>
</table>
| Morphine sulfate | 30mg | 10mg | 3–7 | Adults — IM/IV 2–10mg Q 2–3hrs  
Children — IM/IV 0.1–0.2mg/kg/dose  
Roxanol 20mg/mL, 10mg/2.5mL — Titrate to effective dose Q 4 hours PO — Logical starting dose is 10–30mg Q 4hours PO  
MS Contin/Oramorph SR (Sustained release)— 15, 30, 60, 100mg tabs (MS contin has a 200mg tab) |
| Hydro- morphine (Dilaudid) | 4–6mg | 1.5mg | 2–4 | IM/IV/SC: 1–2mg Q 4–6 hours  
PO: 2–4mg Q 4–6 hours (2, 4, 8mg tabs or 5mg/5mL liquid)  
Rectal: One supr. PR Q 6–8 hours Available 3mg  
Not recommended for children |
| Methadone (Dolophine) | See § below | 2.5–3mg | 8–12 | Adults — PO: 2.5–10mg Q 3–4 hours  
Methadone should be used by experienced clinicians only |
| Meperidine (Demerol) | 300mg | 75–100mg | 2–4 | Adults — IV/IM/PO: 50–100mg Q 3–4 hours (20, 100mg tabs)  
Children — IV/IM/PO: 0.1–0.2mg/kg/dose Q 4–6 hours Available 3mg  
Not recommended for children |
| Oxycodone (Oxyir, Percocet, Percodan OxyContin) | 20mg | NA | 4–6 | Oxyn (oxycodeine 5mg caps or 20mg/mL liquid)  
OxyContin (controlled release) — every 12 hours available 10, 20, 40, 80mg  
Percocet 2.5/325 (oxycodeine 2.5mg/acetaminophen 325mg)  
Percocet 5/325 (oxycodeine 5mg/acetaminophen 325mg)  
Percocet 7.5/325 (oxycodeine 7.5mg/acetaminophen 325mg)  
Percocet 10/325 (oxycodeine 10mg/acetaminophen 325mg)  
Percodan (oxycodeine 4.5mg/paracetamol 325mg) |
| Hydrocodone (Narco, Lortab, Vicodin, Vicoprofen) | 30mg | NA | 3–8 | Lortab 10/325 (hydrocodone 10mg/acetaminophen 325mg)  
Lortab 7.5/325 (hydrocodone 7.5mg/acetaminophen 325mg)  
Lortab 5/325 (hydrocodone 5mg/acetaminophen 325mg)  
Lortab 2.5/325 (hydrocodone 2.5mg/acetaminophen 325mg)  
Lortab elixir (hydrocodone 15mg/acetaminophen 325mg/elixir 15mL)  
Vicodin (hydrocodone 5mg/acetaminophen 325mg)  
Vicodin ES (hydrocodone 7.5mg/acetaminophen 325mg)  
Vicoprofen (hydrocodone 7.5mg/paracetamol 325mg) |
| Codeine® (Tylenol #2, #3, #4, Empirin #2, #3, #4) | 200mg | 120mg | 4–6 | Note: Cough suppressant at 15–30mg Q4 hours  
Note: PO doses > 65 not recommended due to decreased incremental analgesia.  
Tf2 = codeine15mg/acetaminophen 300mg  
Tf3 = codeine30mg/acetaminophen 300mg  
Tf4 = codeine60mg/acetaminophen 300mg  
Elixir: codeine 12mg/acetaminophen 120mg/5mL |
| Fentanyl (Duranesc) Duragesic transdermal system patch | 25mcg/hr = morphine 60mg PO/24 hours | 72 | Patches in doses of 25, 50, 75, 100mcg/hour  
Note: Should not be used to treat acute pain  
Dose — give every 3 days |

* Consider reducing calculated parental dose when switching from PO to IV/IM to accommodate for cross sensitivity and absorption variation.

† Duration of action is immediate release preparations (not sustained release).

‡ All doses are for adults unless otherwise specified. Maximum 4g acetaminophen per day. Medications are generally dosed every 4–6 hours unless otherwise specified.

§ The oral morphine to oral methadone conversion ratio increases as the 24 h oral morphine goes up.

‖ Refer to conversion guidelines in the package insert.

## SIDE EFFECTS OF OPIOIDS

A. Respiratory depression/arrest  
B. Sedation  
C. Nausea and vomiting: May administer an anti-nausea med concurrently with opioid  
D. Constipation  
E. Tolerance and dependence  
F. Histamine reaction including hypotension and itching: Less with synthetic opioids (Dilaudid and Fentanyl). May be helped with Benadryl
III. NON-OPIOID PAIN MANAGEMENT

(May use as adjunct to narcotics to decrease duration of narcotic use)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ADULT DOSE</th>
<th>PEDIATRIC DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (Tylenol)</td>
<td>650–1000mg Q4–6 hours PRN (Max. daily dose is 4g)</td>
<td>10–15mg/kg/dose Q4–6 hours PRN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supplied: Liquid — 160mg/5mL (One teaspoon)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chewable tablets — 80mg/tab</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>200–800mg Q8 hours (Max. daily dose is 3200mg)</td>
<td>5–10mg/kg/dose Q8 hours PRN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supplied: 100mg/5mL (One teaspoon)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>325–650mg Q4–6 hours PRN (Max. daily dose is 3600mg)</td>
<td>For anti-rheumatic doses or for treatment of Kawasaki’s dz., consult other sources</td>
</tr>
<tr>
<td>Ketorolac (Toradol)</td>
<td>IM: 30–60mg IM loading dose PO: 10mg Q4–6 hours PRN</td>
<td>Not recommended for children</td>
</tr>
<tr>
<td></td>
<td>Do not exceed 5 days (injection plus oral)</td>
<td></td>
</tr>
<tr>
<td>Tramadol (Ultram)</td>
<td>50–100mg PO Q4–6 hours PRN</td>
<td>Not recommended for children</td>
</tr>
<tr>
<td>Tramadol/ Acetaminophen (Ultracet)</td>
<td>1–2 PO Q4–6 hours PRN</td>
<td>Not recommended for children</td>
</tr>
<tr>
<td>Celecoxib (Celebrex)</td>
<td>100–200mg PO QD For acute pain may give 400–800mg PO on day 1 and 200mg PO QD afterward</td>
<td>Not recommended for children</td>
</tr>
</tbody>
</table>

1. Efficacy (analgesic effect) is equal between the cox-2 inhibitors and traditional NSAIDs.
2. The patients taking cox-2 inhibitors had fewer symptomatic and complicated ulcers than the patients receiving traditional NSAIDS. This effect was negated in patients taking low dose aspirin.
3. The cox-2 inhibitors are better tolerated with less adverse effects including abdominal pain, dyspepsia and other GI side effects, but their cost is significantly higher.
4. The “number needed to treat” (when treated for one year) to prevent one UGI event was 66 with Celecoxib vs. traditional NSAIDs.

IV. OTHER MODALITIES TO TREAT PAIN

A. Neuropathic pain
   1. Antidepressants: e.g., Amitriptyline (Elavil), Imipramine (Tofranil), Duloxetine (Cymbalta)
   2. Anticonvulsants: e.g., Carbamazepine (Tegretol), Gabapentin (Neurontin), Divalproex (Depakote), Phenytoin (Dilantin), Pregabalin (Lyrica)
   3. Local anesthetics: Capsaicin (Zostrix)
B. Bone metastasis
   1. Pamidronate (Aredia)
   2. Calcitonin (Calcimar)
C. Generalized chronic pain: Antidepressants, e.g., Amitriptyline (Elavil), Imipramine (Tofranil)
D. Other: Physical therapy, exercise, massage, transcutaneous electrical nerve stimulation (TENS), radiation therapy, chemotherapy, psychotherapy, pastoral care

V. PREEMPTIVE ANALGESIA

A. Administration of local anesthetics, nerve blocks, epidural blocks, opiates, and anti-inflammatory drugs prior to noxious stimuli (i.e., surgery) can reduce the sensitization of pain receptors and lead to better post-op pain control
B. Administration of general anesthesia with a volatile drug such as Forane does not prevent sensitization

CLINICAL PEARLS

- There is no maximum dose of opioid analgesics
- Endoscopic studies reveal gastric or duodenal ulcers in 15–30% of patients who regularly take NSAIDs, but many are asymptomatic
Pain medicines are frequently underdosed. Pain medicines should generally be scheduled and given in doses adequate to relieve pain. This practice will reduce possibility of addiction.

To initiate pain management, begin with the most benign medicine which will still control the pain. Often involves starting with a non-opioid analgesic and titrating upward.

It is questionable whether Acetaminophen with Codeine is any more effective than Acetaminophen without Codeine.

References
I. INTRODUCTION
Preoperative assessment is mandatory in all patients undergoing both cardiac and noncardiac surgery. Evaluation includes history and physical on all patients, with lab, EKG, cardiac stress testing, and PFTs added individually as needed. Preoperative evaluation should be performed within 30 days of surgery.

II. HISTORY
A. Current symptoms: Emphasis is placed on cardiac and pulmonary symptoms, including chest pain at rest or with exertion, peripheral vascular symptoms, dyspnea with exertion, claudication, orthopnea, PND, palpitations, light-headedness, syncope, current fever or cough.
B. Medications
1. Include over-the-counter meds, vitamins, and herbal supplements. Meds listed should be stopped 5–7 days preoperatively if possible: Aspirin and any related product, NSAIDs, Vitamin E, garlic (inhibits platelet aggregation), ginseng, ginkgo, St. John’s Wort, kava, ephedra/Ma Huang.
2. Patient should continue blood pressure medicines and any bronchodilators until morning of surgery (with the exception of diuretics, which should not be taken on morning of surgery).
3. Patients on chronic corticosteroids should receive a stress dose of steroid (Hydrocortisone) about 30–60 minutes preoperatively.
4. Warfarin (Coumadin): See section VIII.C.
5. Diabetes meds: Avoid oral hypoglycemics on AM of surgery. Patients on insulin pump should continue basal rate but avoid any bolus infusion. Sliding scale insulin will be used in hospital until post-op intake is resumed. Patient should take a ½ dose of Lantus the evening prior to surgery.
C. Past medical history
1. Previous anesthesia reaction
2. History of DVT, PE, or clotting disorder
3. Previous stress testing or revascularization
4. Age > 70, history of MI/angina/LV dysfunction/arrhythmia, pO₂ < 60mmHg, pCO₂ > 50mmHg are all clinical predictors of increased perioperative cardiac risk.
D. Social history
1. Tobacco and alcohol use, caffeine use if in excessive amounts
2. Exercise: Helps to determine patient’s functional capacity. Functional capacity can be expressed in metabolic equivalents (METs). Perioperative cardiac risk is increased in patients unable to meet a 4 MET demand.
   a. 1–4 METs: Eating, dressing, walking around house
   b. 4–10 METs: Climbing a flight of stairs without symptoms, walking briskly, running a short distance, playing golf
   c. > 10 METs: Swimming, tennis, football, jogging

III. PHYSICAL EXAMINATION
A. Vitals: Heart rate and rhythm, BP
B. HEENT: Dentition/dentures, neck examination (thyroid, carotid bruits, pulses)
C. Cardiac: Heart murmurs (AS), gallop, cardiomegaly, JVD, peripheral edema, orthopnea
D. Abdominal: Pulsatile mass, hepatosplenomegaly
E. Pulmonary: Rales (CHF), wheezes (COPD), rhonchi, pleural effusions, clubbing
F. Neurological: Mini-mental status examination if applicable, cranial nerve examination
G. General: Jaundice, cyanosis, anemia, dehydration
### IV. INDICATIONS FOR LABORATORY, ECG, AND RADIOLOGICAL TESTING

#### LOCAL & CONSCIOUS SEDATION

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Healthy Asymptomatic Patients</th>
<th>MAC (Monitored Anesthesia Care)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General &amp; Spinal Anesthetic</td>
<td>No additional testing necessary</td>
<td>If symptomatic, order additional lab testing under medical history section</td>
</tr>
</tbody>
</table>

#### GENERAL & SPINAL ANESTHETIC

1) **LOW RISK SURGERY WITH MINIMUM BLOOD LOSS (< 500 CC) AND < 2 HOURS**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Healthy Asymptomatic Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male &lt; 50 years old</td>
<td>No additional testing</td>
</tr>
<tr>
<td>Female &lt; 50 years old</td>
<td>No additional testing</td>
</tr>
<tr>
<td>50 – 74 years old</td>
<td>Hgb, EKG</td>
</tr>
<tr>
<td>&gt; 75 years old</td>
<td>Hgb, EKG, Creat</td>
</tr>
</tbody>
</table>

2) **HIGH RISK SURGERY: IF PATIENT MATCHES CRITERIA, ASSIGN FOLLOWING LAB**

- surgery time > 2 hours
- peripheral artery vascular procedure
- major fluid shift or blood loss > 500 cc
- intra-abdominal general surgery
- major neurosurgery e.g. craniotomy or fix and fusion
- major orthopedic
- hysterectomy
- cardiac/major vascular-thoracic surgery

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Lab Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC, Type &amp; Screen/Gross</td>
<td></td>
</tr>
<tr>
<td>Type &amp; Screen/Gross</td>
<td>K+</td>
</tr>
</tbody>
</table>

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#### MEDICAL HISTORY SECTION

<table>
<thead>
<tr>
<th>Condition</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable Coronary Artery Disease</td>
<td>Hgb, EKG</td>
</tr>
<tr>
<td>Unstable Coronary Artery Disease</td>
<td>Hgb, EKG, CXR</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>K+, Creat, EKG</td>
</tr>
<tr>
<td>Digoxin</td>
<td>K+, Creat, EKG</td>
</tr>
<tr>
<td>Dysrhythmias</td>
<td>K+, Creat, EKG</td>
</tr>
<tr>
<td>Hypertension (HTN)</td>
<td>Blood pressure, EKG, K+</td>
</tr>
<tr>
<td>Pulmonary Disease</td>
<td>EKG, CXR, Only obtain if signs &amp; symptoms suggest pulmonary disease</td>
</tr>
<tr>
<td>Smoker &gt; 1 pack/day</td>
<td>PFT</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Na+</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Creat, EKG</td>
</tr>
<tr>
<td>Cerebrovascular Accident (CVA)</td>
<td>CBC, EKG</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Creat, EKG</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>CBC, ptt, plt</td>
</tr>
<tr>
<td>Malignancy</td>
<td>CBC, ptt, plt, T&amp;F or T&amp;C</td>
</tr>
<tr>
<td>Radiation Therapy</td>
<td>WBC, EKG, CXR</td>
</tr>
<tr>
<td>Leukemia</td>
<td>CBC, plt, plt</td>
</tr>
<tr>
<td>Steroids</td>
<td>glucose, Na+, K+</td>
</tr>
</tbody>
</table>

#### V. INDICATIONS FOR TESTING IN PATIENTS WITH CARDIOVASCULAR DISEASE

- Elective surgery should be delayed for at least 6 months post-MI
- Semi-elective surgery may be performed 4–6 months post-MI with intensive monitoring
- Stable angina, CHF, and arrhythmias should be maximally medically managed prior to surgery
- Indications for cardiac stress testing or cardiac catheterization prior to elective or semi-elective noncardiac surgery (see algorithm on next page)
ACCF/AHA Guidelines

Stepwise Approach to Preoperative Cardiac Assessment

Figure 1. Cardiac Evaluation and Care Algorithm for Noncardiac Surgery Based on Active Clinical Conditions, Known Cardiovascular Disease, or Cardiac Risk for Patients 50 Years of Age or Greater

Need for emergent noncardiac surgery?

Yes

Operating room

Proceed with planned surgery

Perioperative surveillance and postoperative risk stratification and risk factor management

No

Step 1

Step 2

Step 3

Step 4

Step 5

3 or more clinical risk factors

Vascular surgery

Consider testing if it will change management

Class IIa, LOE B

1-2 clinical risk factors

Intermediaterisk surgery

or consider noninvasive testing (Class III, LOE B) if it will change management

No clinical risk factors

Continued on next page
HR indicates heart rate; LOE, level of evidence; and MET, metabolic equivalent.

† Clinical risk factors include ischemic heart disease, compensated or prior heart failure, diabetes mellitus, renal insufficiency, and cerebrovascular disease.

‡ Noninvasive testing may be considered before surgery in specific patients with risk factors if it will change management.

¶ Consider perioperative beta blockade (see Table 11) for populations in which this has been shown to reduce cardiac morbidity/mortality.

**Recommendations for Perioperative Cardiac Assessment**

**CLASS I**

1. Patients who have a need for emergency noncardiac surgery should proceed to the operating room and continue perioperative surveillance and postoperative risk stratification and risk factor management. (Level of Evidence: C)

2. Patients with active cardiac conditions* should be evaluated and treated per ACC/AHA guidelines and, if appropriate, consider proceeding to the operating room. (Level of Evidence: B)

3. Patients undergoing low-risk surgery are recommended to proceed to planned surgery.† (Level of Evidence: B)

4. Patients with poor (less than 4 METs) or unknown functional capacity and no clinical risk factors‡ should proceed with planned surgery.† (Level of Evidence: B)

**CLASS IIa**

1. It is probably recommended that patients with functional capacity greater than or equal to 4 METs without symptoms§ proceed to planned surgery.¶ (Level of Evidence: B)

2. It is probably recommended that patients with poor (less than 4 METs) or unknown functional capacity and 3 or more clinical risk factors‡ who are scheduled for vascular surgery consider testing if it will change management.¶ (Level of Evidence: B)

3. It is probably recommended that patients with poor (less than 4 METs) or unknown functional capacity and 3 or more clinical risk factors‡ who are scheduled for intermediate-risk surgery proceed with planned surgery with heart rate control.¶ (Level of Evidence: B)

4. It is probably recommended that patients with poor (less than 4 METs) or unknown functional capacity and 1 or 2 clinical risk factors‡ who are scheduled for vascular or intermediate-risk surgery proceed with planned surgery with heart rate control.¶ (Level of Evidence: B)

**CLASS IIb**

1. Noninvasive testing might be considered if it will change management for patients with poor (less than 4 METs) or unknown functional capacity and 3 or more clinical risk factors‡ who are scheduled for intermediate-risk surgery. (Level of Evidence: B)

2. Noninvasive testing might be considered if it will change management for patients with poor (less than 4 METs) or unknown functional capacity and 1 or 2 clinical risk factors‡ who are scheduled for vascular or intermediate-risk surgery. (Level of Evidence: B)


**VI. INDICATIONS FOR PULMONARY FUNCTION TESTING IN PATIENTS WITH PULMONARY DISEASE**

**A.** Pulmonary function testing is indicated if the patient has a history of COPD, SOB, or orthopnea —and—

1. There is a need to determine reversibility of bronchospasm with bronchodilators (reversibility is defined as a 15% improvement in the FEV1 by the American Thoracic Society); —or—

2. A need to determine baseline condition in anticipation of post-op intubation; —or—

3. Patient is scheduled for lung resection

**B.** Test results indicating a significantly increased morbidity and mortality following surgery:

1. If FEV1 < 2 liters or < 60% predicted
2. Vital capacity (VC) or MVV < 50% of predicted
3. Arterial pCO2 > 45nm HG

**C.** Preoperative ABG in patients with severe COPD is recommended; this data may be
helpful in determining postoperative ventilator settings


VII. PERIOPERATIVE USE OF β-BLOCKERS

A. New information suggests that perioperative cardiac complications may be prevented with use of β-blockers

B. Candidates for perioperative β-blockade
   1. Patients with known coronary vascular disease and undergoing vascular surgery, — or —
   2. Patients already receiving β-blockers to treat angina, arrhythmia or HTN
   3. Consider β-blockers in patients with multiple cardiac risk factors undergoing intermediate or high risk procedures

C. Ideally perioperative β-blockers would be started at least 7 days preoperatively and continued 7–10 days postoperatively

D. Atenolol or Bisoprolol are the β-blockers included in recent studies

VIII. PERIOPERATIVE MANAGEMENT OF ANTICOAGULANTS

A. Aspirin can be continued before and after surgery for patients with a high thrombosis risk, such as a recent stent or MI. Also continue ASA for low bleeding-risk procedures such as minor dental, dermatological or cataract surgeries. If ASA stopped, should be done 7–10 days preoperatively

B. Clopidogrel (Plavix) should be stopped 7–10 days prior to surgery. If patient has had drug-eluting stent placed in last year, surgery should be delayed if possible until patient on Plavix for full year, or cardiac consultation should be obtained preoperatively

C. Warfarin can be continued for minor dental or dermatological procedures. For more invasive procedures, stop Warfarin 5 days prior to surgery. Restart 12–24 hrs. after surgery. Bridging therapy with Lovenox (LMWH) should be started 2 days after stopping Warfarin, held on surgical day, then resumed 24–72 hours after surgery until Warfarin is restarted and becomes therapeutic. Bridge therapy should be used on those patients at moderate to high risk of thrombosis

D. NSAIDs should be stopped 5–7 days preoperatively

IX. STATINS

A. 2 small studies have shown a reduced incidence of perioperative mortality and MI in high-risk patients who used a statin pre-operatively

B. Statins are believed to improve atherosclerotic plaque stability

C. Current evidence provides preliminary support for use in patients at high risk or perioperative mortality

CLINICAL PEARLS

• Patients should be questioned routinely regarding need for endocarditis prophylaxis (see Chapter 40, Endocarditis Prophylaxis)

References


X. Care of Patients with Psychiatric Disorders

108. Anxiety, Obsessive-Compulsive Disorder & PTSD .......................................... 427
109. Depression ............................................................................................................. 432
110. Sexual Dysfunction ............................................................................................... 438
111. Alcohol & Other Substance Use Disorders ......................................................... 444
108. Anxiety, Obsessive-Compulsive Disorder & PTSD

I. INTRODUCTION

A. Disorders include:
   1. Generalized anxiety disorder (GAD)
   2. Panic disorder with and without agoraphobia
   3. Obsessive-compulsive disorder (OCD), including hoarding disorder, body dysmorphic disorder, trichotillomania (compulsion to pull out one’s own hair), excoriation (skin-picking) disorder
   4. Adjustment disorder with mixed anxiety and depression
   5. Phobic disorder
   6. Post traumatic stress disorder (PTSD)
   7. Social anxiety disorder
   8. Substance induced anxiety disorder

B. Panic disorder is the most common of the anxiety disorders in which patients will seek treatment and can be very disabling with severe financial, social, and occupational consequences for the patient

C. Patients with panic disorder often have many physical complaints. Delineate between symptoms resulting from the panic disorder and those which are non-psychiatric in origin

D. Rule out organic causes for the patient’s symptoms of anxiety

E. Those with very high anxiety and panic attacks think of themselves as “crazy” when they are not. Let them know they have a common, treatable condition

II. MEDICAL CAUSES OF ANXIETY

Before treating for anxiety disorder, a complete history and physical and lab work (if indicated) will be necessary to rule out other organic causes. New onset anxiety in an older patient should be a red flag to evaluate for other causes

A. Endocrine: Hyperthyroid, hypoglycemia, carcinoid syndrome, parathyroid dysfunction, pheochromocytoma, adrenal dysfunction, and hypothyroid

B. Inflammatory: Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), polyarteritis nodosa, temporal arteritis

C. Neurologic: CNS tumors, migraine, subarachnoid hemorrhage, syphilis, multiple sclerosis, Wilson’s disease, Huntington’s chorea, seizure disorders, TLE encephalitis

D. Cardiopulmonary: Angina, pulmonary insufficiency, CHF, pulmonary embolism, COPD, asthma, arrhythmia

E. Nutritional: Pellagra, B₁₂ deficiency

F. Metabolic: Porphyria

G. Pharmacologic: Alcohol and drug abuse or withdrawal, amphetamines, caffeine, sympathomimetics, tobacco

H. Assess for other psychiatric disorders such as depression

I. PANDAS in children: Autoimmune neuropsychiatric disorders associated with Group A streptococcal infections

III. GUIDELINES FOR TREATMENT OF ALL ANXIETY DISORDERS

A. Consideration should be given to non-pharmacologic approaches (cognitive-behavior therapy is indicated regardless of pharmacologic or non-pharmacologic approaches). Avoid caffeine

B. Define underlying conflicts and stresses, coping mechanisms and support systems

C. Consider if psychosocial factors or the patient’s personality place the patient at risk for abuse or addiction, which is fairly common
D. Individualize anxiolytic therapy. SSRIs are first line treatment. Benzodiazepines should be prescribed for only short periods (2–5 weeks) to avoid tolerance and rebound anxiety/rebound insomnia.

E. Goal of therapy should be clearly discussed with the patient.

F. In the elderly:
   1. Start with half dose regimen
   2. Avoid frequent dosing adjustments
   3. Watch for signs of confusion, sedation, ataxia

— PART I: GENERALIZED ANXIETY DISORDER (GAD) —

I. EPIDEMIOLOGY
A. Prevalence is 5% of the general population; female to male ratio is 2:1
B. Age of onset is in the 20s, although there is a clear rise in diagnosis of children and adolescents
C. 15–17% of first degree relatives have GAD
D. Over half onset in childhood or adolescence. Course is chronic waxing/waning

II. DIAGNOSTIC—DSM-V

<table>
<thead>
<tr>
<th>Diagnostic Criteria for 300.02 Generalized Anxiety Disorder</th>
</tr>
</thead>
</table>
| A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, 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 three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months): Note: Only one item is required in children.
| 1. Restlessness or feeling keyed up or on edge.
| 2. Being easily fatigued.
| 3. Difficulty concentrating or mind going blank.
| 4. Irritability.
| 5. Muscle tension.
| 6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).
| D. The anxiety, worry or physical symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
| E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hypothyroidism).
| F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).


III. DIFFERENTIAL DIAGNOSIS
A. Agitated depression
B. Panic disorder  
C. Social phobia  
D. Obsessive compulsive disorder  
E. Hypochondriasis  
F. Drug and/or alcohol dependency  
G. Medications (Sympathomimetics, Yohimbine, Desipramine)  
H. Anxiety disorder due to a General Medical Condition

IV. TREATMENT

A. Remove exacerbating factors: Caffeine, tobacco, drugs, alcohol
B. Psychotherapy: Cognitive-behavioral therapy or group psychotherapy may help in treating a generalized anxiety disorder
C. Exercise: Aerobic exercise is 20 minutes of uninterrupted exercise with heart rate >120, performed a minimum of 3× a week. Smart phone apps are available for these even with no previous experience with regular exercise to help them start safely and encourage them
D. Medications—SSRIs are first-line. Benzodiazepines are indicated for short term, not as chronic therapy (see below)
E. Serotonin selective reuptake inhibitors (SSRIs)—Drug of first choice for anxiety. May also be used for social anxiety disorder, posttraumatic stress disorder (PTSD), panic disorder and obsessive-compulsive disorder (OCD). May take several weeks to start working. Start at half dose for 3–5 days, then increase to usual daily dosage. Avoid abrupt withdrawal  
   1. Efficacious without addictive properties. Consider starting at ½ the antidepressant dose to avoid initially exacerbating anxiety  
   2. May use BDZ initially when starting SSRIs as the SSRI may not decrease symptoms for the first several weeks  
   3. Escitalopram (Lexapro 20mg/day), Sertraline (Zoloft 50–100mg/day), Citalopram (Celexa 20mg/day), Paroxetine (Paxil 20mg/day or Paxil CR 25mg/day), Fluoxetine (Prozac 20mg/day)
F. Selective serotonin-norepinephrine reuptake inhibitor  
   1. Duloxetine (Cymbalta): Starting dose for an adult is 30mg once daily; usual dose for an adult is 60mg once daily (may titrate up to 120mg/day given BID)  
   2. Venlafaxine (Effexor): Starting dose for an adult is 37.5–75mg once daily; usual adult dose is 150–225mg but may titrate up to 300mg/day  
   3. Mirtazapine (Remeron): 15–45mg PO QHS  
   4. Desvenlafaxine (Pristiq): 50mg PO QD  
   5. Side effects in this class include nausea, anorexia, diaphoresis, headache, insomnia
G. Anxiolytic: Non-Benzodiazepine  
   1. Buspirone (BuSpar) 5mg PO BID–TID (gradually increase to 30–60mg/day). Does not have the sedative, withdrawal, or abuse potential seen with the Benzodiazepines. Effects of the drug may take several weeks to become evident  
   2. Side effects: Dizziness, drowsiness, headache. Buspirone is usually not effective to patients previously exposed to Benzodiazepines
H. Propranolol (Inderal): Starting dose 10–20mg TID–QID. Useful for prominent and somatic (as opposed to psychotic) complaints (i.e., palpitations, trembling, restlessness, motor tension). Note: Not approved for anxiety or other psychiatric problems
I. Benzodiazepines: Have the potential for abuse and dependence. Very effective for short-term treatment of anxiety or while waiting for other meds to start working. No evidence that they are more effective than no pharmacologic treatment when used for long periods of time. All are equally efficacious. Indicated for short duration (2–8 weeks). Long term use results in tolerance, abuse potential, and rebound anxiety and insomnia  
   1. Diazepam (Valium): 15–25mg/day; given its long half-life, there is a lower probability of withdrawal symptoms compared to other drugs in this class  
   2. Lorazepam (Ativan): 0.5–1mg PO BID–TID  
   3. Clonazepam (Klonopin): 0.5mg PO BID (may increase to 2–10mg/day); long half-life without rapid peak levels  
   4. Side effects: Drowsiness, fatigue, ataxia, unsteadiness, memory impairment in elderly
PART II: PANIC DISORDER

I. EPIDEMIOLOGY
A. 2–4% prevalence in the general population
B. Age of onset: Usually late 20s
C. Female to male ratio: Without agoraphobia (irrational fear of being in open or public places), 2–3 times more common in women
D. Co-morbidity with depression, substance use, personality disorders is up to 90%

II. DIAGNOSIS OF PANIC DISORDER—DSM-V

<table>
<thead>
<tr>
<th>Diagnostic Criteria for 300.01 Panic Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Recurrent unexpected panic attacks. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four (or more) of the following symptoms occur:</td>
</tr>
<tr>
<td>- Palpitations, pounding heart, or accelerated heart rate.</td>
</tr>
<tr>
<td>- Sweating.</td>
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<tr>
<td>- Trembling or shaking.</td>
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<tr>
<td>- Sensations of shortness of breath or smothering.</td>
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<tr>
<td>- Feelings of choking.</td>
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<tr>
<td>- Chest pain or discomfort.</td>
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<tr>
<td>- Nausea or abdominal distress.</td>
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<tr>
<td>- Feeling dizzy, unsteady, light-headed, or faint.</td>
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<tr>
<td>- Chills or heat sensations.</td>
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<tr>
<td>- Paresthesias (numbness or tingling sensations).</td>
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<tr>
<td>- Derealization (feelings of unreality) or depersonalization (being detached from oneself).</td>
</tr>
<tr>
<td>- Fear of losing control or “going crazy.”</td>
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<tr>
<td>- Fear of dying.</td>
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<tr>
<td>Note: Culture-specific symptoms (e.g., tinnitus, neck soreness, headache, uncontrollable screaming or crying) may be seen. Such symptoms should not count as one of the four required symptoms.</td>
</tr>
<tr>
<td>B. At least one of the attacks has been followed by 1 month (or more) of one or both of the following:</td>
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<tr>
<td>- Persistent concern or worry about additional panic attacks or their consequences (e.g., losing control, having a heart attack, “going crazy”).</td>
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<tr>
<td>- A significant maladaptive change in behavior related to the attacks (e.g., behaviors designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations).</td>
</tr>
<tr>
<td>C. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism, cardiopulmonary disorders).</td>
</tr>
<tr>
<td>D. The disturbance is not better explained by another mental disorder (e.g., the panic attacks do not occur only in response to feared social situations, as in social anxiety disorder; in response to circumscribed phobic objects or situations, as in specific phobia; in response to obsessions, as in obsessive-compulsive disorder; in response to reminders of traumatic events, as in posttraumatic stress disorder; or in response to separation from attachment figures, as in separation anxiety disorder).</td>
</tr>
</tbody>
</table>

III. Medical conditions that can mimic panic disorder
A. Parkinson’s disease, Huntington’s. SLE, TIA, Wilson’s
B. Myocardial infarction
C. Angina
D. Supraventricular tachycardia
E. Pulmonary embolus, asthma
F. Simple partial seizures
G. Hypoglycemia
H. Pheochromocytoma, Addison’s disease, Cushing’s syndrome
I. Carcinoid syndrome
J. Hyperthyroidism
K. Others: anemia, hypoparathyroidism, brain neoplasm, B12 deficiency, heavy metal poisoning

IV. TREATMENT: The goals of treating panic attacks include prevention of future attacks and relief of anticipatory anxiety (which will enable patients overcome avoidance behaviors)

- Before initiating treatment, discuss previous therapies (psychotherapy or drugs) the patient may have encountered, and the results of the particular therapies
- This condition may be chronic, so rapid resolution of symptoms may not occur

A. Selective serotonin reuptake inhibitors (SSRIs): First Line Treatment, along with CBT (therapy). All generally started at ½ antidepressant dose
1. Sertraline (Zoloft): Starting dose of 25–50mg QD; may titrate up to 200mg QD
2. Paroxetine (Paxil): Starting dose of 10–20mg QD; may titrate up to 40mg QD
3. Fluoxetine (Prozac): Starting dose of 10–20mg QD; may titrate up to 60mg QD
4. Citalopram (Celexa): Starting dose of 10–20mg QD; may titrate up to 40mg QD
5. Escitalopram (Lexapro): Starting dose of 10mg QD; may titrate up to 20mg QD
6. Fluvoxamine (Luvox): Starting dose of 50mg QD; may titrate up to 150mg QD

B. Tricyclic antidepressants
1. Imipramine: 150–200mg QD
2. Nortriptyline: 50–150mg QD
3. Desipramine: 150–200mg QD
4. Clomipramine: 50–150mg QD

C. β-blocker—Propranolol (Inderal): Starting dose of 10–20mg TID-QID; may titrate up to 80mg TID-QID

D. Benzodiazepines: Rapid onset of action. Reduce the anticipatory anxiety that most patients experience with panic disorder. Used most often in the acute setting of panic disorder especially when symptoms are severely disabling. Long-term use of this class of drugs is not recommended due to the risks of abuse and/or dependence. Side effects: Drowsiness, ataxia, dizziness, cognitive impairment, hypotension
1. Alprazolam may be started at 0.75–1.5mg/day, with most patients responding to 1.5–6mg (if given in XR, may use QD; otherwise total daily dose should be divided TID). Short ½, apt to cause rebound anxiety and withdrawal symptoms. Use with caution as Alprazolam has the highest level of abuse and street value
2. Clonazepam may be started at 0.5–1.5mg/day with most patients responding to 1.0–4.0mg (usually divided into BID dosing)
3. Lorazepam may be started at 1–2mg/day with most patients responding to 2–6mg (usually divided into BID dosing)
4. Diazepam may be started at 10mg/day with most patients responding from 10–60 mg (usually divided into BID dosing)

E. Psychotherapy: Cognitive-behavioral therapy, cognitive therapy, or group therapy are some nonpharmacologic options for treating panic disorder

F. Behavioral: Avoidance of places where attacks might occur or if this cannot be done, then brief exposure initially with increases over time. Avoidance should slowly be confronted. Continued avoidance could result in serious disability and increased anticipatory anxiety
109. Depression

Care of Patients with Psychiatric Disorders

CLINICAL PEARLS

- Separation anxiety disorder in childhood may predispose to depression and anxiety disorders later in life
- Patients with panic disorder and other anxiety disorders are at increased risk for drug abuse, especially alcohol and anxiolytics. Alcohol, marijuana, opiates used to self medicate initially, but leads to secondary problems
- Depression screening is helpful to reduce the high risk of co-morbidity with anxiety. Treatment of depression can help to reduce anxiety
- Medications prescribed won’t work if patient is still self medicating with other substances

References


Michael B. Weinstock, MD
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Christine Costanzo, MD
Budd Ferrante, EdD

109. Depression

I. INTRODUCTION

A. Lifetime prevalence is 17%; 12 month prevalence is 6.6%; 15% commit suicide; many are not recognized, many are incompletely treated. The incidence is similar to patients with ischemic heart disease
B. Proven therapies (pharmacologic and psychotherapeutic) are available with 50–60% responding to any individual antidepressants and 80% responding to at least 1 medication
C. Recurrent episodes of depression occur in 75%–85%. One-third of patients will have another episode within 1 year of stopping treatment and ½ will have another episode in their lifetimes

II. SCREENING

A. The following “2 question case finding instrument” has a 96% sensitivity, and a 57% specificity. If answers to either of the questions is positive, then proceed to establish diagnosis according to full DSM-V criteria listed below. The 2 questions are:
   1. During the past month, have you often been bothered by feeling down, depressed, or hopeless?
   2. During the past month, have you often been bothered by having little interest or pleasure in doing things?

III. DIAGNOSIS

A. DSM-V Criteria for Major Depression
   1. At least 5 of the following symptoms have been present during the same 2 week period and represent a change from previous functioning; at least 1 of the symptoms is depressed mood or loss of interest or pleasure
      a. Depressed mood most of the day
b. Diminished interest or pleasure in all, or almost all, activities most of the day
c. Significant weight loss or weight gain or a decrease or increase in appetite
d. Insomnia or hypersomnia
e. Psychomotor agitation or retardation
f. Fatigue or loss of energy
g. Feelings of worthlessness or excessive or inappropriate guilt
h. Diminished ability to think or concentrate
i. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or
   a suicide attempt or a specific plan for committing suicide

2. The symptoms cause clinically significant distress or impairment in social, occupa-
tional, or other important areas of functioning
3. The symptoms are not due to the direct physiological effects of a substance (drug of
   abuse or prescribed medication) or a general medical condition

B. A mnemonic for symptoms of Major Depression is: SIG E CAPS:

- S: Sleep (insomnia or hypersomnia)
- I: Interest (loss of interest)
- G: Guilt
- E: Energy (feeling of fatigue)
- C: Concentration (inability to concentrate)
- A: Appetite (increased or decreased)
- P: Psychomotor (agitation or retardation)
- S: Suicidality (ideation, plan)

C. Diagnosis may be missed if patient presents with anorexia, weight loss, constipation,
problems with sleeping, loss of libido, or other somatic complaints including pain (or
vague aches and pains)

IV. MEDICAL CAUSES OF DEPRESSION
A. Endocrine: Hypo- or hyperthyroidism, hyperparathyroidism, Cushing’s disease, diabe-
etes, Addison’s disease, or menopause
B. Infectious: AIDS, tertiary syphilis, tuberculosis, mononucleosis, or hepatitis
C. Inflammatory: Systemic lupus erythematosus (SLE), rheumatoid arthritis and other
   connective tissue diseases
D. Neurologic: Multiple sclerosis (MS), Parkinson’s disease, complex partial seizures, CNS
   tumors, dementia, stroke, or head injuries
E. Nutritional: Vitamin deficiencies (B12, folate, niacin, thiamine, or C)
F. Pharmacologic: β-blockers, corticosteroids, contraceptives, Cimetidine (Tagamet), Phe-
   nothiazines, α-methyldopa, anticholinesterases or interferon
G. Post-MI, pancreatic tumors, paraneoplastic syndromes

V. MANAGEMENT—General considerations
A. Antidepressant meds and structured psychotherapy are both effective treatments and
   may be combined if not effective alone
B. Patients with dysthymia may also respond to antidepressant therapy
C. Bereavement may lead to major depression and patient with depressive symptoms
   persisting more than 2 months should be offered therapy
D. Other psychiatric disorders such as anxiety, mania, psychosis, and substance use may
   co-exist with major depression
E. Patients should be assessed for suicidal tendencies by asking: “Do you ever think of
   hurting yourself or taking your own life?” If the answer is yes, then ask: “Do you
currently have a plan?” If the answer is yes, then ask “What is your plan?”
F. Risk factors for suicide include age > 65, male, white or Native American, single,
divorced, separated or widowed, unemployed, history of psychiatric admission, family
or personal history of suicide attempt, drug or alcohol use, recent severely stressful life
event, panic attacks or severe anxiety, severe physical illness, severe hopelessness or
anhedonia, specific plan, access to firearms or other lethal means
G. Choice of antidepressant meds: (See 2 tables below). No specific meds have been proven most effective for major depression, but certain meds will also work for co-existing conditions (panic, obsessive-compulsive, pain) and some have more side effects than others. Selective serotonin reuptake inhibitors (SSRIs) have become widely prescribed secondary to their favorable side-effect profile. General considerations include:

1. Select a med by taking into account side effects, interactions, treatment of co-existing conditions, and cost
2. Start a med gradually and increase dose over 5–10 days
3. Follow-up—Re-evaluate patient every 1–2 weeks for acute phase of treatment (first 6–10 weeks). Although the full therapeutic effect may not occur for 4–6 weeks, if there is no effect after 3–4 weeks, then increase the dose. If still inadequate response, then:
   a. Change to a new SSRI if SSRI was chosen initially
   b. Combine 2 antidepressants from different classes
   c. Change to different class of antidepressant or augment treatment
   d. Augment treatment with Lithium, atypical antipsychotic agent, Lamotrigine or T3
   e. Additional measures if unsuccessful include psychotherapy (at any time during treatment) or electroconvulsive therapy (ECT)

4. Duration of therapy—Average treatment duration is 6 months for an episode. Patients with 2 or more episodes of major depression lasting more than 2 years should continue medications for at least 2 years and possibly for life. Patients and family should be informed about the high risk for subsequent episodes. Early discontinuation (treatment duration < 6 months) is associated with 77% higher risk of relapse (compared to continuing treatment)

5. SSRIs
   a. Fluoxetine (Prozac) has the longest half life and should be used with caution in patients with bipolar disorder as it can aggravate the manic state. It is the only SSRI approved use and effective in children and adolescents
   b. SSRIs are less effective than tricyclic antidepressants (TCAs) or selective norepinephrine-reuptake inhibitors for depression with physical symptoms or pain
   c. Failure to respond to a specific SSRI does not predict nonresponse to another SSRI. If stopping short-acting serotonergic meds (e.g., Citalopram, Paroxetine, Sertraline, or Venlafaxine), then gradually decrease dose to prevent a discontinuation syndrome which may include tinnitus, vertigo, or paresthesias
   d. Vilazodone (Viibryd), a 5HT1A receptor agonist is a new drug approved for MDD. Dose: 10mg QD x 7d, then titrate by doubling the dose every 7 days to the final dose of 40mg QD

6. Tricyclic antidepressants
   a. Avoid using in patients with ischemic heart disease or arrhythmias
   b. Obtain ECG before starting in patients > 50 and repeat ECG before increasing dose if first degree AV block or bundle branch block

7. Bupropion (Wellbutrin) may increase the risk of seizures with daily dose exceeding 450mg for XR formulation, 400mg for SR, or single dose > 150mg for IR formulation

8. Trazodone (Desyrel) may rarely cause priapism

9. Venlafaxine (Effexor), Duloxetine (Cymbalta), Desvenlafaxine (Pristiq), Levomilnacipran (Fetzima)—(dual action antidepressant) has higher rates of remission than SSRIs or TCAs in severe depression. Effective for treatment of chronic pain. Only Duloxetine has the indication for chronic pain
   a. Desvenlafaxine 50mg QD
   b. Levomilnacipran 20mg × 2d, then increase by increments of 40mg QD every 2d as needed to max 120mg QD

10. Vortioxetine (Brintellix), a SSRI. 5HT1A agonist and 5HT3 antagonist. Dose: 10mg QD, then increase to 20mg QD. In 2D6 poor metabolizers, use only 10mg QD. Has many drug interactions

11. Discontinuing therapy: Meds should be slowly decreased over 2–3 months with monthly follow-up to telephone consultation. If depression recurs, then restart meds for additional 3–6 months
H. Other therapies

1. Exercise: A study of 156 patients (published in Arch Int Med in 1999—see References) compared 156 patients randomized to aerobic exercise, **Sertraline (Zoloft)**, or both (average age 50) and found at 16 weeks that there was no difference between the groups, though the groups receiving medication did show a faster initial response. Conclusion: Exercise is a comparable antidepressant therapy to medication, though the initial response is not as rapid.

2. Cognitive-behavioral therapy: Identifying any pessimistic or self-critical thoughts and decreasing behavior which causes depression.

3. Problem-solving therapy: Identifying specific problems and taking steps to solve them.

4. Interpersonal psychotherapy: Clarify/resolve interpersonal difficulties.

5. Electroconvulsive therapy
   a. Useful for refractory depression.
   b. Works well in the elderly population (especially when antidepressant side effects are not tolerated).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient history</strong></td>
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<tr>
<td>Age group</td>
<td></td>
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<tr>
<td>Children and adolescents</td>
<td>SSRI (fluoxetine)</td>
</tr>
<tr>
<td>Adults &lt;65 yr</td>
<td>SSRI, NRI, or SNRI</td>
</tr>
<tr>
<td>Adults ≥65 yr</td>
<td>SRI</td>
</tr>
<tr>
<td>Family history of response</td>
<td>Same medication that was effective in first-degree relative</td>
</tr>
<tr>
<td>Past response</td>
<td>Same medication that was effective previously</td>
</tr>
<tr>
<td><strong>Depression characteristic</strong></td>
<td></td>
</tr>
<tr>
<td>Bipolar depression</td>
<td>Mood stabilizer (lithium or lamotrigine) plus antidepressant</td>
</tr>
<tr>
<td>Psychotic depression</td>
<td>Antidepressant plus antipsychotic (atypical)</td>
</tr>
<tr>
<td>Depression with features of obsessive–compulsive disorder</td>
<td>SSRI</td>
</tr>
<tr>
<td>Panic attacks</td>
<td>SSRI</td>
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<tr>
<td>Agitated depression</td>
<td>Sedating antidepressant</td>
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<td>Depression with psychomotor retardation</td>
<td>Nonsedating antidepressant (NRI, SSRI)</td>
</tr>
<tr>
<td>Medication-resistant depression</td>
<td>Electroconvulsive therapy or combination of medications</td>
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<tr>
<td><strong>Coexisting medical conditions</strong></td>
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<td>Heart disease</td>
<td>Nontricyclic antidepressants</td>
</tr>
<tr>
<td>Stroke</td>
<td>Caution with SNRIs or NRIs and blood pressure</td>
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<tr>
<td>Pain</td>
<td>Duloxetine, venlafaxine</td>
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<tr>
<td><strong>Concern regarding side effects</strong></td>
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<tr>
<td>Gastrointestinal symptoms</td>
<td>Nontricyclic antidepressant</td>
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<tr>
<td>Anticholinergic symptoms</td>
<td>Nontricyclic antidepressant</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>Non-SSRI antidepressant, except possibly Vilazodone</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Avoid atypical antipsychotics, except Lurasidone</td>
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<tr>
<td>Postural hypotension</td>
<td>NRI</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Avoid atypical antipsychotics, except possible Lurasidone</td>
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</table>


## Classification, Doses, Safety, and Side Effects of Antidepressants

### Mechanism of Action and Functional Classification

<table>
<thead>
<tr>
<th>Mechanism of Action and Functional Classification</th>
<th>Starting Dose</th>
<th>Standard Dose</th>
<th>Lethality in OD</th>
<th>Insomnia &amp; Atylation</th>
<th>Sedation</th>
<th>Hypertension</th>
<th>Anticholinergic Effects</th>
<th>Nausea or GI Effects</th>
<th>Sexual Dysfunction</th>
<th>Weight Gain</th>
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<tbody>
<tr>
<td>Reuptake Inhibitors</td>
<td>baskets</td>
<td>baskets</td>
<td>baskets</td>
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<tr>
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<td>Mixed-action newer agents</td>
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<tr>
<td>Mirtazapine (Remeron)</td>
<td>30</td>
<td>30–60</td>
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<td>5</td>
<td>2</td>
<td>0/2</td>
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<td>5</td>
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<tr>
<td>Nefazodone (Serzone)</td>
<td>100</td>
<td>300–600</td>
<td>1</td>
<td>0/2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0/2</td>
<td>2</td>
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<tr>
<td>Trazodone (Desyrel)</td>
<td>50–100</td>
<td>200–800</td>
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<td>5</td>
<td>2</td>
<td>0/2</td>
<td>2</td>
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</table>

* These doses are standard in psychiatric practice but may not always conform to doses recommended in the Physician’s Desk Reference or drug package insert. More detailed reviews of side effects for all classes of antidepressants may be found in the Guidelines of the American Psychiatric Association 2000 and the Agency for Health Care Policy and Research 1999.

† Symptoms include dry mouth, constipation, sweating, blurred vision, and urinary retention.


### CLINICAL PEARLS

- Differentiate between depression and bipolar disorder as therapies are different
- Easiest way to differentiate between depression and bipolar disorder is to determine if there is a history of a single hypomanic episode, which rules out unipolar depression. Refer to DSM-5 for criteria
• Indefinite antidepressant maintenance therapy may be necessary after a third episode of major depression
• Depressive episodes which occur early in life predict a more severe course

References
110. Sexual Dysfunction

— PART ONE: MALE —

I. INTRODUCTION
A. Definition: Consistent inability to achieve and/or maintain an erect penis which is adequate for satisfactory sexual performance
B. Affects 15–25% males > 65. About 80% of cases are secondary to organic disease. Affects 10–30 million men in US
C. May have negative impact on self esteem, relationships, and quality of life

II. DIFFERENTIAL DIAGNOSIS
A. Psychogenic: e.g., Performance anxiety, stress or relationship discord, anxiety/depression, etc.
B. Organic
   1. Vasculogenic: Most common are arterial/inflow problems (e.g., DM, CAD, etc.)
   2. Neurogenic: e.g., Spinal cord injury, multiple sclerosis, herniated disc, etc.
   3. Hormonal: e.g., Hypogonadism, hyperprolactinemia, hypo/hyper-thyroidism
   4. Mechanical: Peyronie’s disease, anatomic abnormalities
C. Iatrogenic
   1. Meds (see III. F. below)
   2. Environmental: e.g., Alcohol, cigarettes, drugs of abuse

III. HISTORY
A. Techniques to initiate discussion of sexual topics in a nonthreatening manner
   1. Consider asking: Many men (with diabetes, CHF, etc.) experience sexual problems. Has this happened to you?
   2. Are you currently sexually active? Do you or your partner have any sexual issues that you would like to discuss?
B. Distinguish loss of libido vs. loss of erections: If libido and erections are intact, the cause is usually psychogenic
C. Onset and duration of impotence: Gradual loss of erections over time suggests organic cause
D. Erections: Difficulty in obtaining or maintaining erections and presence of nocturnal erections. If normal erections do occur, then the cause is usually psychogenic
E. Past medical history: Diabetes mellitus, coronary artery disease, peripheral vascular disease, hypertension, hyperlipidemia, hypogonadism, multiple sclerosis, neurologic disease, thyroid disorders, renal failure, adrenal disorders
F. Medications
   1. Antihypertensives
      a. Diuretics: Thiazides, Spironolactone
      b. Sympathomlytics: Methyl dopa (Aldomet), Clonidine (Catapres), Reserpine, β-blockers
      c. β-blockers (especially non-selective β-blockers)
   2. Psychiatric meds: Tricyclics, SSRIs, MAOIs, anxiolytics (Benzodiazepines)
   3. Antiandrogens: Digoxin, histamine H1 receptor blockers
   4. Others: Ketoconazole (Nizoral), Niacin, Phenobarbital, Phenytoin (Dilantin), anabolic steroids, corticosteroids, Finasteride (Proscar), Gemfibrozil (Lopid)
G. Drugs: Alcohol, nicotine, illicit drug use. Male erectile disorder 85% greater in smokers
H. Past surgical history: Pelvic surgery or spinal cord injury
I. Social history: Recent divorce, death of a spouse, new partner, marital/relationship discord, history of sexual abuse, increased stress (job change, move, death or illness in family, new baby, new diagnosis of concerning medical condition), substance, tobacco, or alcohol use

IV. PHYSICAL
A. General: Overt appearance/dress/speech may show signs of anxiety or depression
B. Vascular disease: Check blood pressure, auscultate vessels for bruits, signs of HTN or
Care of Patients with Psychiatric Disorders

110. Sexual Dysfunction

- Ischemic heart disease, lack of hair on legs may indicate peripheral vascular disease

C. Secondary sexual characteristics: Masculinization, beard, and body hair changes

D. Neurological exam: Peripheral sensory exam plus other (see rectal exam)

E. Genital: Penile scarring or plaque formation (Peyronie's disease), hypospadias, phimosis, hypogonadism, testicular abnormalities, tunics and erectile tissue

F. Rectal
   1. Prostate exam (DRE)
   2. Check rectal tone
   3. Superficial anal reflex (to assess sacral cord function—perform by touching perianal skin and note contraction of external anal sphincter muscles
   4. Bulbocavernous reflex (to assess sacral cord function—perform by placing a finger in the rectum and then squeeze the glans penis and noting contraction of the anal sphincter and bulbocavernous muscle)

G. Consider psychological evaluation—especially if younger male

Presence of sexual problems?
   Yes
      Erectile dysfunction?
         Yes
            Evaluate for other sexual dysfunction
         No
      No further evaluation

Detailed medical, sexual, and social history
Focused physical examination
Laboratory evaluation: screen for unrecognized systemic disease** testosterone†/prolactin.

Abnormal
   Hormonal cause likely
      Low testosterone
      Check luteinizing hormone/follicle-stimulating hormone
      Normal-low
      High
      Pituitary imaging
      Evaluate medical causes
      Medical therapy/referral

Persistent erectile dysfunction
   Psychogenic cause likely
   Neuropathic cause likely
   Vascular cause likely
   and/or
      Trial of therapy (education, oral medications, intraurethral medications, vacuum constriction device, etc.)
   or
      Consider sex therapy/psychiatric referral

Persistent erectile dysfunction
   Referral. Patient requests more extensive evaluation. Refractory to primary care therapy

*Screening panel: complete blood count, urinalysis, renal function, lipid profile, fasting blood sugar, and thyroid function.
†First-morning, free testosterone level.


V. LABORATORY AND DIAGNOSTIC TESTS (If necessary after history and physical exam):
See flow chart above

A. Labs: CBC, chemistry, glucose, HgbA1c, lipid profile, PSA, testosterone, thyroid function tests, urinalysis

B. If testosterone is abnormal: Check FSH, LH, prolactin

C. Nocturnal penile tumescence testing: If erections are obtained, this suggests psychogenic etiology. Test is not necessary if the history indicates that patient has erections

D. Injection of vasoactive substance into penis: If results in erection, vascular cause is excluded; also done to determine therapeutic options

E. Color Doppler ultrasonography: If there is a suggestion of vascular disease

VI. TREATMENT OF ORGANIC IMPOTENCE (Listed in increasing order of invasiveness):
For treatment of psychogenic impotence, refer to other sources
A. Minimize meds with side effects of sexual dysfunction, or change to a different class of agents

B. Smoking cessation, alcohol in moderation, healthy diet, regular exercise

C. Phosphodiesterase type 5 (PDE5) inhibitors: First-line agents. Increase penile cGMP, resulting in relaxation of smooth muscle cells

1. 4 drugs available: Sildenafil (Viagra), Vardenafil (Levitra), Tadalafil (Cialis), Avanafil (Stendra)

2. All have similar efficacy. A meta-analysis of 14 trials showed that 83% of men taking Sildenafil had a successful intercourse as compared to 45% men taking placebo

3. Pharmacokinetic differences: Both Sildenafil and Vardenafil have half-life of approx 4 hr, and Avanafil has a 5 hr half-life, but the half-life of Tadalafil is 17.5 hr. Unlike Sildenafil and Vardenafil, absorption of Tadalafil and Avanafil are not affected by a fatty meal

4. Contraindicated in patients with high or intermediate risk of coronary artery disease and nitrate use

5. Side effects are similar in all 4 drugs: Headache, flushing, nasal congestion, dyspepsia, myalgia, vision disturbances and rare cases of non-arteritic anterior ischemic optic neuropathy (NAION) causing sudden vision loss. Acute hearing loss has also been reported

6. Drug interactions: Can cause hypotension when use with α-blockers. CYP3A4 inhibitors (e.g., Protease Inhibitors, Macrolides, Azoles) increase PDE5 inhibitors serum concentration

7. For as-needed use: Instruct patient to take medication 1 hr before anticipated sexual activity. Medication should not be used more than once per 24 hr
   a. Sildenafil (Viagra): Initial dose 50mg, may increase to 100mg
   b. Vardenafil (Levitra): Initial dose 10mg, may increase to 20mg
   c. Tadalafil (Cialis): Initial dose 10mg, may increase to 20mg
   d. Avanafil (Stendra): Initial dose 100mg, may increase to 200mg

8. Cialis has recently been approved for once-daily treatment (2.5mg QD, may increase to 5mg QD if needed)

D. Prostaglandin E1 (Alprostadil): Increases the concentration of cAMP and decreases intracellular calcium concentration, resulting in relaxation of smooth-muscle cells

1. Intraurethral suppository (MUSE): Supervise initial application. Initially, 125 or 250mcg suppository is inserted into urethra after urination. May adjust dose in stepwise increments on separate occasion. Maximum 2 suppositories/day

2. Intracavernosal injection (Caverject): Supervise initial self-injection. Start with 2.5mcg dose and adjust dose on separate visit. Maximum ≤ 3 ×/wk, with at least 24 hr between doses

E. Testosterone-replacement therapy: Used in men with whom a low bioavailable testosterone level has been confirmed

1. Evaluate after 1 to 3 months and at least annually thereafter for testosterone levels, erectile function, and adverse effects

2. Commonly used dosage forms are:
   a. IM injection: Depo-testosterone (testosterone cypionate in oil): 100mg Q wk or 200–300mg Q2–3 wk
   b. Transdermal patch (Androderm): 1 x 4mg/d system applied nightly x 24 h to upper arms, thighs, back or abdomen
   c. Topical gel:
      i. Androgel 1.62%: Start at 40.5mg (2 pumps, or 1 x 40.5 mg packet) once daily in the morning. Apply to shoulders and upper arms
      ii. Androgel 1%: Start at 50mg (4 pumps, 2 x 25mg packets, or 1 x 50mg packet) once daily in the morning. Apply to shoulders and upper arms
      iii. Fortesta 2%: Start at 40mg (4 pumps) once daily in the morning. Apply to thighs
      iv. Testim: Start at 50mg (1 tube) once daily. Apply to shoulders and/or upper arms
   d. Topical spray: Axiron 60mg (1 pump actuation of 30mg to each axilla) applied once daily in the morning
e. Buccal tablet: Striant 30mg (1 buccal system) to the gum region twice daily, morning and evening
f. Implant: Testopel 75mg pellet—150 to 450mg SC every 3 to 6 months. Less dosing flexibility
g. Oral tab (Methyltestosterone, Fluoxymesterone) should not be used due to risk of hepatotoxicity

3. Adverse effects: Skin reactions with patch, gynecomastia, sleep apnea, exacerbate BPH, prostate cancer, reduced HDL-C, erythrocytosis, LFT elevation, and reduced fertility

F. Yohimbine: Available as a dietary supplement. No efficacy data found
1. It blocks presynaptic α₂-adrenergic receptors, resulting in increased penile blood flow
2. Dose: 5.4mg PO TID
3. Side effects: Increased urinary output, elevated blood pressure and heart rate, increased motor activity, nervousness, irritability, and tremor

G. Vacuum erection devices: Consist of a hollow cylinder placed over the penis, a vacuum is generated and a rubber ring is rolled onto the erect penis to the base to trap blood maintaining the erection. Can be uncomfortable and may be associated with ecchymoses

H. Penile prosthetic device: surgically implanted into the penis. 2 types of prostheses: malleable and inflatable. Consider after less invasive treatment failed

I. Psychotherapy: Useful for patients in whom erectile dysfunction has psychogenic or social components

— PART TWO: FEMALE —

I. INTRODUCTION: Sexual dysfunction in women is common and should be brought up by the physician during the history. Estimated that 19–50% of women have at least occasional sexual dysfunction

II. DIFFERENTIAL DIAGNOSIS
A. Inhibited sexual desire
B. Inhibited arousal
C. Orgasmic dysfunction
D. Pain with sexual intercourse: Dyspareunia/vaginismus

III. HISTORY
A. Family background: Repressive background/upbringing
B. Onset and duration: Primary vs. secondary
C. Relationship to stage of sexual intercourse: Problems with lack of adequate lubrication, pain with deep thrusting (if this is causing the cervix to be moved it may indicate infection, pelvic mass, etc.)
D. Trauma: Rape, abusive relationship, sexual abuse or incest (childhood or adult)
E. Sexual orientation
F. Life changes in the past year: Losses, pregnancy, stresses
G. Relationship with sexual partner(s): New partner, marital/relationship discord, inexperience, inhibition
H. Menarche-menopause
I. Pregnancy or post-partum
J. Past medical history: Chronic illness, sexually transmitted diseases, HIV/AIDS, cancer
K. Drugs: Alcohol, nicotine, IV drugs
L. Meds
1. Psychoactive meds: e.g., BDZ, SSRIs, MAOIs, TCAs
2. Cardiovascular and antihypertensives: e.g., β-blockers, Clonidine, Digoxin, Spironolactone, anti-lipids, Methyldopa (Aldomet)
3. Hormonal preparations: Danazol, OCPs, GnRh agonists (Lupron, Synarel)
4. Anticholinergics
5. Antihistamines
6. Others: Ketoconazole (Nizoral), Phenytoin (Dilantin), histamine H2 receptor blockers

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IV. PHYSICAL
A. General: Vital signs for HTN and signs of ischemic heart disease or other chronic medical condition
B. Genital: Discharge, vulvar dystrophy, dermatitis, vaginismus, ulcerations (HSV)
C. Surgical changes: Female circumcision, clitoral adhesions, episiotomy
D. Pelvic exam: Adnexal tenderness and signs of endometriosis such as uterosacral nodularity and decreased pelvic organ mobility
E. Rectal exam: Rectocele, infections/ulcerations, mass, blood/heme testing

V. MANAGEMENT: Treat secondary factors first and/or concurrently with the interventions listed below
A. Decreased libido: See table below, C. 3.
   1. Estrogen replacement therapy if postmenopausal (or with surgical menopause)
   2. The short-term addition of androgens has been helpful in some women in restoring sexual desire
   3. If secondary to relationship or marital strife, address these problems or refer for therapy. Address other aspects (listed in history) including religious taboos, social restrictions, sexual identity conflicts, guilt, history of abuse, inexperience, stressors
   4. Consider altering or prolonging arousal phase, use of erotic materials, interventions to reduce anxiety
B. Orgasmic problems
   1. Primary anorgasmia (never experienced orgasm in any situation)
      a. Causes: May be due to fear of pregnancy, satisfaction, losing control. Anxiety is often a factor
      b. Treatment
         i. Usually very successful
         ii. Extinguish the woman's subconscious over control and enhance sensory stimulation
         iii. Focus on erotic thoughts and fantasies. Consider "spectatoring" (observing oneself from a third-party perspective)
         iv. Self-stimulation or prolonged stimulation with partner (up to 1hr). Consider use of a vibrator
         v. Heighten arousal and lubrication before penetration
   2. Secondary anorgasmia
      a. In-depth exploration of differences in life situation now and in the past (when she was able to obtain an orgasm)
      b. Use the above techniques
C. Dyspareunia
   1. Superficial: Occurs with attempted penetration. May be due to irritative conditions such as infections/dermatitis or to vaginismus
      a. Vaginismus is painful reflex spasm of the perivaginal muscles due to fear of sex (young and inexperienced, often from strict homes) or prior rape or incest
      b. May be complete (occurs whenever there is penetration) or situational
      c. Gradual muscle relaxation and vaginal dilation. Have patient alternatively relax and contract pelvic muscles. Vaginal dilation may be with patient's finger, partner's finger, or commercial dilator (may use tampon). Success rates close to 90%
      d. Psychotherapy
   2. Vaginal: Pain related to friction and often secondary to irritation from inadequate vaginal lubrication (may be physiologic or from decreased arousal)
      a. Consider trial of prolonged arousal phase
      b. Lubricants such as K-Y jelly, Lubrin, Replens
      c. Vaginal creams containing estrogen can reverse vaginal atrophy in peri-menopausal women
      d. Low dose oral contraceptive therapy or hormone replacement therapy can alleviate vaginal dryness
   3. Deep: Pain related to thrusting, often from pelvic disease
a. Endometriosis
b. Ovarian cysts/mass
c. May require further work-up

### Basic Treatment Strategies for Female Sexual Dysfunction

<table>
<thead>
<tr>
<th>Provided education</th>
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<tbody>
<tr>
<td>Provide information and education (e.g., about normal anatomy, sexual function, normal changes of aging, pregnancy, menopause). Provide booklets, encourage reading; discuss sexual issues when a medical condition is diagnosed, a new medication is started, and during pre- and postoperative periods; give permission for sexual experimentation.</td>
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<tr>
<th>Enhance stimulation and eliminate routine</th>
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<tr>
<td>Encourage use of erotic materials (videos, books); suggest masturbation to maximize familiarity with pleasurable sensations; encourage communication during sexual activity; recommend use of vibrators; discuss varying positions, times of day or places; suggest making a “date” for sexual activity.</td>
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<th>Provide distraction techniques</th>
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<tr>
<td>Encourage erotic or nonerotic fantasy; recommend pelvic muscle contraction and relaxation (similar to Kegel exercise) exercises with intercourse; recommend use of background music, videos or television.</td>
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<th>Encourage noncoital behaviors***</th>
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<tr>
<td>Recommend sensual massage, sensate-focus exercises (sensual massage with no involvement of sexual areas, where one partner provides the massage and the receiving partner provides feedback as to what feels good; aimed to promote comfort and communication between partners); oral or noncoital stimulation, with or without orgasm.</td>
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<tr>
<th>Minimize dyspareunia</th>
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<tr>
<td>Superficial: female astride for control of penetration, topical lidocaine, warm baths before intercourse, biofeedback. Vaginal: same as for superficial dyspareunia but with the addition of lubricants. Deep: position changes so that force is away from pain and deep thrusts are minimized, nonsteroidal anti-inflammatory drugs before intercourse.</td>
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*—Provide information for obtaining one discreetly.
**—Helpful in eliminating anxiety, increasing relaxation and diminishing spectatoring.
***—Also helpful if partner has erectile dysfunction.


### CLINICAL PEARLS

- Premature ejaculation is usually psychogenic (performance anxiety)
- 40% of men in their 40’s report occasional difficulty in obtaining or maintaining an erection, this number rises to 70% at 70
- At 60, men have an average of 1 erection per week
- Most patients feel that sexual function is an appropriate topic to be addressed by their primary care providers
- 8–10% of adult women in the US have never had an orgasm. 10% achieve orgasm with fantasy alone

### References

111. ALCOHOL & OTHER SUBSTANCE USE DISORDERS

I. GENERAL

A. Almost 12 million people in the US are dependent on alcohol or illicit drugs
B. Drug dependence costs the US about $67 billion/yr and alcoholism costs $185 billion/yr
C. About 100,000 Americans die each year because of alcohol-related causes (including traffic accidents and cirrhosis)
D. Concomitant medical disorders are high among substance abuse patients and include HTN, CAD, chronic liver disease, hepatitis C, depression, and anxiety

II. GENERAL EVALUATION OF ALCOHOL OR DRUG DEPENDENCE

A. Definitions
   1. Abuse: A pathological pattern of use involving social, occupational, or functional impairment
   2. Dependence: Abuse plus evidence of tolerance

B. Screening, Brief Intervention, and Referral to Treatment (SBIRT): an approach recommended by the Substance Abuse and Mental Health Services Administration
   1. Screening quickly assesses the severity of substance use and identifies the appropriate level of treatment
   2. Brief intervention focuses on increasing insight and awareness regarding substance use and motivation toward behavioral change. Motivational interviewing is often used during intervention
   3. Referral to treatment provides those identified as needing more extensive treatment with access to specialty care

C. Screening
   1. Eliciting an alcohol and drug history
      a. Ask patients: “Have you ever had a health, legal, or personal problem as a result of alcohol or drugs?” and “When was your last drink or use of drugs?”
      b. Answering “yes” to the first question and “within the last 24 hours” to the second question is almost 95% sensitive for diagnosing alcoholism
      c. Asking a patient “How much do you drink?” or “Do you use drugs?” often results in dishonest answers
   2. CAGE Questions: 2 out of 4 positive answers to the CAGE questions is also fairly sensitive and specific for alcoholism
      a. Have you ever tried to Cut down?
      b. Do you get Annoyed when people question your drinking?
      c. Do you feel Guilty about drinking?
      d. Have you ever needed an Eye opener?
   3. Other: Inconsistent mild hypertension, insomnia or anxiety, unexplained hepatitis or cirrhosis, pancreatitis without stones

D. Laboratory abnormalities in patients with alcoholism
   1. Elevated GGT (> 35 units)
   2. High or high-normal MCV (> 95)
   3. AST/ALT >2 (suggests alcohol-induced liver disease)
   4. Serum uric acid > 7mg/dL
   5. Serum triglycerides > 180mg/dL

III. EVALUATION & MANAGEMENT OF SEDATIVE (ALCOHOL & BENZODIAZEPINE) DEPENDENCE
A. Signs and symptoms of withdrawal include sweating, anxiety/agitation, tremor, auditory or visual disturbance, n/v, tactile disturbance, HA, disorientation, and at the most severe seizures. If patients have these symptoms on presentation, medications are indicated.

B. Alcohol withdrawal seizures occur within 12–24 hrs of stopping drinking. Alcohol withdrawal delirium (DT's) usually occurs 48–72 hrs after cessation, mortality up to 20%. Symptomatic hyperactivity

C. Predictors of DT's: Prior history of severe withdrawal symptoms, high blood alcohol level without signs of intoxication, withdrawal signs with high blood alcohol level, concurrent use of sedative hypnotics, concurrent hepatitis, pancreatitis.

D. Duration of symptoms: Peak in 72 hrs and meds are generally not necessary after 7 days (though patients may complain of difficulty with sleep for several weeks).

E. Medications
1. For alcohol withdrawal

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Effects</th>
</tr>
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<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Chlordiazepoxide, diazepam, oxazepam, lorazepam</td>
<td>Decreased severity of withdrawal symptoms; reduced risk of seizures and delirium tremens</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine</td>
<td>Decreased severity of withdrawal symptoms</td>
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Adjunctive agents

- Beta-blockers: Atenolol, propranolol
  - Improvement in vital signs; reduction in craving

- Alpha-agonists: Clonidine
  - Decreased severity of withdrawal symptoms

*Dosing follows one of three strategies. With fixed-dose therapy, a set amount of medication is given at regular intervals (e.g., 50 to 100 mg of chlordiazepoxide four times daily), with the dose tapered from day 4 to day 7. With a loading-dose strategy, a moderate-to-high dose of a long-acting benzodiazepine (e.g., 20 mg of diazepam) is given initially to provide sedation; the level is allowed to decrease through metabolism. With symptom-triggered therapy, the first dose of 5 mg of diazepam is given when the score for symptoms is at least 8 on the Clinical Institute Withdrawal Assessment for Alcohol scale. The severity of symptoms is measured one hour after this and each subsequent dose of diazepam and then at least every eight hours, with the frequency of monitoring increased if symptoms worsen. The dose is adjusted (e.g., from 5 mg of diazepam to 10 mg three times daily) according to the severity of the symptoms.


2. Treatment of alcohol dependence:
   a. Disulfiram (Antabuse):
      i. Inhibits intermediate metabolism of alcohol, causing flushing, sweating, and tachycardia if patient drinks
      ii. The dose range is 125–500mg QD
      iii. Side effects include metallic taste, dermatitis, hepatotoxic effects, optic neuritis, peripheral neuropathy, and psychotic reactions
      iv. Monitor LFTs and drug interactions. Avoid alcohol in diet, OTC medications, or toiletries. Contraindicated in patients taking Metronidazole and those with CAD
   b. Acamprosate (Campral):
      i. Stabilizes glutamate and GABA systems
      ii. The dose is 666 mg TID. Reduce dose to 333 TID in patients with CrCl 30–50mL/min
      iii. Side effects include diarrhea, somnolence, rare cases of suicidality
      iv. Contraindicated in CrCl <30mL/min
   c. Naltrexone: Blocks opioid receptors, reduces reward in response to drinking and craving. Indicated for treatment of alcohol dependence and opioid dependence. Side effects include N/V, anorexia, HA, dizziness, fatigue, somnolence, anxiety, precipitation of opioid withdrawal, hepatotoxic effects at high doses
i. Oral Naltrexone (ReVia): 50mg QD
ii. Extended-release injectable Naltrexone (Vivitrol): 380mg IM in the gluteal monthly. Side effects are same as oral Naltrexone, plus injection reaction, joint pain, muscle aches, depression, suicidality in rare cases, pneumonitis

F. Rehabilitation oriented treatment: At 1 year about 40–60% are continuously abstinent and an additional 15–30% have not resumed dependent use. Predictors of poor adherence include low socioeconomic status, co-morbid psychiatric conditions, and lack of support system

IV. EVALUATION & MANAGEMENT OF OPIOID (HEROIN & METHADONE) DEPENDENCE

A. Signs and symptoms of withdrawal resemble a severe flu. Symptoms include papillary dilation, lacrimation, rhinorrhea, piloerection (goosebumps), yawning, sneezing, n/v/d

B. Duration of symptoms:
   1. Heroin withdrawal—Peak in 36–72 hrs and last for 7–10 days
   2. Methadone withdrawal—Peak in 72–96 hrs and for 14 days or longer

C. Meds: Decrease dose of Methadone by 3–5% each day

D. Buprenorphine alone (Subutex) SL tablets are used in office-based treatment by physicians who are certified to prescribe these drugs

E. Buprenorphine combined with Naloxone (Suboxone): Given as SL tab or SL film
   1. Naloxone is a safety feature—if the person tries to use the medication IV, withdrawal will occur. Eliminates IV use. With sublingual use, only Buprenorphine gets absorbed, not the Naloxone
   2. Buprenorphine is a high affinity partial agonist at the mu receptor that binds tightly; additional opiate use after taking it will have little or no CNS effect

F. Medication treatment for opioid withdrawal*
   1. Medication
      a. Opioid agonists: Methadone (20–35mg daily) or Buprenorphine (4–16mg daily), tapered over several days or weeks
      i. Withdrawal symptoms are decreased in severity
      ii. Methadone and other opioid agonists are currently restricted to inpatient settings or licensed programs; Buprenorphine is now approved by the FDA for this purpose
      b. Nonopioid drugs: Clonidine (0.2mg, 3 × daily) or Lofexidine (0.2mg twice daily), administered for approximately 10 days for Heroin and 14 days for Methadone
      i. Withdrawal symptoms are decreased in severity
      ii. Lofexidine is less likely to produce hypotension but is not currently approved by the FDA for this purpose
   2. Rapid and ultra-rapid detoxification
      a. Protocols include a variety of medications: Opioid antagonists (Noloxone or Naltrexone), Clonidine, sedatives, antiemetic agents, analgesics, anesthetics
      i. Withdrawal is precipitated with an opioid antagonist, and symptoms are managed with a variety of adjuvant medications
      ii. Patients are awake or lightly sedated for rapid detoxification; they are under heavy sedation or general anesthesia for ultra-rapid detoxification
      iii. Both methods require special training, equipment, or both. Research on efficacy is limited


G. Naltrexone: ReVia and Vivitrol

H. Meds for relief of symptoms
   1. Abdominal cramping: Dicyclomine (Bentyl) 20mg PO QID PRN
   2. Pain relief: Ibuprofen and/or Acetaminophen
   3. Diarrhea: Kaopectate 30cc PO QID PRN
4. Insomnia: Diphenhydramine (Benadryl) 25–50mg PO QHS PRN

I. Rehabilitation oriented treatment: At 1 year about 40% are abstinent. Predictors of poor adherence include low socioeconomic status, co-morbid psychiatric conditions, and lack of support system

V. EVALUATION & MANAGEMENT OF STIMULANT (COCOAINE & AMPHETAMINE) DEPENDENCE

A. Signs and symptoms of withdrawal resemble depressive symptoms and include dysphoria with disturbances in sleep and appetite. Severe symptoms may include paranoia, delusions, compulsive behavior and may require Benzodiazepines or neuroleptics for the first 48 hrs. Irritability is very common

B. Duration of symptoms: Severe symptoms last 8–48 hrs and minor symptoms may last weeks to months. Relapse and depression are common

C. Medication treatment for stimulant withdrawal*

1. Indirect dopamine agonists: e.g., Methylphenidate, Amantadine
   a. Improved treatment retention of each agent in a study, data very limited

2. Adrenergic antagonists: e.g., Propranolol
   a. Improved treatment retention and cocaine use reduced in patients with severe withdrawal symptoms in a study

3. Antidepressants: e.g., Desipramine, Bupropion
   a. Medications well tolerated but do not appear effective during stimulant withdrawal


CLINICAL PEARLS

- Follow-up outpatient care is important in preventing relapses
- Denial is an integral part of alcohol or drug abuse—family denial may be as strong as patient denial
- For every abuser there is an enabler—both need rehabilitation
- AA, NA, cocaine anonymous are good free resources. Other resource for mental health: NAMI (National Alliance on Mental Illness)

References
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112. Periodic Health Screening in the Elderly

I. HISTORY: “Yearly physical” should be more comprehensive than the episodic visits. Updating the history is perhaps most important component. Little agreement on how often the “yearly physical” should occur but it should be at some routine to avoid chaotic and episodic care. During visit note:

A. Medical and family history
B. Dietary intake
C. Tobacco, alcohol and drug use
D. Mental status changes
E. Review of systems
F. Physical activity
G. Functional status at home
H. Mood (depression screening)
I. New diagnoses, meds or hospitalizations since last visit

II. PHYSICAL EXAMINATION

A. Height, weight, blood pressure
B. Visual acuity and fundus exam
C. Ear exam and hearing test
D. Thyroid exam
E. Heart, Lungs and abdomen
F. Breast exam
G. Pelvic if indicated (see below)
H. Digital rectal exam
I. Neurologic exam
J. Skin exam

III. LABORATORY

A. Prostate specific antigen (PSA): US Preventive Services Task Force (USPSTF) recommends not screening asymptomatic men but several major organizations including the American Cancer Society and the American Urological Association do recommend screening
B. Cholesterol: USPSTF recommends every 5yrs until 65. Research is unclear after 65 (see Chapter 44, Hyperlipidemia)
C. Thyroid: Consider this in women and in anyone on Lithium or Amiodarone (Cordarone)
D. Glucose: Obtain in obese patients or those with family history of DM or personal history of gestational diabetes (see Chapter 56, for ADA recommendations on screening)
E. HIV: High risk populations only

IV. OTHER TESTING

A. Colorectal screening: USPSTF recommends screening at 50 with fecal occult blood testing (FOBT) and/or sigmoidoscopy at unspecified intervals. Others recommend FOBT annually and/or sigmoidoscopy every 5yrs
B. Mammogram: USPSTF recommends every 1–2yrs starting at 50. Others recommend starting at 40. Benefits of screening after 69 are not known
C. Pap smears: USPSTF recommends screening every 3yrs after becoming sexually active. Others recommend every 1–3yrs
D. EKG: Not recommended in asymptomatic patients
Recommendations for Screening by Age

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*R = recommended, x = some organizations recommend this interval.
FOBT= Fecal occult blood testing, BP=Blood pressure, PSA=Prostate specific antigen

V. PREVENTIVE CARE

A. History and physical: USPSTF recommends periodic screening but gives no frequency
B. Obesity: USPSTF recommends periodic screening but gives no frequency
C. Glaucoma: USPSTF gives no recommendation for or against screening for glaucoma by the family doctor
D. Immunizations: USPSTF recommends using the schedule recommended by the Advisory Committee on Immunization Practices (endorsed by the AAFP)—dT every 10yrs, Influenza vaccine yearly, pneumococcal vaccine once, hepatitis B for high risk patients, zoster vaccine once
E. Fall prevention (see Chapter 114, Falls in the Elderly)
F. Nutrition: Diet should be balanced and contain fresh fruits and vegetables. Consider calcium and Vitamin D supplementation and daily Aspirin if indicated
G. Mental health: Be aware of the high incidence of dementia and of depression particularly in the widowed (see Chapter 109, Depression)

CLINICAL PEARLS

- Tailor preventive program to needs and desires of patient. Present recommendations that have good evidence (USPSTF) and try to get patient to follow them
- Approximately 25% of men and 38% of women between 65–75 are overweight
- Annual incidence of falls in people in the community between 70–75 is 25–35%; 5–10% of all falls result in serious injury
- Cerebrovascular disease is third leading cause of death in the US
- Screening for lung cancer in asymptomatic patients is not recommended
- The American College of Physicians (ACP), the Canadian Task Force (CTF), and the USPSTF have all recommended against screening asymptomatic patients without risk factors with resting ECGs or exercise stress tests
- Consider chemoprophylaxis with Aspirin if > 40 with risk factors for MI

References
2001 Recommendations for adults—www.milwaukeemedicalsociety.org/default.cfm?t=47
113. Drugs To Be Cautious Of in the Elderly

I. GERIATRIC DRUG USE ISSUES
   A. Though the elderly make up only 13% of the population, they consume $\frac{3}{4}$ of all prescribed medications
   B. The average home-dwelling elder uses 4.5 different prescription drugs at the same time, while the nursing home resident receives an average of 7 drugs
   C. Polypharmacy and age-related physiological changes contribute to the increased incidence of adverse drug events and nonadherence in the elderly population
   D. Approximately 30% of hospital admissions in elderly patients may be linked to drug-related problems including toxic effects and/or interactions. Subtle but important side effects such as sedation or cognitive impairment resulting in falls may go unrecognized

II. EFFECTS OF AGING ON PHARMACOTHERAPY
   A. Altered absorption: Drug absorption may decrease as a result of low acid production (e.g., Ketoconazole). The significance of changes in the GI tract during aging is not clear
   B. Changes in drug distribution
      1. Elderly persons have more body fat, less total body water and lean body mass than younger adults. Therefore, lipid-soluble drugs (e.g., Diazepam) will have increased body store and hence prolonged effects. On the other hand, water-soluble drugs (e.g., Cimetidine and Lithium) and drugs bound to muscle (e.g., Digoxin) will have higher serum concentrations and hence increased toxicity
      2. Serum albumin concentration often declines, especially in frail elderly. Drugs that are highly protein bound (e.g., Phenytoin, Warfarin) will have increased pharmacologic action because there will be more drug available in free (active) form
   C. Drug clearance and aging
      1. Hepatic metabolism of certain drugs may diminish with age. Drugs that undergo Phase I metabolism (e.g., Diazepam, Alprazolam) will have a prolonged activity
      2. Renal elimination of drugs is affected as renal function declines by approximately 10% each decade after 40. Serum creatinine may overestimate renal function in the elderly because of decreased muscle mass. Creatinine clearance (CrCl) is a more useful measurement of renal function (see Chapter 123, Formulas, for estimation of CrCl). Drugs that depend on renal elimination (e.g., Aminoglycosides, Quinolones, Digoxin, H₂ blockers) will require dosage adjustment according to CrCl
   D. Pharmacodynamics: Older patients appear to be more sensitive to Benzodiazepines, Opiates, Warfarin, and agents with anticholinergic side effects. The apparent increase in receptor sensitivity can result in greater therapeutic effect as well as an increased potential for toxicity

III. RECOGNIZING AND PREVENTING ADVERSE DRUG REACTIONS
   A. Adverse drug reactions may mimic the characteristics of disease states. Drug induced cognitive impairment may be mistaken for senile dementia and may increase risk of falls. Drugs with strong anticholinergic properties can cause many somatic symptoms such as dry mouth, constipation, confusion, and urinary retention
   B. The susceptibility of older persons to adverse drug reactions can be assessed by determining the risk associated with specific drugs.
   C. Use the acronym MASTER developed by Garnett and Barr as a guide for rational drug therapy in the elderly:
      - Minimize number of drugs used and simplify medication schedules. Discontinue drug whenever possible
      - Alternatives should be considered. Avoid drugs that pose high risk to older persons. Select the most cost-effective alternative
      - Start low, go slow. Start at the lowest possible dosage and increase slowly
      - Titrate the dose according to response. Monitor plasma levels if applicable. Monitor patients for adverse reactions
Educate patients about their drug therapy and their potential side effects. Be aware of visual, hearing and memory impairment and adjust instruction accordingly. Encourage and routinely check for adherence.

Review regularly patient’s meds, including OTC products and home remedies. Assess for drug-disease and drug-drug interactions.

IV. COMMONLY PRESCRIBED DRUGS REQUIRING SPECIAL CONSIDERATIONS

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Drugs</th>
<th>Concerns</th>
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<tbody>
<tr>
<td>Antiarrhythmic drugs (Class Ia, Ic, III)</td>
<td>Amiodarone, Dofetilide (Tikosyn), Dronedarone (Multaq), Flecaïnine (Tambocor), Ibutilide (Corvert), Procainamide, Propafenone (Rythmol), Quinidine, Sotalol (Betapace)</td>
<td>Data suggest that rate control is preferred over rhythm control for most older patients. Amiodarone (Cordarone): Multiple toxicities, including thyroid disease, pulmonary disorders, and QT interval prolongation. Drug interactions with Warfarin and Digoxin. Dronedarone (Multaq): Worsen outcomes in patients who have permanent atrial fibrillation or heart failure. Disopyramide (Nospac): Potential negative isotope and may induce heart failure; strong anticholinergic.</td>
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<tr>
<td>Anti-infective</td>
<td>Nitrofurantoin (Macroantin)</td>
<td>Potential for pulmonary toxicity. Avoid long-term use. Avoid in patients with CrC&lt; 60 mL/min.</td>
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<td>Antihistamines, first generation</td>
<td>e.g., Brompheniramine, Chlorpheniramine, Diphenhydramine (oral), Hydroxyzine, Promethazine</td>
<td>Highly anticholinergic: confusion, sedation, dry mouth, urinary retention, falls. Should not be used as a hypnotic. Use of Diphenhydramine in acute treatment of severe allergic reaction may be appropriate.</td>
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<tr>
<td>Antiparkinson agents</td>
<td>Benztropine (oral), Trihexyphenidyl</td>
<td>Not recommended for prevention of extrapyramidal symptoms with antipsychotics; more effective agents available for treatment of Parkinson disease.</td>
</tr>
<tr>
<td>Antispasmodics</td>
<td>Belladonna Alkaloids, Cnidium-Chlordiazepoxide (Librax), Dicyclomine (Bentyl), Hyoscymine (Levsin), Propantheline, Scopolamine</td>
<td>Highly anticholinergic, uncertain effectiveness. May use in short-term palliative care to decrease secretions.</td>
</tr>
<tr>
<td>Antithrombotics</td>
<td>Dipyridamole, oral short acting (Persantine)</td>
<td>May cause orthostatic hypotension; more effective alternative available.</td>
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<tr>
<td>Ticlopidine (Ticlid)</td>
<td>Safe effective alternatives available.</td>
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<tr>
<td>Cardiovascular</td>
<td>Alpha-Blockers: Doxazosin (Cardura), Prazosin (Minipress), Terazosin (Hytrin)</td>
<td>High risk of orthostatic hypotension. Other common adverse effects: dizziness, headache, incontinence. Avoid use as an antihypertensive.</td>
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<tr>
<td>Alpha Agonist, Central: Clonidine (Catapres), Guanabenz (Wytensin), Guanfacine, Methyldopa, Reserpine (&gt;0.1mg/d)</td>
<td>High risk of CNS adverse effects. May cause bradycardia and orthostatic hypotension. Avoid clonidine as a first line antihypertensive. Avoid others for treatment of hypertension.</td>
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<td>Digoxin &gt;0.125mg/d</td>
<td>Higher dosages do not provide additional benefit and may increase risk of toxicity. Risk of toxicity due to slow renal clearance, decrease in muscle mass, and increase in receptor sensitivity.</td>
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<tr>
<td>Nifedipine, immediate release</td>
<td>Hypotension; risk of myocardial ischemia.</td>
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<tr>
<td>Spironolactone &gt;25mg/d</td>
<td>Risk of hyperkalemia in dose &gt;25 mg/d or taking concomitant NSAID, ACE inhibitor, ARB, or potassium supplement. Avoid in patients with heart failure or with CrCl &lt; 30 mL/min.</td>
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<tr>
<td>CNS drugs: TCAs</td>
<td>TCA, Tertiary: Amtriptyline, Clomipramine, Desipramine, Imipramine, Trimipramine,</td>
<td>Highly anticholinergic, sedating, orthostatic hypotension.</td>
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### Beers Criteria for Potentially Inappropriate Drugs To Avoid in Older Adults (continued)

<table>
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<tr>
<th>Drug Category</th>
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<th>Concerns</th>
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<tr>
<td><strong>CNS: antipsychotics</strong></td>
<td>First-generation (conventional) agents</td>
<td>Increased risk of CVA (stroke) and mortality in persons with dementia Avoid use for behavior problems of dementia unless nonpharmacological options have failed and patient is threat to self or others Thioridazine (Melleril): first-generation; highly anticholinergic and risk of QT-interval prolongation</td>
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<td></td>
<td>Second-generation (atypical) agents</td>
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<td><strong>CNS: barbiturates</strong></td>
<td>e.g., Butalbital, Phenobarbital</td>
<td>High rate of physical dependence; tolerance to sleep benefits; risk of overdose even at low dosages Drug interactions Avoid except when used to control seizure</td>
</tr>
<tr>
<td><strong>CNS: miscellaneous</strong></td>
<td>Meprobamate</td>
<td>High rate of physical dependence; very sedating</td>
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<td>Nonbenzodiazepine Hypnotics: Eszopiclone (Lunesta), Zolpidem (Ambien), Zaleplon (Sonata)</td>
<td>Adverse events similar to those of Benzodiazepines (e.g., delirium, falls, fractures) Avoid use &gt;90 days Zolpidem (Ambien): abnormal thinking, behavior changes, complex behaviors; next-morning impairment</td>
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<td>Androgens: Methyltestosterone, Testosterone</td>
<td>Potential for cardiac problems Contraindicated in men with prostate cancer Use only for moderate to severe hypogonadism</td>
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<td></td>
<td>Desiccated Thyroid (Armour Thyroid)</td>
<td>Concerns about cardiac effects Safer alternative available</td>
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<td>Estrogen with or without Progestins</td>
<td>Potential for breast and endometrial cancer Avoid oral and topical patch Topical vaginal cream at low doses is acceptable for the management of dyspareunia, lower UTIs and other vaginal symptoms; dosage &lt;25µg twice/wk is safe and effective for treatment of vaginal dryness in women with breast cancer</td>
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<td>Growth hormone</td>
<td>Effect on body composition is small Associated with edema, arthralgia, carpal tunnel syndrome, gynecomastia, impaired fasting glucose Avoid except as hormone replacement after pituitary gland removal</td>
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<td>Megestrol</td>
<td>Minimal effect on weight Risk of thrombotic events and possibly death</td>
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<td>Sliding Scale Insulin</td>
<td>Risk of hypoglycemia without improvement in glycemic control</td>
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<td>Sulfonylureas, Long Acting</td>
<td>Chlorpropamide: prolonged t1/2 can cause prolonged hypoglycemia; syndrome of inappropriate antidiuretic hormone secretion Glyburide (Diabeta, Micronase): increased risk of prolonged hypoglycemia</td>
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<td><strong>Gastrointestinal</strong></td>
<td>Metoclopramide</td>
<td>Can cause extrapyramidal effects including tardive dyskinesia Avoid use unless for gastroparesis</td>
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<td>Mineral Oil, oral</td>
<td>Potential for aspiration and adverse effects Use safer alternative</td>
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<tr>
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<td>Trimethobenzamide (Tigan)</td>
<td>Low efficacy High extrapyramidal effects</td>
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### Beers Criteria for Potentially Inappropriate Drugs To Avoid in Older Adults (continued)

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Drugs</th>
<th>Concerns</th>
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| Pain          | Meperidine | Neurotoxic metabolite may accumulate  
Use safer alternative |
| NSAIDS        | Increase renal toxicity and BP  
Increased risk of GI bleeding and peptic ulcer disease in high-risk patients: >75 yo, taking steroids, anticoagulants, or antiplatelets  
Avoid chronic use: GI ulcers, gross bleeding, or perforation in ~1% patients treated with NSAID x 3-6 months and ~2-4% patients treated x 1 year. Risk increases with longer duration of use  
Use with a PPI or misoprostol can reduce GI risk  
Indomethacin has the most CNS adverse effect among all the NSAIDs  
Use ketorolac (Toradol) only for short-term  
Avoid NSAIDs with long half life, e.g., Piroxicam (Feldene) |
| Pentazocine (Talwin) | Mixed agonist and antagonist  
More adverse effects than other narcotic agents  
Use safer alternative |
| Skeletal muscle relaxants: Carisoprodol (Soma), Chlorzoxazone (Paraflex), Cyclobenzaprine (Flexeril), Metaxalone (Skelaxin), Methocarbamol (Robaxin), Orphenadrine (Norflex) | Poorly tolerated by older adults  
Anticholinergic adverse effects, sedation, risk of falls and fracture |


**References**


I. BACKGROUND/EPIDEMIOLOGY: Note: This chapter explores “falls” due to reasons other than syncope

A. Falls in the elderly are common: They are the leading cause of death from injury in persons over age 65
   1. Death rate 10 per 100,000 in persons between ages 65 and 74
   2. 147 per 100,000 in persons over age 85
   3. Falls are the leading cause of injury-related ER visits in persons over age 65

B. Epidemiology: 33% of community dwelling persons and 60% of nursing home residents fall each year. 20–30% of falls result in moderate to severe injuries that reduce mobility and independence

C. Fractures account for 75% of serious injuries
   1. Most common sites are wrist, hip and vertebrae with hip fractures as most severe
   2. 25% of elderly persons with hip fractures die within 6 months
   3. 95% of hip fractures are due to falls

D. Over 50% of those who fall have multiple episodes. Women are 3 times as likely to be hospitalized for fall related injuries. Falls can be marker for functional decline and poor health. Falls can be non-specific presenting sign of many acute illnesses (pneumonia, UTI, MI)

E. Screening all adults older than age 65 with H&P and risk factor assessment can decrease falls and fall related injuries

II. EVALUATION

A. Demographic: Older age, white race, homebound, living situation

B. Historical:
   1. Fall circumstances and environmental hazards
   2. Previous falls
   3. Acute illness
   4. Chronic conditions, including neuromuscular disorders, anemia, CHF, chronic weakness secondary to cancer, etc.
   5. Meds/Substances: May contribute to falls including; alcohol, benzodiazepines, narcotics, barbiturates, anti-depressants, anti-psychotics, anti-hypertensives, cardiac meds, anti-cholinergics meds, hypoglycemic meds, diuretics, seizure meds (Carbamazepine toxicity), Phenothiazine and NSAIDs
   6. Others: Use of cane or walker, postprandial hypotension, insomnia, urinary urgency, pedal/peripheral edema (increase weight of legs may make them difficult to lift)
   7. History: CATASTROPHE mnemonic
      C Caregiver and housing
      A Alcohol (including withdrawal)
      T Treatment (meds including compliance)
      A Affect (depression or lack of initiative)
      S Syncope (any episodes of fainting)
      T Teetering (dizziness)
      R Recent illness
      O Ocular problems
      P Pain with mobility
      H Hearing (necessary to avoid hazards)
      E Environmental hazards

C. Physical
   1. Neurological examination: assessment of cognitive impairment/dementia/delirium, proprioception, neuropathy, muscle strength
   2. Reduced vision, hearing, proprioception and vestibular function
3. Gait and mobility assessment: Difficulty rising from chair, get up and go test > 9 sec (age 60–69), >10.2 sec (age 70–79), >12.7 sec (age 80–99), postural instability
4. Cardiovascular status: heart rate and rhythm, postural hypotension
5. Examination of foot problems and footwear
6. Musculoskeletal examination: Pain (arthritis), deformity

D. Testing (if indicated)
1. Laboratory tests are not routinely performed in event of falls, but may be needed depending on results of H&P
2. Consider: CBC, serum electrolytes, BUN, creatinine, glucose, B12, TSH, blood cultures, urine analysis, urine culture
3. EKG, cardiac testing
4. Imaging studies: To look for etiology of falls and sequelae of falls

E. Environmental hazards: Most falls are in or around home
1. Poor lighting (change 60 watts to 100 watt bulbs)
2. Unsafe stairways
3. Loose rugs and other tripping hazards
4. No bathroom grab bars or nonskid bathtubs

III. DIFFERENTIAL DIAGNOSIS
I HATE FALLING mnemonic
I Inflammation of joints (or joint deformity)
H Hypotension (orthostatic BP changes)
A Auditory and visual abnormalities
T Tremor (Parkinson’s disease or other causes of tremor)
E Equilibrium (balance) problem
F Foot problems
A Arrhythmia, heart block or valvular disease
L Leg length discrepancy
L Lack of conditioning (generalized weakness)
I Illness
N Nutrition (poor, weight loss)
G Gait disturbance

IV. INTERVENTIONS: Individualized risk assessment with corresponding multifactorial intervention should be performed. The general approach is to treat medical conditions, minimize offending medications, alter environmental hazards, and pursue strength and balance training
A. Postural hypotension
1. Decrease dose or discontinue meds causing orthostatic hypotension
2. Rehydration
3. Pressure stocking
4. Dorsiflexion exercises
5. Behavioral recommendations (elevate head of bed, rise slowly)
6. If indicated, Floctrocortisone (Florinef) 0.1mg PO BID–TID, Midodrine 10mg PO TID
7. Dual chamber pacing should be considered for older persons with cardioinhibitory carotid sinus hypersensitivity with unexplained recurrent falls

B. Sedative-hypnotic use
1. Educate regarding appropriate use
2. Taper and discontinue if possible
3. Non-benzodiazepine treatment of sleep disorders

C. Polypharmacy
1. Review meds frequently, assess for risks and benefits
2. Minimize or discontinue medication
3. Check toxicity of medication (e.g., Digoxin) and if medications started recently
4. Change meds to less centrally acting, short duration of action, less side effects and interaction

D. Environmental hazards
1. Home safety evaluation and modification of risk factors
2. Improve lighting (reduce glare, shadows, install night lights)
3. Remove tripping hazards (loose rugs, uneven floor surfaces, clutter)
4. Improve stairways safety (secure handrails, contrasting tape on steps, nonskid surfaces)
5. Improve bathroom safety (grab bars, nonskid bathtub, and raised toilets seats)
6. If patient is confined to bed, bed rails, bedside cushions

E. Gait and mobility impairment
1. Balance and gait training, strengthening exercise, Tai Chi
2. Appropriate footwear, treat foot disorders (callus, bunion)
3. Proper assistive devices (cane, walker)
4. Check vitamin deficiency and cervical spondylosis
5. Reduced muscle strength or joint range of motion- muscle strengthening exercises (resistance exercises)

F. Sensory deficit (reduced vision, hearing or vestibular dysfunction)
1. Refraction, cataract extraction
2. Hearing aid, cerumen removal
3. ENT and ophthalmology evaluation

G. Dementia
1. Increase supervision
2. Orientation cues

H. Interventions to reduce fall-related injuries
1. Osteoporosis screening and treatment
2. Personal emergency response systems

V. PREVENTION
A. Strategies
1. The American Geriatric Society (AGS) and British Geriatrics society (BGS) recommend that all adults over age 65 be screened annually for falls or balance impairment
2. All community dwelling elderly, nursing home resident and elderly recently hospitalized for extended period should receive multifactorial risk assessment and interventions tailored to their need
3. Correct environmental hazards, medications modifications, hip protectors and protective flooring
4. Home support, involve family, physical and occupational therapy, balance and strengthening training and provide follow up

B. Vitamin D supplementation
1. Elderly patients with Vitamin D deficiency are at a greater risk for loss of muscle strength and muscle mass and subsequent falls
2. In a meta analysis of 5 RCTs, Vitamin D use reduced the risk of falls in the elderly by 22% compared to placebo (JAMA 2004; 291:1999, reference below), RCT of nursing home residents showed Vitamin D supplementation of 800 IU daily reduced fall incidence by 50% over 5 months compared to placebo (Broe KE et al. J Am Ger Soc 2007;55:234)
3. AGS/BGS and US preventive task force recommend Vitamin D supplementation of at least 800 IU per day for those at increased risk of falls

CLINICAL PEARLS
• Falls most often multifactorial with influence from declining sensory function, strength and balance combined with coexistent medical conditions, medication side effects and environmental hazards
• Elderly patients on benzodiazepines have a 29 times increased risk of falling
• In elderly women with hip fractures, mortality is approximately 20% in the first year
• Confusion may be reason for fall or result of fall. Subdural hematoma is treatable and often overlooked sequela of falling

References
115. Vertebral Compression Fractures

I. GENERAL
A. Osteoporosis is the most common bone disorder—at least 25% of American postmenopausal women will experience at least 1 osteoporotic vertebral compression fracture
B. Approximately 70,000 vertebral compression fractures result in hospitalization each year
C. Vertebral compression fractures are associated with an increased mortality corresponding to the number of vertebrae involved
D. 30% of symptomatic patients who seek treatment do not respond to nonsurgical treatments
E. Please see Chapter 93, Low Back Pain and Chapter 77, Osteoporosis

II. HISTORY & PHYSICAL EXAM
A. Most are asymptomatic at time of diagnosis, but those who present with pain report sudden onset of localized pain in relationship to atraumatic activities (bending forward, standing from seated, vigorous coughing or sneezing)
B. Risk factors: Advancing age, history of prior osteoporotic vertebral fracture, low peak bone mass, low body weight, recent weight loss, history of fractures in the family, cigarette smoking
C. Physical Exam
1. Height: Loss of height of greater than 3cm increases likelihood of vertebral fracture and should be evaluated with a lateral thoracolumbar radiograph
2. Focal kyphosis or loss of lumbar lordosis
3. Localized boney tenderness at the involved vertebral level

III. TESTING
A. Plain Radiographs: May demonstrate classic “wedge” fracture indicative of loss of anterior vertebral body height. The most frequent site is thoracolumbar junction then midthoracic spine
1. Acute fracture: Well-demarcated fracture lines or discontinuity of cortical margin
2. Chronic fracture: Sclerosis of fracture lines, dense cortical margin, osteophytes
B. Magnetic Resonance Imaging (MRI): To diagnose acute vertebral compression fractures with normal plain radiographs
1. Useful for identifying minimally compressed fractures
2. Differentiation of acute from chronic fractures
3. Diagnosis of compression fractures caused by tumor or infection
C. Computed Tomography (CT) with thin cuts: Helpful in evaluating for unstable crush fractures
D. Bone scintigraphy: Use limited by radionuclide uptake that may persist for up to 2 years after acute fracture

IV. MANAGEMENT: Most patients have predictable pain improvement over 6–8 weeks, but
some have persistent pain and disability

A. Nonsurgical Management

1. Prevention: Focusing on attainment of peak bone mass and prevention of postmenopausal bone loss. See Chapter 77, Section VI. A. 1–7

2. Bracing and Rehabilitation
   a. Continuous Hyperextension Bracing: May be beneficial in the first 6–8 weeks as pain improves. Often poorly tolerated. Efficacy in preventing further vertebral collapse not established
   b. Rehabilitation: Should commence after pain resolution. Focus on fall prevention and education. Back extension exercises are superior to abdominal flexion exercises in lowering incidence of new fractures

3. Medications:
   b. Salmon Calcitonin
      i. First-line treatment for reduction of acute bone pain
      ii. Significant reduction in pain as early as 1 week into treatment and the benefit may last for 4 weeks
      iii. Dose: **Calcitonin nasal spray (Miacalcin)**—1 spray (200 IU) alternating nostrils QD

B. Surgical Management: Vertebral augmentation procedures are indicated for patients with chronic pain after compression fracture. Decompression and fixation procedures are indicated with progressive neurologic loss, severe unrelenting pain, and significant deformity

1. Vertebroplasty: To improve strength and stability of fractured vertebra
   a. Indication: Failure of conservative management of a vertebral compression fracture in which patients continue to have debilitating pain. Pain should be localized and attributable to the fractured vertebra. Success rates for pain relief and functional improvement between 78% and 90%
   b. Contraindications: Severe wedge deformity fractures, comminuted burst fractures, spinal canal compromise greater than 20%, myelopathy, inability to lie prone, severe cardiopulmonary disease, uncorrected coagulopathy, inability to localize source of pain, allergy to cement or radiopaque dye, and local or systemic infection
   c. Technique: Injection of a mixture of polymethylmethacrylate (PMMA) and barium into the involved vertebra using fluoroscopic guidance
   d. Complications: PMMA leakage, radiculopathy, cord compression, postoperative infection, worsened pain, rib fractures, pneumothorax. Death secondary to pulmonary embolization

2. Kyphoplasty: To restore vertebral body height and improve strength
   a. Indications: Same as for vertebroplasty. Rates of pain relief and functional improvement equivalent to vertebroplasty
   b. Contraindications and Complications: See vertebroplasty, B. 1. above
   c. Technique: Similar to vertebroplasty. In this procedure an inflatable balloon or tamp is inserted into vertebral body to create a low-pressure cavity for the injection of PMMA
   d. Advantages: Improved deformity correction and decreased potential for cement leakage. Restoration of vertebral height however does not correlate with pain relief or functional improvement
   e. Disadvantages: Cost effectiveness less than for vertebroplasty. Success rates may depend on the age of fracture

CLINICAL PEARLS

- Vertebral compression fractures are associated with an increased mortality corresponding to the number of vertebrae involved
- Most patients will have pain improvement over 6–8 weeks
- **Salmon Calcitonin, Acetaminophen, salicylates, and nonsteroidal anti-inflammatory**
medications are all first-line treatments for pain associated with vertebral compression fractures

- Vertebroplasty or kyphoplasty are indicated for patients with chronic pain after compression fracture

References
Rizer, MK. Osteoporosis. Prim Care 2006;33:943–51.

Daniel S Berger, MD
Jeffrey W. Milks, MD
John M. Bertman, MD
Jim Cassady, MD

116. Urinary Incontinence in the Elderly

I. BACKGROUND

A. Prevalence and Impact

1. Urinary incontinence (UI) affects 15–35% of adults over age 65 in the community, and 50–70% of individuals in long-term care facilities
2. The prevalence of UI impacts women 2:1 until approximately age 80, after which men and women approach equality
3. UI is often not spontaneously reported. In a US survey of a multiethnic population, only 45% of women who reported urinary incontinence occurring at least once a week ever sought care. It is a source of embarrassment, social isolation, and can contribute to caregiver burdens which can impact the decision to institutionalize

B. Pathophysiology of Incontinence

1. Urethral sphincter mechanisms include smooth muscle stimulated by sympathetic innervation from T11–L2 and distal striated muscle which contracts due to cholinergic stimulation from the sacral micturition center
2. Detrusor activity contracts via parasympathetic control from the spinal cord level S2–S4

II. CLASSIFICATION OF URINARY INCONTINENCE

A. Stress Incontinence (SI)

1. Urinary leakage associated with increased abdominal pressure, such as cough, sneeze, or change in position
2. Generally associated with poor anatomic support
3. Risk factors include the female gender, childbirth, vaginal atrophic changes and prior medical interventions including surgical and radiation therapy
4. α-adrenergic blocking agents may increase symptoms
5. Male SI is usually associated with prior prostate surgery

B. Urge Incontinence (UI)

1. Urinary leakage associated with an abrupt desire to void
2. UI is most often caused by detrusor overactivity (DO)
3. Most situations are idiopathic, but aggravating features include infection, interstitial cystitis, neoplasm, and bladder stones
4. DO may coexist with impaired contractility (IC), which will result in an elevated residual volume. This subset of UI will require additional caution when pharmacological management is prescribed

C. Overflow Incontinence (OI)

1. Urine loss from an over-distended bladder
2. Consider outlet obstruction (BPH, stricture, pelvic organ prolapse), fecal impaction,
anticholinergic medications, or neuropathic etiology

D. **Functional Incontinence (FI)**
   1. Physical elements that impede toileting (DJD, acute injury, restraints)
   2. Impaired willingness to reach toilet (dementia, delirium, depression, medication effect)

### III. HISTORY

A. **Current impact**
   1. Determine duration, severity, social impact, and precipitating features of current symptoms
   2. Does motivation exist to restore continence?

B. **Comorbid conditions**
   1. Evaluate current and past history including diabetes mellitus, neurological history, bowel history, and urogynecological history
   2. Review prior applicable surgical history

C. **Medication review**
   1. Focus will depend in part on above history
   2. Attention to \( \alpha \)-blockers, diuretics, anticholinergics, calcium channel blockers (impaired contractility), thiazolidinediones (fluid retention), and ACE inhibitors (cough) may be of interest depending on symptoms and historical relationship to a new agent

### IV. PHYSICAL EXAM

A. **Cognition and functional status**
   1. Mini-Mental Status Exam (MMSE) when appropriate (See Chapter 117, Evaluation of Mental Status Changes in the Elderly, III. E.)
   2. Do physical features impede toileting?

B. **Cardiovascular screen:** Attention to volume overload contributing to nocturia

C. **Abdominal/pelvic/rectal exam as indicated based on history**
   1. Abdominal exam including evaluation for distended bladder/abdominal mass
   2. Rectal exam including tone, perianal sensation, evaluation for mass, or fecal impaction
   3. Pelvic exam including evaluation for inflammation, infection, atrophic changes, cystocele, rectocele, pelvic organ descent, or urethral hypermobility

D. **Neurological screen**
   1. Index of suspicion will be based on history
   2. Evaluate for peripheral neuropathy, acute lumbar disc disease, and central nervous system disorders including normal pressure hydrocephalus (NPH) if history dictates

### V. LAB/FOCUSED TESTING:

A. **Urinalysis and culture**
   1. Hematuria—always demands explanation (see Chapter 79, Hematuria)
   2. Glycosuria—needs further evaluation for diabetes

B. **Blood work**
   1. Renal function as indicated (example BPH, diabetes mellitus, hypertension)
   2. Glucose, possible TSH, B12, calcium

C. **Post void residual (PVR) volume**
   1. Ultrasound or via catheter
   2. While a PVR of < 50mL is normal, a PVR of < 100 is generally considered adequate voiding in an elderly patient
   3. Volume in excess of 200mL is abnormal. These patients should be screened for hydronephrosis and referral for urodynamic testing should be considered

D. **Bladder Record** (voiding diary)
   1. Benefit will depend on history
   2. Requires patient motivation, intact cognition, or motivated caregiver (for additional resources, including a printable voiding diary form and patient education material, visit website of National Association for Continence: www.nafc.org)

### VI. MANAGEMENT

A. **Stress Incontinence**
   1. Pelvic floor muscle exercises (Kegel exercises). Consider referral to a pelvic floor...
116. Urinary Incontinence in the Elderly  
Care of the Geriatric Patient

physical therapist to increase success. Pelvic floor muscle training plus bladder training is superior in resolving urinary incontinence in women compared to drug therapy, electrostimulation, medical devices, injectable bulking agents, and local estrogen therapy.

2. Pelvic floor electrical stimulation (biofeedback)—performed by pelvic floor physical therapists.

3. There are currently no FDA approved pharmacological interventions for stress incontinence.

4. α-adrenergic stimulants or topical estrogen therapy may be considered, but literature support is lacking.

5. Duloxetine (Cymbalta) may increase sphincter contraction.

6. Pessaries—occlusive device for intravaginal support.

7. Surgical treatment
   a. Periurethral collagen injection
   b. Retropubic urethropexy
   c. Suburethral sling

8. Stress incontinence in men is usually a consequence of prior prostate surgery, and an artificial sphincter may be corrective.

B. Urge Incontinence

1. Bladder training (timed voiding), biofeedback, pelvic floor exercises, pelvic floor electrical stimulation.

2. Pharmacologic treatment—anticholinergic agents (see below); caution indicated with anticholinergics in elderly patients, especially those with cognitive dysfunction.

3. Sacral nerve root neuromodulation with implanted stimulator device.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Formulations</th>
<th>Adverse Events/Comments (Metabolism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimuscarinics</td>
<td></td>
<td></td>
<td>Class adverse events: dry mouth, blurry vision, dry eyes, delirium/confusion, constipation</td>
</tr>
<tr>
<td>Oxybutynin (Ditropan, Ditropan XL, Gelnique, Oxytrol for Women)</td>
<td>2.5–5 mg q8–12h</td>
<td>T: 5; S: 5 mg/5 mL; SR: 5, 10, 15</td>
<td>Dry mouth and constipation less with XL and pch than immediate release Pch/Gel. rotate sites to reduce skin irritation (L)</td>
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<tr>
<td></td>
<td>1 g gel topically (apply pch 2×/wk)</td>
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<tr>
<td></td>
<td></td>
<td>Transdermal pch 39 cm²</td>
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<tr>
<td>Tolterodine (Detrol, Detrol LA)</td>
<td>2 mg q12h</td>
<td>T: 1, 2; C: ER 2, 4</td>
<td>Withdraw from tx trials for drug-related AEs not different from placebo; P450 interactions (L, CYP3A4 and CYP2D6)</td>
</tr>
<tr>
<td></td>
<td>4 mg/d</td>
<td></td>
<td></td>
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<tr>
<td>Tropium (Sanctura, Sanctura XR)</td>
<td>20 mg q12–24h (on empty stomach)</td>
<td>T: 20; C: ER 60</td>
<td>Dyspepsia, headache; caution in liver dysfunction; dose once daily at hs in patients ≥75 yr old or with CrCl &lt;30 mL/min; XR formulation not recommended if CrCl &lt;30 mL/min (L, K)</td>
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<tr>
<td></td>
<td>60 mg/d (XR)</td>
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<tr>
<td>Darifenacin (Enablex)</td>
<td>7.5–15 mg/d</td>
<td>T: 7.5, 15</td>
<td>Gastric retention; not recommended in severe liver impairment. Withdrawal from tx trials for drug-related AEs not different from placebo. (L, CYP3A4 and CYP2D6)</td>
</tr>
<tr>
<td>Solifenacin (VESicare)</td>
<td>5–10 mg/d</td>
<td>T: 5, 10</td>
<td>Same as darifenacin; max dose 5 mg if CrCl &lt;30 mL/min or moderate liver impairment. Women with urge UI who have taken other antimuscarinics that have failed may benefit from a trial dose of the 5-mg dose (no additional benefit at the 10-mg dose) (L, CYP3A4)</td>
</tr>
<tr>
<td>Fesoterodine (TOVIAZ)</td>
<td>4–8 mg/d</td>
<td>T: 4, 8</td>
<td>Max dose 4 mg if CrCl &lt;30 mL/min (L, CYP2D6)</td>
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<tr>
<td>β-agonist</td>
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<tr>
<td>Mirabegron (Myrbetriq)</td>
<td>25–50 mg/d</td>
<td>T: 25, 50</td>
<td>Hypertension (monitor BP), nausea, headache, dizziness, tachycardias (AF). Max dose 25 mg if CrCl &lt;30 mL/min; not recommended in severe kidney or severe liver impairment; raises digoxin and reduces metoprolol levels. Do not use in combination with antimuscarinics. (L, CYP2D6)</td>
</tr>
</tbody>
</table>
C. Overflow Incontinence
1. Remove any offending pharmacological agents (anticholinergics)
2. Intermittent catheterization
3. Address constipation/fecal impaction
4. In males, address prostatic hypertrophy with selective α-adrenergic agents (Tamsulosin) and possibly 5 α-reductase inhibitors (Finasteride, Dutasteride). See Chapter 81, Benign Prostatic Hyperplasia. Failure to respond will require urological consultation and probable surgical intervention (many modalities available)
5. In males, the digital rectal exam (DRE) and PSA may assist in the evaluation for prostatic malignancy. A baseline PSA is indicated prior to the initiation of a 5 α-reductase inhibitor
6. Treat any reversible neurological syndromes (e.g., peripheral neuropathy secondary to B₁₂ deficiency, hypothyroidism)

D. Functional Incontinence
1. Treat the offending debility as condition permits
2. Improve access to toileting

E. Indwelling Catheters—Indications (Note: Avoid indwelling catheter when possible)
1. Skin breakdown (healing is impaired by urinary incontinence)
2. Failure of intermittent catheterization due to mechanical features, lack of patient dexterity or available willing caregiver, or strong patient preference for an indwelling catheter
3. Care of the terminally ill or severely impaired where toileting is impractical and incontinence is uncomfortable
4. Monitoring of urinary output (short term) or for the collection of a needed accurate 24 hour urine specimen

CLINICAL PEARLS
• Urinary incontinence is often under reported
• Use medications with caution in the frail elderly and in those with cognitive dysfunction
• Utilize nonpharmacological therapy for stress and urge incontinence first or in conjunction with medication
• Always evaluate hematuria
• DIAPPERS mnemonic for acute or transient incontinence:
  D - Delirium
  I - Infection
  A - Atrophy
  P - Pharmaceuticals
  P - Psychological disorders
  E - Excessive urine output (diuresis, hyperglycemia)
  R - Restricted mobility
  S - Stool impaction

References
117. Evaluation of Mental Status Changes

Daniel S. Berger, MD
Jeffrey W. Milks, MD
Michael B. Weinstock, MD
Edward T. Bope, MD
Jim Cassady, MD

IN THE ELDERLY

I. APPROACH TO THE PATIENT/DEFINITIONS: Historical data is crucial to distinguish acute vs. chronic change in cognition. Seek information from old records, family members, and caregivers

A. Delirium
1. Definition: Acute decline in normal attention and cognition
2. Often initiates cascade of events that may culminate in the loss of independence, increased mortality, and the inability to return to prior functional status

B. Dementia
1. Definition: Chronic disorder characterized by a decline in memory and at least one other cognitive domain (aphasia, apraxia, agnosia, executive function)
2. Findings represent a decline from prior level of function and must be of sufficient severity to interfere with daily function
3. Impairment occurs in a clear sensorium. The presence of obtundation or stupor suggests delirium

II. DELIRIUM

A. Epidemiology and risk factors
1. Delirium is often under-recognized by attending physicians and nurses
2. Delirium complicates hospital stays for at least 20% of elderly patients
3. Predisposing risk factors: a) age greater than >65 years; b) male gender; c) predisposing cognitive impairment; d) functional dependence; e) sensory impairment (hearing/vision); f) dehydration; g) polypharmacy; h) preexisting neurological disease; i) HIV; and j) severe illness

B. Prevention strategies
1. Yale Delirium Prevention Trial (1999) targeted 6 risk factors for delirium
   a. Orientation and therapeutic activities for cognitive impairment
   b. Early mobilization
   c. Nonpharmacological approaches to minimize the use of antipsychotic drug
   d. Interventions to prevent sleep deprivation
   e. Communication methods and adaptive equipment (eyewear, hearing aids) for sensory impairment
   f. Early intervention for volume depletion
2. Incidence of delirium and total days of delirium reduced by 30%
3. Similar benefit reproduced in a randomized trial involving hip fracture patients

C. Approach to Evaluation
1. Secure the diagnosis: Confusion Assessment Method (CAM). Note: To meet criteria, acute and fluctuating course must be present with inattention plus either disorganized thinking or altered level of consciousness
   a. Acute and fluctuating course
   b. Inattention
   c. Disorganized thinking
   d. Altered level of consciousness, usually manifested by a reduced awareness of the environment. This disturbance may be hyperactive, marked by agitation and vigilance, or hypoactive, marked by lethargy. Hypoactive delirium is easily missed for days
2. History is critical
   a. Multiple observations, including information from family, friends, caregivers
   b. Be aware of “suspicious labels” such as poor historian, “gomer,” social admission, uncooperative on exam—these labels may represent delirium
3. Physical exam is symptom based:
a. Attention to oxygenation, urinary retention, fecal impaction, dehydration, infection
b. Evaluate for appropriate control of pain (uncontrolled pain is an independent risk factor for delirium)

4. Medication review:
   a. Hypnotics/benzodiazepines
   b. Narcotics (especially Meperidine)
   c. Anticholinergics
   d. H2 antagonists
   e. Polypharmacy
   f. Withdrawal syndromes

g. Consider any drugs with a temporal relationship to symptoms

D. LAB/Imaging/Special Studies: Delirium may be the only noted sign of a life-threatening illness such as sepsis, pneumonia, or an acute myocardial infarction
1. Basic lab usually entails CBC, basic metabolic panel, including calcium, UA, cultures as appropriate. LP only with clinical suspicion
2. Chest x-ray, EKG
3. Brain imaging is usually done, but in the absence of specific focal neurological findings, the yield is low
4. An EEG may be considered for suspicion of atypical seizure

E. Treatment
1. Nonpharmacologic
   a. Attempt to engage in activity
   b. Remove restraints and Foley catheters if clinically feasible
   c. Be sure eyeglasses and hearing aids are available and functional
   d. Engage family/familiar items from home
   e. Remove any obvious offending pharmacological agents or stimuli
2. Pharmacological measures
   a. Haloperidol 0.5–2mg PO, IM, or IV generally considered the agent of choice
   b. Consider atypical antipsychotics in select circumstances
   c. Consider QT prolongation when using antipsychotics, including potential additive effect from the current pharmacological regime
   d. Consider Trazodone for HS sedation
   e. Avoid benzodiazepines unless treating withdrawal (if alcohol withdrawal, also add thiamine and check magnesium)

Pharmacologic Treatment of Delirium

<table>
<thead>
<tr>
<th>Class and Drug</th>
<th>Dose</th>
<th>Adverse Effects</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Antipsychotic</td>
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<tr>
<td>Haloperidol</td>
<td>0.5–1.0 mg twice daily orally, with additional doses every 4 hr as needed (peak effect, 4–6 hr), 0.5–1.0 mg intramuscularly; observe after 30–60 min and repeat if needed</td>
<td>Extrapyramidal symptoms, especially if dose is &gt;3 mg per day; Prolonged corrected QT interval on electrocardiogram; Avoid in patients with withdrawal syndrome, hepatic insufficiency, neuroleptic malignant syndrome</td>
<td>Usually agent of choice; Effectiveness demonstrated in randomized, controlled trials; Avoid intravenous use because of short duration of action</td>
</tr>
<tr>
<td>Atypical antipsychotic</td>
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<tr>
<td>Risperidone</td>
<td>0.5–5.0 mg once daily</td>
<td>Extrapyramidal effects equivalent to or slightly less than those with haloperidol; Prolonged corrected QT interval on electrocardiogram</td>
<td>Tested only in small uncontrolled studies; Associated with increased mortality rate among older patients with dementia</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5–5.0 mg once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25 mg twice daily</td>
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<tr>
<td>Benzodiazepine</td>
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<tr>
<td>Lorazepam</td>
<td>0.5–1.0 mg orally, with additional doses every 4 hr as needed*</td>
<td>Paradoxical excitement, respiratory depression, oversedation</td>
<td>Second-line agent; Associated with prolongation and worsening of delirium symptoms demonstrated in clinical trial; Reserve for use in patients undergoing sedative and alcohol withdrawal, those with Parkinson’s disease, and those with neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>Antidepressant</td>
<td></td>
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<tr>
<td>Trazodone</td>
<td>25–150 mg orally at bedtime</td>
<td>Oversedation</td>
<td>Tested only in uncontrolled studies</td>
</tr>
</tbody>
</table>

*Intravenous use of lorazepam should be reserved for emergencies

III. DEMENTIA

A. Epidemiology
1. The incidence of dementia doubles every 5 years after age 60
2. The greatest risk factors for dementia of the Alzheimer’s type include age and family history. The Apolipoprotein E gene (APOE) on chromosome 19 influences risk
3. Risk factors for vascular dementia mimic factors that influence general atherosclerotic disease including hypertension, hyperlipidemia, smoking, and diabetes mellitus
4. The natural course of dementia is a progressive decline—death usually within 8–10 years post-diagnosis. Process is often interrupted by an interval fatal medical event from a comorbid condition
5. The pathology of Alzheimer’s dementia (AD) is an area of intense research and debate
   a. Central event in AD may be abnormal metabolism of amyloid precursor protein (APP), resulting in the pathological accumulation of beta amyloid
   b. Further refinement of the pathophysiology of AD holds promise for more effective prevention measures and definitive pharmacological intervention
6. Although AD and other dementing illness are common with aging, they should not be considered part of the normal aging process

B. Major Subtypes of Dementia
1. The specific illnesses producing the clinical syndrome of dementia are multiple
   a. The number in part is dependent on how specific entities are subdivided
   b. Pathology is often mixed, at least from a clinical standpoint
2. Alzheimer’s disease: 65–75% of the cases
   a. Onset is insidious, and may not be detected in early stages
   b. A subset of patients with cognitive defects not producing functional impairment has been labeled mild cognitive impairment, with a typical conversion rate to AD at a rate of approximately 12% per year
3. Vascular dementia: 15–25% of cases
   a. It may coexist with any degenerative dementia
   b. Risk factors are discussed under epidemiology/historical data
   c. Vascular disease is an independent risk factor for the development of dementia with typical Alzheimer-like neuropathology
4. Dementia with Lewy bodies—competes with vascular dementia as the second most common form of dementia
   a. The movement disorder of dementia with Lewy bodies mimics Parkinson’s disease. A distinguishing feature is that dementia is apparent prior to or within the first year of the onset of the movement disorder
   b. Multiple other neurodegenerative disorders may present with Parkinsonism, including progressive supranuclear palsy and a group of disorders now identified as multisystem atrophy
5. Frontotemporal dementia—onset between 45 and 65 years of age
   a. Typically presents with a disturbance of behavior, disinhibition, and impaired judgment. Memory is relatively preserved during the earlier stages
   b. Positron emission tomography (PET) imaging may be particularly useful in establishing this diagnosis
   c. These individuals may interface with the legal/criminal justice system until properly diagnosed
6. Normal pressure hydrocephalus—rare form of dementia, with a characteristic triad of dementia, gait disturbance, and incontinence (“wet, wobbly, and wacky”). Early intervention with shunting may significantly improve gait disturbance and incontinence
7. Multiple other diseases and CNS toxic responses may present with cognitive dysfunction including: a) prion disease; b) Huntington chorea; c) neoplasm; d) encephalitis; e) B12 deficiency; f) metabolic disorders; g) neurosyphilis; h) thyroid disorders; i) hypercalcemia; j) vasculitis; k) heavy metal toxicity

C. Approach to Evaluation: History—As with the delirium, historical data is critical
1. The onset of dementia is insidious, delirium and CNS toxic syndromes will be commonly abrupt
2. Duration of symptoms is critical
3. Review of potential provoking events or medications inc. OTC meds and herbal meds
4. Identification of disturbances of behavior, delusions, suspicions, or hallucinations
5. Explore past medical history including vascular risk
6. Pertinent family history

D. Approach to Evaluation: Physical Exam
1. General appearance/hygiene
2. Attention to underlying cardiovascular disease
3. Neurological exam including level of alertness, strength, reflexes, gait/balance, proprioceptive sense, vibratory sense, monofilament testing

E. Cognitive Screening
1. Mini-Mental Status Exam (MMSE)
   a. Easily performed/universal utility
   b. Score < 24 is strongly suggestive of dementia
   c. Average loss of 3 points per year in an untreated patient with AD
   d. Not used to diagnose dementia, but used to establish a baseline for future evaluations and to document change over time or response to therapy
2. Clock Draw—Adds additional quick screen of executive function
3. Consider screening depression scale
   a. Symptoms may represent pseudodementia
   b. Depressive symptoms are common with AD
   c. If cognitive function resolves with correction of depression, periodic monitoring for cognitive decline is warranted
4. Proceed with referral for formal neuropsychiatric testing for uncertain situations

Sample Questions from The Mini-Mental State Exam (MMSE)

Orientation to Time
“What is the date?”

Registration
“Listen carefully. I am going to say three words. You say them back after I stop.
Ready? Here they are…
APPLE (pause), PENNY (pause), TABLE (pause).
Now repeat those words back to me.” [Repeat up to 5 times, but score only the first trial.]

Naming
“What is this?” [Point to a pencil or pen.]

Reading
“Please read this and do what it says.”
[Show examinee the words on the stimulus form.]
CLOSE YOUR EYES

F. Lab and Imaging
1. Basic profile includes CBC, basic metabolic panel, TSH, serum B₁₂, and liver function
2. Consider HIV, vasculitis screen, syphilis serology, and heavy metal screening as clinically indicated
3. Lumbar Puncture: Consider to evaluate a rapidly progressive dementia and is required to further evaluate a positive syphilis serology
4. Neuroimaging
   a. MRI provides excellent anatomical detail
   b. A noncontrast CT has the advantage of speed which may be appropriate for a
G. Management: Nonpharmacological
- Multiple interventions may have utility in behavior management. The Alzheimer’s association is an excellent resource, www.alz.org
- Attention to home safety including fall risk, fire hazards, wandering dangers and potential for financial predators
- The timing of driving cessation is critical for the patient and society. For an excellent reference consult: Assessing and Counseling Older Drivers—www.nhtsa.gov
- Consider new medical illness with abrupt change in behavior or cognition (e.g., UTI, fecal impaction)
- Be cautious of specific drug toxicity—eliminate unnecessary medications (e.g., anticholinergic agents, hypnotics)

H. Management of dementia: Pharmacological
- 1. Cholinesterase inhibitors
   - a. Modest symptomatic benefit for cognition (may slow decline of MMSE from 3 points to 1.5 points after 1 year)
   - b. Potential to improve behavioral concerns
   - c. Improvement in non-cognitive symptoms may delay nursing home placement
   - d. All share potential for cholinergic symptoms, including nausea, diarrhea, anorexia, and bradydysrhythmia
   - e. Consult table for specific agents and doses
   - f. Early intervention appears reasonable to gain the most benefit
- 2. Memantine, an N-methyl-D-aspartate antagonist, is approved for moderate to severe dementia—constipating effect blends well with cholinesterase inhibitors
- 3. Ginko biloba—Has been suggested as beneficial but not FDA regulated
- 4. Vitamin E—2005 trial found no benefit and may increase mortality
- 5. Atherosclerotic risk factors—Control hypertension and lipids per recommendations

<table>
<thead>
<tr>
<th>Medication</th>
<th>Formulations</th>
<th>Dosing (Metabolism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinesterase Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donepezil (Aricept)</td>
<td>T: 5, 10, 23; ODT: 5, 10; S: 5 mg/mL</td>
<td>Start at 5 mg/d, increase to 10 mg/d after 1 mo (CYP2D6, -3A4); must be on 10 mg/d ≥ 3 mo to consider increasing to 23 mg/d in moderate to severe AD. Avoid if hx of syncope. (L)</td>
</tr>
<tr>
<td>Galantamine (Razadyne)</td>
<td>T: 4, 8, 12; S: 4 mg/mL</td>
<td>Start at 4 mg q12h, increase to 8 mg q12h after 4 wk; recommended dosage 8 or 12 mg q12h (CYP2D6, -3A4). Avoid if hx of syncope. (L)</td>
</tr>
<tr>
<td>(Razadyne ER)</td>
<td>C: 8, 16, 24</td>
<td>Start at 1 capsule daily, preferably with food; titrate as above</td>
</tr>
<tr>
<td>Rivastigmine (Exelon)</td>
<td>C: 1.5, 3, 4.5, 6; S: 2 mg/mL; pch: 4.6, 9.5</td>
<td>Start at 1.5 mg q12h and gradually titrate up to minimally effective dosage of 3 mg q12h; continue up to 6 mg q12h as tolerated; for pch, start at 4.6 mg/d, may be increased after ≥ 4 wk to 9.5 mg/d (recommended effective dosage): retitrate if drug is stopped. Avoid if hx of syncope. (K)</td>
</tr>
<tr>
<td>Memantine (Namenda [NMDA antagonist])</td>
<td>T: 5, 10; S: 2 mg/mL</td>
<td>Start at 5 mg/d, increase by 5 mg at weekly intervals to max of 10 mg q12h; if CrCl &lt;30 mL/min, max of 5 mg q12h (K)</td>
</tr>
<tr>
<td>(Namenda XR)</td>
<td>C: 7, 14, 21, 28</td>
<td>Start at 7 mg/d, increase by 7 mg at weekly intervals to max of 18 mg; if severe renal impairment, max of 14 mg daily (L)</td>
</tr>
</tbody>
</table>

- a Cholinesterase inhibitors. Continue if improvement or stabilization occurs; stopping medications can lead to rapid decline.
- b Approved by FDA for moderate to severe AD.
- c Increased mortality found in controlled studies of mild cognitive impairment.
- d Tablets will be discontinued in Aug 2014.

I. Management of behavioral aspects of dementia: Pharmacological—Establish goals and if not successful, then explore alternative approaches

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Medication</th>
<th>Dosage</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation in context of psychosis</td>
<td>Aripiprazole a, b (Abilify)</td>
<td>2.5–12.5 mg/d</td>
<td>T: 5, 10, 15, 20, 30</td>
</tr>
<tr>
<td></td>
<td>Olanzapine a, b (Zyprexa) (Zydis)</td>
<td>2.5–10 mg/d</td>
<td>T: 2.5, 5, 7.5, 15, 20 ODT: 5, 10, 15, 20</td>
</tr>
<tr>
<td></td>
<td>Quetiapine a, b (Seroquel)</td>
<td>12.5–100 mg/d</td>
<td>T: 25, 100, 200, 300</td>
</tr>
<tr>
<td></td>
<td>Risperidone a, b (Risperdal)</td>
<td>0.25–3 mg/d</td>
<td>T: 0.25, 0.5, 1, 2, 3, 4, S: 1 mg/mL</td>
</tr>
<tr>
<td>Agitation in context of depression</td>
<td>SSRI, eg, citalopram (Celexa)</td>
<td>10–20 mg/d</td>
<td>T: 20, 40; S: 2 mg/mL</td>
</tr>
<tr>
<td>Anxiety, mild to moderate irritability</td>
<td>Buspirone (BuSpar)</td>
<td>15–60 mg/d c</td>
<td>T: 5, 7.5, 10, 15, 30</td>
</tr>
<tr>
<td>Trazodone (Desyrel)</td>
<td>50–100 mg/d d</td>
<td>T: 50, 100, 150, 300</td>
<td></td>
</tr>
<tr>
<td>Agitation or aggression unresponsive to first-line tx</td>
<td>Carbamazepine (Tegretol)</td>
<td>300–400 mg/d a</td>
<td>T: 200; ChT: 100; S: sus 100/5 mL</td>
</tr>
<tr>
<td></td>
<td>Divalproex sodium (Depakote, Epival)</td>
<td>500–1500 mg/d f</td>
<td>T: 125, 250, 500; S: syr 250 mg/mL; sprinkle capsule: 125</td>
</tr>
<tr>
<td></td>
<td>Olanzapine b, g (Zyprexa IntraMuscular)</td>
<td>2.5–5 mg IM</td>
<td>inj</td>
</tr>
<tr>
<td>Sexual aggression, impulse-control symptoms in men</td>
<td>Second-generation antipsychotic or divalproex</td>
<td>See dosages above</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If no response, estrogen (Premarin) or</td>
<td>0.625–1.25 mg/d</td>
<td>T: 0.3, 0.625, 0.9, 1.25, 2.5</td>
</tr>
<tr>
<td></td>
<td>medroxyprogesterone (Depo-Provera)</td>
<td>100 mg IM/wk</td>
<td>inj</td>
</tr>
</tbody>
</table>

a Avoid.
b Increased risk of mortality and cerebrovascular events compared with placebo; use with particular caution in patients with cerebrovascular disease or hypovolemia.
c Can be given q12h; allow 2–4 wk for adequate trial.
d Small divided daytime dosage and larger bedtime dosage; watch for sedation and orthostasis.
e Monitor serum levels; periodic CBCs, platelet counts secondary to agranulocytosis risk. Beware of drug-drug interactions.
f Can monitor serum levels; usually well tolerated; check CBC, platelets for agranulocytosis, thrombocytopenia risk in older adults.
g For acute use only; initial dose 2.5–5 mg, second dose (2.5–5 mg) can be given after 2 h, max of 3 injections in 24 h (max daily dose 20 mg); should not be administered for >3 consecutive d.


CLINICAL PEARLS: DELIRIUM
- Delirium is common and often not recognized. Prevention is critical
- Delirium may alter the trajectory of underlying dementia. Delirium persists much longer than previously recognized, sometimes blurring the boundary between delirium and dementia
- Pharmacological management of the symptoms of delirium is largely empirical. Goals of management should be set, and adjustments based on clinical response
- Mortality rates among hospitalized patients with delirium range from 27–76%, statistics comparable to acute myocardial infarction or sepsis

CLINICAL PEARLS: DEMENTIA
- When the clinical course does not follow typical landmarks, reconsider the differential diagnosis
- Consider the potential to prolong QT interval when prescribing an antipsychotic (EKG)
- When dementia with Lewy bodies is suspect, antipsychotic agents should be used with caution due to marked sensitivity including potential for neuroleptic malignant syndrome
- Autonomic dysfunction, with the common manifestation of postural hypotension, is common with advancing dementia and may increase risk of falls, behavioral distur-
References
Weaver JD. The utility of PET brain imaging in the initial evaluation of dementia. JAMA 2007;8:150–7.
For Medicare guidelines for PET scans: www.petscaninfo.com/portals/pat/medicare_guidelines_alzheimers
119. End of Life Care

I. BACKGROUND/INTRODUCTION
As the population ages, the percentage of patients who will need end of life care will increase. Common diagnoses requiring care include stroke, end stage congestive heart failure, end stage COPD, and end stage renal disease. Symptom management is one of the primary tenets of palliative care.

II. SYMPTOM MANAGEMENT—Objective is to control symptoms by the fastest, most efficacious route. This may be oral, subcutaneous, IV or rectal.

A. Pain
1. Opioids are the mainstay of pain control
2. Adequate pain control is necessary to decrease anxiety
3. Respiratory depression is very rare with adequate pain management
4. Morphine and hydromorphone are the preferred opioids. They are available for administration via multiple routes
5. Dosage is dependent on opioid naïvety and other medications

B. Dyspnea
1. Dyspnea follows a complex pathway in a similar region of the brain to pain. Treatment is often a multiple modality regimen
2. Pain medication: Morphine and Hydromorphone
   a. Morphine oral solution 2.5mg Q 1 hr PRN for opioid naïve and titrate dose
   b. If on opioid, use half of the scheduled dose for BTD 1 hr PRN; titrate dose as needed
3. Lorazepam (Ativan) is the preferred benzodiazepine. Start at 0.25mg Q 8 hr or Q 12 hr
4. Pursed lip breathing and a fan at bedside
5. Social support and distraction (e.g., listening to music) may be helpful

C. Anxiety
1. Lorazepam is preferred.
2. Do not recommend using long-acting benzodiazepine such as Diazepam (Valium)

D. Secretions
1. Glycopyrrolate (Robinul) 1–2mg PO BID-TID PRN, 0.2mg IM/IV Q 4–8 hrs PRN
2. Mouth care is essential for patient and family members

E. Delirium
1. Address the underlying cause, e.g., pain, dyspnea, medications; treat that first
2. Consider Haloperidol or Chlorpromazine (Thorazine)

F. Nausea/Vomiting
1. Identify the source of nausea and vomiting then treat accordingly
2. Increased intracranial pressure responds best to steroids, e.g., Dexamethasone
3. Nausea due to chemotherapy responds to Ondansetron (Zofran)
4. Nausea due to constipation responds to Metoclopramide (Reglan)
5. Nausea and vomiting from anxiety will respond to Lorazepam
6. Haloperidol is a good choice for nausea and vomiting that is unresponsive to other medications
7. Acupuncture may be considered for nonresponsive nausea and vomiting

G. Constipation
1. Initiate therapy concurrently with prescription of pain meds
2. Ducosate Sodium—consider adding Sennosides in addition as a motility agent
3. Polyethylene Glycol 3350 (Miralax) or Magnesium Citrate
4. If still unresponsive, recommend Lactulose on a scheduled basis
5. Bisacodyl is a good suppository agent that does not cause as much cramping as the oral form

H. Family meetings
1. Address expectations
2. Initiate discussion of the dying process with families so that they are not alarmed by irregular breathing or movements by the patient
3. Recommend stopping all IV medications and blood draws
4. Nutrition has not been shown to prolong life and may cause more harm secondary to aspiration risk

I. Code status
1. See Chapter 118, Addressing Code Status
2. Begin discussion early in process

J. Prognostication
Physicians are very poor prognosticators regarding disease and dying. Remind families that even though the life supportive measures have stopped the patient may continue in the dying process for several days

CLINICAL PEARLS
- End of life care is best provided by a team of providers, nursing, social work, spiritual professional or chaplain, pharmacist, and physician
- Easing the dying process for families and patients is an essential component of the physician and patient care continuity relationship. Therefore becoming skilled in this area of care is invaluable to the patient, family and the physician
- Do not use Haloperidol in patients with Lewy Body disorder or Parkinson’s disease because this will make extrapyramidal symptoms worse
- Dyspnea receptors are in the same region of the brain as pain receptors. Therefore the same modalities that work on pain management work for dyspnea. Thus approach should be multi-faceted, including medication, positioning, breathing techniques, and social and spiritual support

References
XII. HIV & AIDS

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121. CD4 Cell Counts & Associated Clinical Manifestations .......................... 484
122. HIV Post-exposure Prophylaxis (PEP) ..................................................... 485
120. AMBULATORY HIV/AIDS MANAGEMENT

The optimal management of patients with HIV/AIDS is a constantly evolving process. These recommendations are intended for physicians with experience in treating patients with HIV/AIDS who have a baseline level of knowledge. These recommendations are for management of adults with HIV and AIDS. These recommendations are current as of February 2013.

I. HISTORY
A. History of present illness: In addition to standard history, ask specifically about: Fatigue, weight loss, weakness, fever, chills, night sweats, lymphadenopathy, rash or skin changes, oral lesions, dysphagia/odynophagia, change in vision, cough, dyspnea, easy bruising, diarrhea, nausea/vomiting, abdominal pain, dysuria, vaginal/penile discharge, yeast infections, anal pain, headaches, confusion/seizures.
B. Past medical history: Hospitalizations/operations, drug allergies, immunizations, meds, history of infectious diseases (varicella/zoster, TB or positive skin tests, HSV, hepatitis, STDs), date of initial diagnosis of HIV and AIDS.
C. Social history: Possible mode of infection, current sexual practices, drug use, smoking and alcohol, diet, stressors, support systems.
D. Medications: An accurate medication history is important since many antiretroviral medications interact with prescription and over the counter medications (e.g., St. John's wort).

II. PHYSICAL EXAMINATION
A. General exam (cachexia)
B. Ophthalmic exam (visual field defects, fundi)
C. Dermatologic exam (seborrheic dermatitis, Kaposi’s sarcoma, tinea, varicella, HSV, etc.)
D. Oral and dental exam (candidiasis, oral hairy leukoplakia, HSV, KS)
E. Pulmonary
F. Cardiovascular
G. Abdominal exam
H. Neurologic exam (baseline)
I. Consider rectal exam (condyloma, perirectal HSV)
J. Genital exam (candida, HSV, chancre, HPV, etc.)

III. LABORATORY AND OTHER DIAGNOSTIC EVALUATIONS

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Other tests</th>
<th>Immunizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential and platelets</td>
<td>Chest radiograph</td>
<td>Pneumococcal vaccine</td>
</tr>
<tr>
<td>Chemistry panel</td>
<td>PPD skin testing (no anergy screen necessary)</td>
<td>Hepatitis B vaccine (if seronegative)</td>
</tr>
<tr>
<td>Liver enzymes</td>
<td>PAP smear (cervical dysplasia risk increased 8–11 times)</td>
<td>Hepatitis A vaccine</td>
</tr>
<tr>
<td>Fasting lipid profiles</td>
<td>Viral load (copies/cc)</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>Resistance testing (even if therapy will be delayed)</td>
<td>Influenza vaccine</td>
</tr>
<tr>
<td>Urinalysis</td>
<td></td>
<td>(Varicella vaccine for household contacts with no history of chickenpox)</td>
</tr>
</tbody>
</table>
A. Laboratory and other tests—see V. below

B. Immunizations

1. Pneumococcal vaccine: Strongly recommended
   a. Recommended for all patients with HIV with CD4 counts over 200. Optional for patients with CD4 counts less than 200 as the response to vaccination is poor. Revaccination Q 5 yrs may be considered
   b. Impact on viral load: May transiently increase the viral load. Viral load testing should be delayed for 4 weeks after the immunization
   c. General: Incidence of pneumococcal pneumonia is increased over 20 times in patients with HIV and the risk of pneumococcal bacteremia is increased 150–300 fold higher than age matched controls without HIV. Pneumococcal vaccine should be given at the earliest opportunity and repeated once at 5 years. 88% of asymptomatic HIV infected patients responded to at least 1 component of the 23-valent vaccines

2. Influenza vaccine: Generally recommended
   a. Recommended by the centers for disease control (CDC)
   b. Impact on viral load: May raise the viral load, therefore, viral load testing should be delayed for 4 weeks after the immunization
   c. General: Patients with HIV do not have worse infections with influenza than non-infected patients, however, the advantage of preventing influenza is that the symptoms will not be confused with symptoms of an opportunistic infection and unnecessary evaluations will be avoided. Other advantages include the increased risk of persons with HIV for bacterial infections that may complicate influenza. Protective antibody titers develop in 52–89% of patients with asymptomatic disease and 13–58% of patients with AIDS

3. Hepatitis B vaccine
   a. Recommended for individuals without evidence of prior exposure to HBV, even if CD4 < 200
   b. General: Patients with HIV and hepatitis B have a 19–37% risk of becoming chronic carriers (3–6 times higher risk than patients without HIV). Response rate to the vaccine is 25–60%

4. Hepatitis A vaccine: Generally recommended for those who engage in anal intercourse, injection drug users, or susceptible patients with chronic liver disease

5. Hemophilis Influenzae type B, diphtheria/tetanus, MMR: Same as for non-infected patients

6. Travel vaccines: Same as for non-infected patients, but no live vaccines

7. Varicella
   a. Vaccine: Not recommended for persons infected with HIV secondary to the risk of disseminated viral infection. It is recommended for household contacts of persons with HIV if they have not had chickenpox
   b. Immune globulin: With significant exposure to chicken pox or shingles in patients without history of either condition (or negative antibody titer) give Varicella Zoster Immune Globulin (VZIG) 5 vials (1.25mL each) IM if < 96hrs post-exposure (preferable within 48hrs)

8. Human Papillomavirus (HPV): women and high risk males 11–26; HPV quadrivalent vaccine, months 0, 2 and 6

9. Vaccines not to give: Oral polio vaccine (OPV), varicella vaccine, other live vaccines

C. Other information: Provide patient with written information on HIV/AIDS, support groups, unsafe and safe sexual and IV drug use practices. Certain sexual practices are safe for patient to continue to engage in (activities which do not exchange body fluids) and should be discussed explicitly with the patient. Past contacts should be notified, but this can be deferred until the doctor patient relationship has been better established. Explain to patient the need for frequent visits and blood tests

IV. PROPHYLAXIS
A. Pneumocystis pneumonia (PCP) prophylaxis
1. Pneumocystis pneumonia is caused by a fungus called *Pneumocystis jiroveci*. It is spread through the air. It is common; most children have antibodies by age 2–4. Most common site is pulmonary, but infection may occur in extra-pulmonary sites as well (e.g., skin, lymph nodes, spleen, brain).
2. Trimethoprim/Sulfamethoxazole (TMP/SMX) is first line for prophylaxis. It is low cost, effective, and it has activity against toxoplasmosis and many bacterial infections in addition to *Pneumocystis jiroveci*. If it is not tolerated due to rash, GI upset, or fever, a desensitization protocol may be attempted.
3. Indications for primary PCP prophylaxis
   a. CD4 < 200 cells/mm³
   b. HIV associated oral thrush
4. TMP/SMX initiation protocol: Tolerated better if started as a low dose (½ DS tab QOD) and gradually increased.
5. TMP/SMX desensitization: Very slow initiation may be attempted for patients who had previous non-anaphylactic reactions to TMP/SMX.
6. Patients who have CD4 count increase to >200 for >3 months may discontinue primary PCP prophylaxis.

**PROPHYLAXIS OF PNEUMOCYSTIS PNEUMONIA (PCP)**

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>DOSE</th>
<th>COST/MO. (AWP 2013)</th>
<th>RELAPSE RATE</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>One SS or DS (preferred) PO daily. May give one DS TW</td>
<td>$10</td>
<td>&lt;5%/yr</td>
<td>Rash, nausea/vomiting, fever, anemia neutropenia, Stevens-Johnson</td>
</tr>
<tr>
<td>Dapsone</td>
<td>100mg PO QD (preferred) or 50mg PO QD</td>
<td>$10 program</td>
<td>5–20%/yr</td>
<td>Rash, agranulocytosis, aplastic anemia, hemolytic anemia in G6PD deficiency.</td>
</tr>
<tr>
<td>Atovaquone/Mepron</td>
<td>1500mg PO QD or 750mg/5cc</td>
<td>$1900</td>
<td>5–20%/yr</td>
<td>Rash (20%), GI intolerance (20%), diarrhea (20%).</td>
</tr>
<tr>
<td>Aerosolized pentamidine</td>
<td>300mg per month administered over 30–45 minutes per Respigard II nebulizer</td>
<td>$120 plus cost of administration</td>
<td>15–25%/yr</td>
<td>Bronchospasm (consider pre-treat with albuterol MDI), increased incidence of upper lobe disease and extra-pulmonary PCP.</td>
</tr>
</tbody>
</table>

B. Mycobacterium avium complex (MAC) prophylaxis
1. Common in food and water. Causes disease in up to 40% of late stage patients with HIV infection who do not take MAC prophylaxis.
2. Indications: CD4 < 50 cells/mm³
3. If Clarithromycin or Azithromycin (Macrolides are preferred agents) are used, then screen for MAC first by obtaining a MAC culture. There is about a 27% incidence of resistance to Macrolides in patients who develop MAC while on prophylaxis with Macrolides.
4. Patients who have CD4 count increase to > 100 for 3 months may discontinue primary prophylaxis.

**PROPHYLAXIS OF MYCOBACTERIUM AVIUM COMPLEX (MAC)**

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>DOSE</th>
<th>COST/MO. (AWP 2013)</th>
<th>SIDE EFFECTS AND PRECAUTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin (Zithromax)</td>
<td>1200mg per week (Two 600mg tabs with or without food) or 600mg twice weekly</td>
<td>$190</td>
<td>GI disturbances</td>
</tr>
<tr>
<td>Clarithromycin (Biaxin)</td>
<td>500mg BID</td>
<td>$270</td>
<td>GI disturbances with protease inhibitors</td>
</tr>
<tr>
<td>Rifabutin (Mycobutin)</td>
<td>300mg QD</td>
<td>$1100</td>
<td>Neutropenia, thrombocytopenia, rash and GI, uveitis, drug-drug interactions with protease inhibitors</td>
</tr>
</tbody>
</table>
C. Tuberculosis (see Chapter 41, Tuberculosis Screening)
D. Cryptococcus
1. Cryptococcus is a fungus, acquired by inhalation
2. Primary prophylaxis not recommended
E. CMV disease (retinitis)
1. CMV is a viral infection often causing blindness as a result of retinitis
2. Screening: Ophthalmologist exam every 6 months with CD4 counts less than 50 cells/mm³ or visual symptoms
3. Primary prophylaxis not recommended

V. ANTIRETROVIRAL THERAPY—HIV enzymes can be inhibited with meds. There is no "cure" for HIV/AIDS, and the viral load will return to detectable once meds are stopped or resistance develops
A. Pathogenesis of HIV
1. HIV is a retrovirus. It is incorporated into CD4 cells by the binding of the HIV envelope protein gp120 to the CD4 receptor and a second receptor (possibly a chemokine receptor). Once inside the cell the HIV RNA is converted into DNA by the enzyme reverse transcriptase and then incorporated into the host cell's DNA. Next, messenger RNA (mRNA) is made which is then translated to make the proteins that will eventually form into the virus. These proteins are cleaved into the active form of HIV by the enzyme HIV protease. These active viral components are then packaged and put into circulation as infectious virions
2. HIV pathogenesis is a very active process. Even during early, asymptomatic disease there are approximately 10 billion HIV viral particles produced and destroyed each day. The half life of plasma virus is about 6hrs
3. In addition to active viral replication in the blood, there is viral replication in the lymphoid system, CSF and other sites
4. Decreases in plasma viral load are not always paralleled by decreases in these other locations or in genital secretions. A patient with a non-detectable plasma viral load should not be considered to be noninfectious
5. There are 6 classes of drugs:
   a. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
   b. Non-Nucleoside reverse transcriptase inhibitors (NNRTIs)
   c. Protease inhibitors (PIs)
   d. Fusion inhibitors
   e. CCR5 antagonists
   f. Integrase strand transfer inhibitors (INSTIs)
B. Viral load testing (the level of HIV RNA in the plasma)
1. The viral load measures the amount of virus in 1 cc of plasma. It ranges from "non-detectable" (< 25 to > 75 copies/cc (depending on the lab) to > 75,000 copies/cc (the upper limit of the test)). The viral load count routinely varies by a factor of 3 (0.5 log). This variability may be decreased by multiple measurements
2. Uses
   a. Viral load is the strongest predictor of progression (should still be correlated with the CD4 count and the clinical picture)
   b. Viral load serves as a surrogate marker for treatment response
3. Limitations: Viral load testing does not test immune function, CD4 regenerative reserve, susceptibility to antiretroviral agents, infectivity, viral phenotype (syncytium vs. non-syncytium inducing forms), virus in lymph nodes, CNS, genital secretions
4. Cost: ~$150–300 per test
5. Method
   a. 2 baseline assays should be done 2–4 weeks apart
   b. Viral load should be checked 2–8 weeks after starting or changing therapy and then every 3–6 months
   c. Testing should be done by the same laboratory using the same test
   d. Wait 4 weeks after vaccinations to perform viral load testing
C. CD4 count
1. CD4 count serves as an indicator of immune function.
2. CD4 count = WBC × percent lymphocytes × lymphocytes that are CD4 cells. Therefore, anything which affects the WBC count may influence the CD4 count (infection, drugs, steroids). CD4 count normally varies by 30%, but this variation can be accounted for by multiple measurements of the CD4 count. Should be checked 2 weeks apart, by the same laboratory to reduce variation. The “% CD4” count stays fairly constant and should be looked at in conjunction with the CD4 count.
3. Should be used in conjunction with the viral load and the clinical picture to make decisions about antiretroviral therapy and prophylaxis for opportunistic infections.
4. Is an independent risk factor for opportunistic infections.
5. Cost: $100–150 per test.

D. Resistance and other testing
1. Perform at time of diagnosis of HIV, even if therapy will not be started at that time. If therapy is delayed, perform again prior to initiating ATV therapy.
2. Recommended test is genotypic testing which tests for mutations in reverse transcriptase (RT) enzymes and protease genes (Note: If integrase inhibitor stand transfer inhibitor (INSTI) resistance is a concern, a INSTI genotype test can be ordered.
3. When changing a regimen and viral load (HIV RNA) levels are above 1,000, testing should be done. If levels are 500–1000, testing may be unsuccessful.
4. Perform testing while the patient is taking ATV therapy (preferable) or within 4 weeks of stopping therapy.
5. Phenotypic testing may be added if there is complex drug resistance, particularly to protease meds.
6. Note: A co-receptor tropism assay should be performed whenever the use of a CCR5 co-receptor antagonist is being considered and for patients who exhibit virologic failure on a CCR5 antagonist.
7. Screen for HLA-B*5701 before starting patients on an abacavir (ABC)-containing regimen to reduce the risk of hypersensitivity reaction (HSR).

E. General considerations with antiretroviral therapy
1. Never use monotherapy.
2. Don’t add a single agent to a failing regimen as there is rapid development of resistance (comparable to monotherapy).
3. When therapy needs to be modified/changed, use 2 or (preferably) 3 fully active agents added to or substituted to the failing regimen.
4. Emphasize adherence at every visit.
5. Monitor drug interactions.
7. Think ahead about what you can change if resistance develops.

F. Initiating antiretroviral therapy in treatment-naïve patients

Panel’s Recommendations

- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of disease progression.
  The strength of and evidence for this recommendation vary by pretreatment CD4 T lymphocyte (CD4) cell count: CD4 count <350 cells/mm^3 (AII); CD4 count 350 to 500 cells/mm^3 (AII); CD4 count >500 cells/mm^3 (AII).
- ART is also recommended for HIV-infected individuals to prevent transmission of HIV.
  The strength of and evidence for this recommendation vary by transmission risks: perinatal transmission (AII); heterosexual transmission (AII); other transmission risk groups (AII).
- Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence (AII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion.
What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient—Panel’s Recommendations

- The optimal antiretroviral (ARV) regimen for a treatment-naïve patient consists of two NRTIs in combination with a third active ARV drug from one of three drug classes: an NNRTI, a PI boosted with ritonavir, or an INSTI (AI).

- The Panel recommends one of the following regimens for ART-naive patients regardless of baseline viral load or CD4 count:

  **NNRTI-Based Regimen:**
  - EFV/TDF/FTC (AI)

  **PI-Based Regimens:**
  - ATV/r plus TDF/FTC (AI)
  - DRV/r plus TDF/FTC (AI)

  **INSTI-Based Regimens:**
  - DTG plus ABC/3TC (AI)—only for patients who are HLA-B*5701 negative
  - DTG plus TDF/FTC (AI)
  - EVG/cobi/TDF/FTC—only for patients with pre-ART CrCl > 70 mL/min (AI)
  - RAL plus TDF/FTC (AI)

- In addition to the regimens listed above, the following regimens are also recommended, but only for patients with pre-ART plasma HIV RNA < 100,000 copies/mL:

  **NNRTI-Based Regimens:**
  - EFV plus ABC/3TC (AI)—only for patients who are HLA-B*5701 negative
  - RPV/TDF/FTC (AI)—only for patients with CD4 count > 200 cells/mm³

  **PI-Based Regimen:**
  - ATV/r plus ABC/3TC (AI)—only for patients who are HLA-B*5701 negative

- On the basis of individual patient characteristics and needs, an Alternative Regimen may in some instances be the optimal regimen for a patient. A list of Alternative Regimens can be found in Table 6.

- Selection of a regimen should be individualized on the basis of virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, comorbid conditions, and cost.

- To assist clinicians in selecting the best treatment for a patient, Table 7 highlights the advantages and disadvantages of different components in a regimen.

a 3TC may substitute for FTC or vice versa.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert Opinion

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; cobi = cobicistat; CrCl = creatinine clearance; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TDF = tenofovir disoproxil fumarate
Based on individual patient characteristics and needs, in some instances, an alternative or other regimen may be a preferred regimen for a specific patient.

**CLINICAL PEARLS**

- Using antiretrovirals during pregnancy can significantly decrease maternal transmission of HIV to the fetus.
- Average fall in CD4 counts without therapy is about 50–80/yr.
- CD4 counts and viral load both independently predict risk for HIV disease progression. Using both together can provide even more diagnostic information.
- Openness and honesty are paramount. Most AIDS patients will also be getting information from sources other than their physician, including the internet and friends infected with HIV. Desperation makes a believer out of a cynic. Ask your patients what other interventions they are trying.

**NATIONAL RESOURCES:**

1. National AIDS Hotline .......................... 800-CDC-INFO (800-342-2437)
2. HIV/AIDS Clinical Trials .......................... 800-448-0440
3. American Foundation for AIDS Research (AMFAR) .......................... 212-806-1600
   www.amfar.org

**References**

HIV & AIDS

121. CD4 Cell Counts & Associated Clinical Manifestations

Transmission
Acute retroviral syndrome
Seroconversion

Peripheral generalized lymphadopathy
Pneumococcal pneumonia*
Candida vaginitis*
ITP*

Thrush
Kaposi's sarcoma*
Lymphoma*
Tuberculosis
HIV-associated dementia
Oral hairy leukoplakia

Wasting
Toxoplasmosis
PCP
Cryptococcosis
Herpes simplex
Candida esophagitis

MAC
CMV

*Conditions that are observed over a broad range of CD4 cell counts

122. HIV Post-Exposure Prophylaxis (PEP)
(Based on 2005 CDC + 2014 AETC Recommendations)

I. TRANSMISSION: HIV is transmitted by transfer of blood or body fluids
   A. Body fluids that are documented to carry sufficient virus include blood, semen, vaginal
      secretions, cerebrospinal fluid (CSF), synovial fluid, pleural fluid, peritoneal fluid,
      pericardial fluid and amniotic fluid
   B. Body fluids not considered to be at risk include feces, nasal secretions, sputum, saliva,
      sweat, tears, urine and vomitus. The safest policy for health care workers is to use
      universal precautions with all body fluids

II. PREVALENCE/Epidemiology
   A. The 3 groups with the highest prevalence of HIV are gay men, IV drug abusers and
      hemophiliacs. Wives of hemophiliac men have a rate of 20–25%. The rate in prostitutes
      varies with location and with concomitant IV drug use. Other routes of infection include
      heterosexual transmission, blood transfusions, pregnancy, breast milk
   B. As of December 1995, all blood is screened for both HIV antibody and antigen. The use of
      this new technique has decreased the risk of HIV infected blood to less than one in
      500,000 units of blood. Non-intimate contact and household exposure does not increase
      risk of transmission of HIV

III. RISK OF TRANSMISSION
   A. Occupational exposure: Pooled data from 23 prospective studies showed that risk after
      occupational exposure to needles and other contaminated devices was 0.33% (20 infections
      after 6,135 exposures). Risk is increased with:
      1. Deep injury
      2. Visible blood on the injuring device
      3. Injection directly into blood vessel
      4. Source patient with high viral titer (high viral load, end-stage AIDS, etc.)
   B. Needle stick: Risk of transmission varies by type of needle (hollow vs. solid), depth of
      penetration, amount of blood transferred, use of gloves, and the amount of virus in
      infected blood (asymptomatic vs. symptomatic patients)
   C. Risk with mucocutaneous exposures: 1 infection in 1,443 mucosal exposures (0.09%)
   D. Risk with exposure to intact skin: No conversions have been documented (no infections
      after 2,712 instances of exposure)
   E. Risk after exposure:

<table>
<thead>
<tr>
<th>RISK OF HIV TRANSMISSION WITH EXPOSURE TO AN HIV-INFECTED SOURCE</th>
<th>Probability/10,000 exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood transfusion</td>
<td>9,000</td>
</tr>
<tr>
<td>Needle sharing (IVDU)</td>
<td>67</td>
</tr>
<tr>
<td>Receptive anal intercourse</td>
<td>50</td>
</tr>
<tr>
<td>Percutaneous-needle stick (occupational exposure)</td>
<td>30</td>
</tr>
<tr>
<td>Receptive penile-vaginal intercourse</td>
<td>10</td>
</tr>
<tr>
<td>Insertive anal intercourse</td>
<td>6.5</td>
</tr>
<tr>
<td>Insertive penile-vaginal intercourse</td>
<td>5</td>
</tr>
<tr>
<td>Receptive oral intercourse</td>
<td>1</td>
</tr>
<tr>
<td>Insertive oral intercourse</td>
<td>.05</td>
</tr>
</tbody>
</table>

Source: CDC. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoc- 
cupational exposure to HIV in the United States: recommendations from the U.S. Department of
preview/mmwrhtml/rr5402a1.htm or http://www.cdc.gov/mmwr/PDF/rr/rr5402.pdf
IV. EVALUATION AND MANAGEMENT OF OCCUPATIONAL HIV EXPOSURES

A. Step one: Evaluate exposure—is there significant risk per type of exposure?
B. Step two: Determine the HIV status of the source
C. Step three: Determine the PEP recommendations. Note: There are 2 types of regimens; basic and expanded (for a more significant exposure)
D. Note: For both occupational and non-occupational exposures, inform the patient of the risk and potential benefit and use the strategy of “shared decision making” to arrive at a plan
E. Monitoring: Baseline and 2 week testing for CBC, renal function and liver function tests.
   If protease inhibitor is included in regimen, then test glucose at 2 weeks
F. Duration: The optimal duration is unknown. Recommendations are 4 weeks

Algorithm for evaluation and treatment of possible occupational HIV exposures

1. Skin integrity is considered compromised if there is evidence of chapped skin, dermatitis, abrasion, or open wound.

2. If drug resistance is suspected, obtain expert consultation. Initiation of oPEP should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.

3. Do not delay giving oPEP while awaiting test results. If source is determined to be HIV-negative, oPEP can be discontinued. Assessment of whether a source pt is in the window period between infection and positive HIV antibody, is not necessary unless acute retroviral syndrome is clinically suspected.

4. oPEP generally not warranted; consider oPEP where exposure to HIV-infected person likely.
V. EVALUATION AND MANAGEMENT OF POSSIBLE NONOCCUPATIONAL HIV EXPOSURES

Algorithm for evaluation and treatment of possible nonoccupational HIV exposures

### Substantial Risk for HIV Exposure

**Exposure of**
- vagina, rectum, eye, mouth,
- or other mucous membrane,
- nonintact skin, or percutaneous contact

**With**
- blood, semen, vaginal secretions, rectal secretions, breast milk, or any body fluid that is visibly contaminated with blood

**When**
- the source is known to be HIV-infected

### Negligible Risk for HIV Exposure

**Exposure of**
- vagina, rectum, eye, mouth,
- or other mucous membrane,
- intact or nonintact skin, or percutaneous contact

**With**
- urine, nasal secretions, saliva, sweat, or tears if not visibly contaminated with blood

**Regardless**
- of the known or suspected HIV status of the source

---


A. Management: Preferred regimens (pick one). See Chapter 113, Ambulatory HIV/AIDS Management, for dosing and side effects

1. **Efavirenz (Sustiva)** plus **Lamivudine (Epivir – 3TC)** plus **Zidovudine (Retrovir – AZT)** or **Tenofovir (Viread)**—note: Avoid **Efavirenz** in pregnant women and women with potential to become pregnant
2. **Lopinavir/Ritonavir (Kaletra)** plus **Lamivudine (Epivir – 3TC)** plus **Zidovudine (Retrovir – AZT)**
3. See above for timing, testing, and duration
CLINICAL PEARLS

- Potential risks from PEP after nonoccupational HIV exposure is a decrease in risk reduction behavior, antiretroviral side effects and toxicity, emergence of resistant strains of HIV, and cost
- The CDC does not recommend post-exposure prophylaxis after exposure to urine. Though considered highly infectious, semen and vaginal secretions have not been implicated in occupation transmission of HIV
- The prevalence of AIDS in US prisons is 14 times that in the general population. Prison rape may represent a high risk exposure

References


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Appendix

Michael B. Weinstock, MD

123. Formulas

A. Anion gap:

\[ \text{AG} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-) \]

Normal = 8–16 mEq / L

B. Creatinine clearance (CrCl):

1. \[ \text{CrCl (male)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{Serum creatinine} \times 72} \]
2. \[ \text{CrCl (female)} = 0.85 \times \text{CrCl (male)} \]

C. Fractional excretion of sodium:

\[ \text{FeNa} = \frac{U_{\text{Na}}}{P_{\text{Na}}} \times 100 \]

D. Serum osmolality:

\[ \text{Osm} = 2(\text{Na}^+ + \text{K}^+) + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8} \]

E. A–a Gradient:

\[ = (713 \times F_1O_2) - (\text{PaCO}_2 \times 1.2) - \text{PaO}_2 \]
Note: Pressures are at sea level
\( F_1O_2 \) at room air is 0.21
Normal A–a Gradient = 5–15

F. Corrected sodium with hyperglycemia:

\[ \text{Corrected Na}^+ = \text{Na}^+ + [1.6 \times (\text{Glucose} - 140)] / 100 \]

G. LDL Cholesterol:

\[ \text{LDL cholesterol} = \text{Total cholesterol} - \text{HDL cholesterol} - \left( \frac{\text{triglycerides}}{5} \right) \]
# 124. Symptomatic Medications: Colds & Flu, Sinusitis, Bronchitis, Etc.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>COMPONENTS</th>
<th>ADULT DOSE</th>
<th>PEDIATRIC DOSAGE</th>
<th>OTC/Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTITUSSIVES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hycodan</td>
<td>Hydrocodone bitartrate 5mg, Homatropine methylbromide 1.5mg, per tab or per 5mL</td>
<td>5mL or 1 tab PO Q4-6h PRN max 6 doses/d &lt; 6 y/o: Not rec. 6-12 y/o: 2.5mL or ½ tab PO Q4-6h PRN</td>
<td>(Class III)</td>
<td></td>
</tr>
<tr>
<td>Robitussin Children’s Cough</td>
<td>Dextromethorphan 7.5mg per 5mL</td>
<td>— &lt; 4 y/o: Not rec. 4-6 y/o: 5mL PO Q6-8h 6-12 y/o: 10mL PO Q6-8h</td>
<td>OTC</td>
<td></td>
</tr>
<tr>
<td>Tessalon Perles</td>
<td>Benzonatate 100mg, 200mg</td>
<td>100mg PO TID max dose 600mg/d &lt; 10 y/o: Not rec. &gt; 10 y/o: Same as adult</td>
<td>Rx</td>
<td></td>
</tr>
<tr>
<td><strong>ANTITUSSIVES, EXPECTORANTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucinex DM</td>
<td>Dextromethorphan 30mg, Guaifenesin 600mg per tab, sustained release 1-2 tabs PO Q12h</td>
<td>&lt; 12 y/o: Not rec.</td>
<td>OTC</td>
<td></td>
</tr>
<tr>
<td>Tussi-Organidin NR liquid</td>
<td>Codeine phosphate 10mg, Guaifenesin 300mg per 5mL 5mL PO Q4h max 40mL/d ≥ 12 y/o: 5mL Q4, max 40mL/d 6-12 y/o: 2.5mL PO max dose 20mL/d</td>
<td>Rx (Class V)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robitussin DM</td>
<td>Dextromethorphan 10mg, Guaifenesin 100mg per 5mL 10mL PO Q4h max 60mL/d</td>
<td>&lt; 12 y/o: Not rec.</td>
<td>OTC</td>
<td></td>
</tr>
<tr>
<td>Gualtuss AC, Virtussin AC</td>
<td>Codeine phosphate 10mg, Guaifenesin 100mg per 5mL 10mL PO Q4h max 60mL/d</td>
<td>&lt; 6 y/o: Not rec. 6-12 y/o: 5mL PO Q4h max 30mL/d</td>
<td>Rx (Class V)</td>
<td></td>
</tr>
<tr>
<td><strong>ANTITUSSIVES, EXPECTORANTS, SYMPATHOMIMETICS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entre-cough</td>
<td>Dextromethorphan 15mg, Guaifenesin 175mg, Pseudoephedrine 30mg per 5mL 10mL PO Q8h max 30mL/d &lt; 6 y/o: Not rec. 6-12 y/o: 5mL PO Q8h max 15mL/d ≥ 12 y/o same dose as adult</td>
<td></td>
<td>OTC</td>
<td></td>
</tr>
<tr>
<td><strong>ANTITUSSIVES, ANTIHISTAMINES, SYMPATHOMIMETICS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimetane DX</td>
<td>Dextromethorphan 10mg, Brompheniramine 2mg, Pseudoephedrine 30mg per 5mL 10mL PO Q4-6h max 40mL/d Under 6 y/o: Not rec. 6-12 y/o: 5mL PO Q4-6h max 20mL/d</td>
<td></td>
<td>Rx</td>
<td></td>
</tr>
<tr>
<td><strong>SYMPATHOMIMETICS</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Sudafed</td>
<td>Pseudoephedrine 15, 30, 60 mg tab; 7.5 mg/0.8 mL drop; 15 mg/5 mL, 30 mg/5 mL liquid</td>
<td>60mg PO Q4-6h max 240 mg/d 4-5 y/o: 15 mg PO q4-6 h, max 60 mg/d 6-12 y/o: 30 mg PO q 4-6 h max 120 mg/d</td>
<td>OTC</td>
<td></td>
</tr>
<tr>
<td><strong>EXPECTORANTS</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Organ-1 NR</td>
<td>Guaifenesin 200 mg tab</td>
<td>200-400 mg PO Q4h max 2400 mg/d 2.5 y/o: 50-100 mg PO Q4h max 600 mg/d 6-12 y/o: 100-200 mg PO Q4h max 1200 mg/d</td>
<td>Rx</td>
<td></td>
</tr>
<tr>
<td>Robitussin, Mucinex Children</td>
<td>Guaifenesin 100 mg/5 mL liquid</td>
<td>10-20 mL PO Q4h 2.5 y/o: 2.5-5 mL PO Q4h max 60 mg/d 6-12 y/o: 5-10 mL PO Q4h max 120 mg/d</td>
<td>OTC</td>
<td></td>
</tr>
<tr>
<td>Mucinex</td>
<td>Guaifenesin 600 mg sustained release tab</td>
<td>1-2 tabs PO Q12h</td>
<td>Not recommended</td>
<td>OTC</td>
</tr>
<tr>
<td>Liquituss GG</td>
<td>Guaifenesin 200 mg/5 mL liquid</td>
<td>5-10 mL PO Q4h max 2400 mg/d</td>
<td>Not recommended</td>
<td>OTC</td>
</tr>
</tbody>
</table>

(Chart continued on next page)
### 124. Symptomatic Medications

<table>
<thead>
<tr>
<th>DRUG</th>
<th>COMPONENTS</th>
<th>ADULT DOSE</th>
<th>PEDIATRIC DOSAGE</th>
<th>OTC/Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIHISTAMINES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allegra</td>
<td>Fexofenadine 30, 60, 180 mg tab; 6 mg/mL susp</td>
<td>60 mg PO BID or 180 mg PO QD</td>
<td>2-11 y/o: 30 mg/5 mL PO BID 6-11 y/o: 30 mg PO BID</td>
<td>OTC</td>
</tr>
<tr>
<td>Benadryl</td>
<td>Diphenhydramine 12.5, 25, 50 mg tab; 12.5 mg/5 mL sol</td>
<td>25-50 mg PO Q 4-6 h max 300 mg/d</td>
<td>6-12 y/o: 12.5-25 mg PO Q4-6h, max 150 mg/d</td>
<td>OTC</td>
</tr>
<tr>
<td>Chlor-Trimeton</td>
<td>Chlorpheniramine 4 mg tab; 12 mg ER tab; 2 mg/5 mL syrup</td>
<td>4 mg PO Q4-6h or 8-16 mg PO Q12h max 24 mg/d</td>
<td>6-12 y/o: 2 mg PO Q4-6h max 12 mg/24h</td>
<td>OTC</td>
</tr>
<tr>
<td>Clarinex</td>
<td>Desloratadine 5 mg tab; 2.5 mg/5 mL syrup</td>
<td>5 mg PO QD</td>
<td>6-11 mo: 1 mg PO QD 1-5 y/o: 1.25 mg PO QD 6-11 y/o: 2.5 mg PO QD</td>
<td>Rx</td>
</tr>
<tr>
<td>Claritin</td>
<td>Loratadine 5, 10 mg tab; 5 mg/5 mL syrup</td>
<td>10 mg PO QD</td>
<td>2-5 y/o: 5 mg PO QD &gt; 6 y/o: 10 mg PO QD</td>
<td>OTC</td>
</tr>
<tr>
<td>Zyrtec</td>
<td>Cetirizine 5, 10 mg; 5 mg/5 mL syrup</td>
<td>5 or 10 mg PO QD</td>
<td>6 mo-11 mo: 2.5 mg PO QD 12mo-23 mo: 2.5 mg PO QD max 2.5 mg BID 2-5 y/o: 2.5-5 mg PO QD 6-11 y/o: 5 or 10 mg PO QD</td>
<td>OTC</td>
</tr>
</tbody>
</table>

**ANTIHISTAMINE, SYMPATHOMIMETICS**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>COMPONENTS</th>
<th>ADULT DOSE</th>
<th>PEDIATRIC DOSAGE</th>
<th>OTC/Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allegra-D 12hr tab</td>
<td>Fexofenadine 60 mg/ pseudoephedrine 120 mg</td>
<td>1 tab PO Q12H</td>
<td>&lt; 12 y/o: Not recommended</td>
<td>OTC</td>
</tr>
<tr>
<td>Allegra-D 24hr tab</td>
<td>Fexofenadine 180 mg/ pseudoephedrine 240 mg</td>
<td>1 tab PO QD</td>
<td>&lt; 12 y/o: Not recommended</td>
<td>OTC</td>
</tr>
<tr>
<td>Claritin-D 12hr tab</td>
<td>Loratadine 5 mg/ pseudoephedrine 120 mg</td>
<td>1 tab PO Q12H</td>
<td>&lt; 12 y/o: Not recommended</td>
<td>OTC</td>
</tr>
<tr>
<td>Claritin-D 24hr tab</td>
<td>Loratadine 10 mg/ pseudoephedrine 240 mg</td>
<td>1 tab PO QD</td>
<td>&lt; 12 y/o: Not recommended</td>
<td>OTC</td>
</tr>
<tr>
<td>Clarinex-D 24 hr tab</td>
<td>Desloratadine 5 mg/ pseudoephedrine 240 mg</td>
<td>1 tab PO QD</td>
<td>Not recommended</td>
<td>Rx</td>
</tr>
<tr>
<td>Triaminic Cold/Allergy Child</td>
<td>Chlorpheniramine 1 mg/ phenylephrine 2.5 mg per 5 mL</td>
<td>—</td>
<td>6-12 y/o: 10 mL Q4-6h 2-6 y/o: 5 mL Q4-6h</td>
<td>OTC</td>
</tr>
<tr>
<td>Zyrtec-D 12 hr tab</td>
<td>Cetirizine 5 mg/ pseudoephedrine 120 mg</td>
<td>1 tab PO Q12H</td>
<td>&lt; 12 y/o: Not recommended</td>
<td>OTC</td>
</tr>
</tbody>
</table>

1. During 2004-2005, CDC reported that an estimated 1,519 children aged < 2 years were treated in US emergency departments for adverse events associated with cough and cold medications. As a result, CDC warns parents not to give common OTC cold medications to children < 2 years old without consulting a doctor. Because of the risk of toxicity, absence of dosing recommendations, and limited published evidence of effectiveness of these medications, clinicians should use caution when prescribing cough and cold medications to children aged < 2 years. Moreover, clinicians should always ask caregivers about their use of OTC combination medications to avoid overdose in children from multiple medications that contain the same ingredient.

2. The availability of pseudoephedrine has been affected by Federal Combat Methamphetamine Epidemic Act, which bans OTC sale of products containing pseudoephedrine. Cold and cough medications containing pseudoephedrine are now sold behind the counter. Many of these products have been reformulated to contain another decongestant, phenylephrine, so that they can be sold OTC.

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## 125. Adult Advanced Cardiac Life Support (ACLS) Protocols


### Cardiac Arrest Algorithm

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Shout for Help/Activate Emergency Response</td>
</tr>
<tr>
<td>2</td>
<td>Start CPR</td>
</tr>
<tr>
<td>3</td>
<td>CPR 2 min</td>
</tr>
<tr>
<td>4</td>
<td>CPR 2 min</td>
</tr>
<tr>
<td>5</td>
<td>CPR 2 min</td>
</tr>
<tr>
<td>6</td>
<td>CPR 2 min</td>
</tr>
<tr>
<td>7</td>
<td>CPR 2 min</td>
</tr>
<tr>
<td>8</td>
<td>CPR 2 min</td>
</tr>
<tr>
<td>9</td>
<td>CPR 2 min</td>
</tr>
<tr>
<td>10</td>
<td>CPR 2 min</td>
</tr>
<tr>
<td>11</td>
<td>CPR 2 min</td>
</tr>
<tr>
<td>12</td>
<td>CPR 2 min</td>
</tr>
</tbody>
</table>

### CPR Quality
- Push hard (2 inches [5cm]) and fast (≥100/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 minutes
- If no advanced airway, 30:2 compression-ventilation ratio
- Quantitative waveform capnography
  - If PETCO₂ <10 mm Hg, attempt to improve CPR quality
  - Intra-arterial pressure
  - If relaxation phase (diastolic) pressure <20 mm Hg, attempt to improve CPR quality

### Return of Spontaneous Circulation (ROSC)
- Pulsatile and blood pressure
- Abrupt sustained increase in PETCO₂ (typically ≥40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

### Shock Energy
- Biphasic: Manufacturer recommendation (e.g. initial dose of 120-200 J), if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered
- Monophasic: 360 J

### Drug Therapy
- Epinephrine IV/IO Dose:
  - 1 mg every 3-5 minutes
- Vasopressin IV/IO Dose:
  - 40 units can replace first or second dose of epinephrine
- Amiodarone IV/IO Dose:
  - First dose: 300 mg bolus. Second dose: 150 mg

### Advanced Airway
- Supraglottic advanced airway or endotracheal intubation
- Waveform capnography to confirm and monitor ET tube placement
- 6-10 breaths per minute with continuous chest compressions

### Reversible Causes
- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypo-hyperkalemia
- Hypothermia
- Tension pneumothorax
- Tamponade, cardiac
- Toxins
- Thrombosis, pulmonary
- Thrombosis, coronary
Bradycardia Algorithm

**Adult Bradycardia (with Pulse)**

1. Assess appropriateness for clinical condition. 
   Heart rate typically <50/min if bradyarrhythmia.

2. Identify and treat underlying cause
   - Maintain patent airway; assist breathing as necessary
   - Oxygen if hypoxic
   - Cardiac monitor to identify rhythm; monitor blood pressure and oximetry
   - IV access
   - 12-Lead ECG if available; do not delay therapy

3. Persistent bradyarrhythmia causing:
   - YES
   - Hypotension?
   - Acutely altered mental status?
   - Signs of shock?
   - Ischemic chest discomfort?
   - Acute heart failure?

4. Monitor and Observe
   - NO

5. Atropine
   - If atropine ineffective:
     - Transcutaneous pacing
     - Dopamine infusion
     - Epinephrine infusion
   - YES

6. Consider
   - Expert consultation
   - Transvenous pacing

**Drug Doses/Details**

- **Atropine IV Dose**:
  - First dose: 0.5 bolus
  - Repeat every 3-5 minutes
  - Maximum: 3 mg

- **Dopamine IV Infusion**:
  - 2-10 mcg/kg per minute

- **Epinephrine IV Infusion**:
  - 2-10 mcg per minute
Tachycardia Algorithm

**Adult Tachycardia (with Pulse)**

1. Assess appropriateness for clinical condition. Heart rate typically ≥150/min if tachyarrhythmia.

2. Identify and treat underlying cause
   - Maintain patent airway; assist breathing as necessary
   - Oxygen if hypoxic
   - Cardiac monitor to identify rhythm; monitor blood pressure and oximetry

3. Persistent tachyarrhythmia causing:
   - Hypotension?
   - Acutely altered mental status?
   - Signs of shock?
   - Ischemic chest discomfort?
   - Acute heart failure?

4. Synchronized cardioversion
   - Consider sedation
   - If regular narrow complex, consider adenosine

5. Wide QRS? ≥ 0.12 second
   - IV access and 12-lead ECG if available
   - Consider adenosine only if regular and monomorphic
   - Consider antiarrhythmic infusion
   - Consider expert consultation

6. Synchronized cardioversion
   - Yes
   - IV access and 12-lead ECG if available
   - Consider adenosine only if regular and monomorphic
   - Consider antiarrhythmic infusion
   - Consider expert consultation

7. NO
   - IV access and 12-lead ECG if available
   - Vagal maneuvers
   - Adenosine if regular
   - β-blocker or calcium channel blocker
   - Consider expert consultation

**Drug Doses/Details**

**Synchronized cardioversion**
- Initial recommended doses:
  - Narrow regular: 50-100 J
  - Narrow irregular: 120-200 J biphasic or 200 J monophasic
  - Wide regular: 100 J
  - Wide irregular: defibrillation dose (NOT synchronized)

**Atropine IV Dose:**
- First dose: 6 mg rapid IV push; follow with NS flush
- Second dose: 12 mg if required

**Antiarrhythmic infusions for Stable Wide-QRS Tachycardia**

- **Procainamide IV Dose:**
  - 20-50 mg/min until arrhythmia suppressed, hypotension ensues, QRS duration increases >90%, or maximum dose 17 mg/kg given.
  - Maintenance infusion: 1-4 mg/min.
  - Avoid if prolonged QT or CHF.

- **Amiodarone IV Dose:**
  - First dose: 150 mg over 10 minutes
  - Follow by maintenance infusion of 1 mg/min for first 6 hours
  - Sotalol IV Dose:
    - 100 mg (1.5 mg/kg) over 5 minutes
    - Avoid if prolonged QT

**Drug Doses/Details**
<table>
<thead>
<tr>
<th>DRUG</th>
<th>INDICATIONS</th>
<th>DOSAGE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>SVT: Stable, regular monomorphic wide QRS as a therapeutic and diagnostic maneuver</td>
<td>6 mg IV as a rapid IV push followed by a 20 mL saline flush; repeat if required as 12 mg IV push</td>
<td>Contraindicated in patients with asthma. Reduce dose (3 mg) in post-cardiac transplant patients, those taking carbamazepine or dipyridamole, and when administered via a central line. Common side effects: transient chest pain, flushing and dyspnea.</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Pulseless VT or VF</td>
<td>300 mg IV, may repeat with 150 mg IV in 3-5 min. Maintenance infusion: 1 mg/min × 6 h then 0.5 mg/min × 18 h. Max dose: 2.2 g/24 h</td>
<td>First-line agent given during cardiac arrest. Total dose over 24 h ≤2.2 g. Side effects: bradycardia, hypotension, phlebitis.</td>
</tr>
<tr>
<td></td>
<td>SVT: Stable VT</td>
<td>150 mg IV infusion over 10 min. May repeat 150 mg dose as needed, followed by a 1 mg/min infusion × 6 h then 0.5 mg/min</td>
<td></td>
</tr>
<tr>
<td>Atropine</td>
<td>Symptomatic bradycardia</td>
<td>0.5 mg IV, repeat q3-5 min as needed to total max dose of 3 mg (0.04 mg/kg)</td>
<td>Dose &lt;0.5 mg may paradoxically slow the heart rate. Use with caution in acute coronary ischemia or MI. May not work in cardiac transplant patients.</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>SVT, control rate in atrial fibrillation or atrial flutter</td>
<td>Atenolol: 5 mg IV over 5 min; repeat 5 mg in 10 min if needed. Metoprolol: 5 mg IV over 1-2 min, repeat q 5 min to a total max dose of 15 mg</td>
<td>Avoid in patients with asthma, COPD, decompenated heart failure and pre-excited AF or flutter. Common side effects: hypotension, bradycardia, precipitation of heart failure.</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Atrial fibrillation/flutter SVT</td>
<td>Diltiazem: Bolus dose: 15-20 mg (0.25 mg/kg) IV over 2 min. May repeat in 15 min at 20-25 mg (0.35 mg/kg) over 2 min. Maintenance infusion: 5-15 mg/h. Titrate to heart rate. Verapamil: 2.5-5 mg IV over 2 min, repeat 5-10 mg in 15-30 min to a total dose of 20-30 mg</td>
<td>Should only be given to patients with narrow QRS. Avoid in patients with heart failure and post-excited AF or flutter or rhythms consistent with VT. Common side effects: hypotension, bradycardia, precipitation of heart failure.</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Symptomatic bradycardia</td>
<td>2-20 µg/kg/min as IV infusion</td>
<td>Titrated to response.</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Pulseless VT or VF, asystole, PEA</td>
<td>1 mg (1:10,000) IV q 3-5 min</td>
<td>2-2.5 mg via ET if IV/IO access unavailable. Use 10 mL of 1:10,000 concentration.</td>
</tr>
<tr>
<td></td>
<td>Symptomatic bradycardia</td>
<td>2-10 µg/kg/min as IV infusion</td>
<td>Titrated to response.</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Pulseless VT or VF</td>
<td>1-1.5 mg/kg IV or IO, may repeat dose of 0.5-0.75 mg/kg in 3-5 min. Max dose: 3 mg/kg Maintenance infusion: 2 gm/500 cc at 2-4 mg/min</td>
<td>Use in cardiac arrest when Amiodarone is unavailable. Side effects: slurred speech, altered consciousness, seizures, bradycardia.</td>
</tr>
</tbody>
</table>

(Chart continued on next page)
### 127. Preparation of Infusion for Adult Emergency Drugs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INDICATIONS</th>
<th>DOSAGE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium sulfate</td>
<td>Cardiac arrest (only for torsades de pointes associated with a long QT interval)</td>
<td>1-2 g diluted in 10 mL D_{5}W IV push</td>
<td>Monitor magnesium levels particularly in patients with impaired renal function. Side effects: Hypotension, CNS toxicity, respiratory depression.</td>
</tr>
<tr>
<td></td>
<td>Torsades de pointes (not in cardiac arrest)</td>
<td>Load dose of 1-2 g in 50-100 mL D_{5}W over 5-60 min IV. Follow with 0.5-1 g/hr IV infusion titrate to control torsades</td>
<td></td>
</tr>
<tr>
<td>Procainamide</td>
<td>Pre-excited atrial fibrillation</td>
<td>20-50 mg/min IV infusion or 100 mg q5 min until arrhythmia suppressed, hypotension, or QRS prolonged by 50%, or total cumulative dose of 17 mg/kg Maintenance infusion: 1-4 mg/min</td>
<td>Avoid in patients with QT prolongation and CHF. Side effects: bradycardia, hypotension, torsades de pointes.</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Cardiac arrest</td>
<td>40 U IVP × 1</td>
<td>Can replace first or second dose of epinephrine.</td>
</tr>
</tbody>
</table>

This table is a summary of ACLS drug dosage recommendations (Circulation 2010;122 :S640–S656). It is intended to serve only as a quick reference. One should refer to appropriate references for detailed information.

**Miriam Chan, PharmD**

### 127. Preparation Of Infusion For Adult Emergency Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Range</th>
<th>Infusion Concentration</th>
<th>Drip Rate (mL/hr) (assume a 70kg patient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>2.0–20mcg/kg/min</td>
<td>500mg/250mL</td>
<td>2mcg/kg/min = 4mL/hr</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2.0–20mcg/kg/min</td>
<td>400mg/250mL</td>
<td>5mcg/kg/min = 13mL/hr</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>2–10mcg/min</td>
<td>2mg/250mL</td>
<td>2mcg/min = 15mL/hr</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>2–10mcg/min</td>
<td>2mg/250mL</td>
<td>2mcg/min = 15mL/hr</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>2–4mcg/min</td>
<td>2g/500mL</td>
<td>2mg/mL = 30mL/hr</td>
</tr>
<tr>
<td>Nitroglycerine (IV)</td>
<td>start 10–20mcg/min</td>
<td>50mg/250mL</td>
<td>10mcg/min = 3mL/hr</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.1–5.0mcg/kg/min</td>
<td>50mg/250mL</td>
<td>0.1mcg/kg/min = 2mL/hr</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.5–30mcg/min</td>
<td>8mg/250mL</td>
<td>0.5mcg/min = 1mL/hr</td>
</tr>
<tr>
<td>Phenylinephrine</td>
<td>start 25–40mcg/min</td>
<td>50mg/250mL</td>
<td>50mcg/min = 15mL/hr</td>
</tr>
<tr>
<td>Procainamide</td>
<td>1–4mg/min</td>
<td>2g/500mL</td>
<td>1mg/min = 15mL/hr</td>
</tr>
</tbody>
</table>
128. Nutrition for 4 Entities: Hypertension, Hyperlipidemia, Diabetes & Obesity

PART 1: HYPERTENSION

I. GENERAL
A. 67 million people in the US have HTN
B. Each increment of 20/10 mmHg doubles the risk of CVD across the entire BP range starting from 115/75 mmHg
C. Lifestyle Modification

<table>
<thead>
<tr>
<th>Modification</th>
<th>Approximate SBP reduction (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>5-20 mmHg/10 kg weight loss</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>4-9 mmHg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>2-4 mmHg</td>
</tr>
</tbody>
</table>

II. NUTRITION & LIFESTYLE MODIFICATIONS
A. Weight reduction of 10 kg or 22 lbs
B. Dash Eating Plan (lowers LDL cholesterol)

**Dash Eating Plan—Number of Daily Servings**

<table>
<thead>
<tr>
<th>Food Groups</th>
<th>1,600 Calories/Day</th>
<th>2,000 Calories/Day</th>
<th>2,600 Calories/Day</th>
<th>3,100 Calories/Day</th>
<th>Serving Sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grains*</td>
<td>6</td>
<td>6-8</td>
<td>10-11</td>
<td>12-13</td>
<td>1 slice bread 1 oz dry cereal** ½ c cooked rice, pasta or cereal</td>
</tr>
<tr>
<td>Vegetables</td>
<td>3-4</td>
<td>4-5</td>
<td>5-6</td>
<td>6</td>
<td>1 c raw leafy vegetables ½ c cut-up raw or cooked vegetables ½ c vegetable juice</td>
</tr>
<tr>
<td>Fruits</td>
<td>4</td>
<td>4-5</td>
<td>5-6</td>
<td>6</td>
<td>1 med fruit ½ c dried fruit ½ c fresh, frozen or canned fruit ½ c fruit juice</td>
</tr>
<tr>
<td>Fat-free or low-fat milk &amp; milk products</td>
<td>2-3</td>
<td>2-3</td>
<td>3</td>
<td>3-4</td>
<td>1 c milk or yogurt 1 ½ oz cheese</td>
</tr>
<tr>
<td>Lean meats, poultry and fish</td>
<td>3-6</td>
<td>6 or less</td>
<td>6</td>
<td>6-9</td>
<td>1 oz cooked meats, poultry or fish 1 egg***</td>
</tr>
<tr>
<td>Nuts, seeds &amp; legumes</td>
<td>3/week</td>
<td>4-5/week</td>
<td>1</td>
<td>1</td>
<td>½ c or 1 ½ oz nuts 2 Tbsp peanut butter 2 Tbsp or ½ oz seeds ½ c cooked legumes (dry beans and peas)</td>
</tr>
<tr>
<td>Fats &amp; oils</td>
<td>2</td>
<td>2-3</td>
<td>3</td>
<td>4</td>
<td>1 tsp soft margarine 1 tsp vegetable oil 1 Tbsp mayonnaise 2 Tbsp salad dressing</td>
</tr>
<tr>
<td>Sweets &amp; added sugars</td>
<td>0</td>
<td>5 or less per week</td>
<td>≤2</td>
<td>≤2</td>
<td>1 Tbsp sugar 1 Tbsp jelly or jam ½ c sorbet, gelatin 1 c lemonade</td>
</tr>
</tbody>
</table>

*Whole grains are recommended for most grain servings as a good source of fiber and nutrients
**Serving sizes vary between ½ cup and ⅛ cups, depending on cereal type
***Since eggs are high in cholesterol, limit egg yolk intake to no more than four per week; two egg whites have the same protein content as 1 oz of meat
APPENDIX

128. Nutrition for 4 Entities


C. Dietary sodium restriction
   1. 2300mg of sodium (2005 US Dietary Guidelines for Americans)
   2. 1500mg of sodium was a lower goal tested and found to be even better for lowering blood pressure. It was particularly effective for middle-aged and older individuals, African Americans and those who already had high blood pressure

D. Physical activity

E. Moderation of alcohol consumption
   1. One drink a day for women; 2 drinks a day for men

| 12 ounces of beer (regular or light, 150 calories) |
| 5 ounces of wine (100 calories) |
| 1 ½ ounces of 80-proof whiskey (100 calories) |

PART 2: HYPERLIPIDEMIA

I. GENERAL
   A. More than 105 million American adults have total blood cholesterol >200mg/dL and 36.6 million > 240mg/dL. 10% of adolescents ages 12–19 have total cholesterol levels of >200mg/dL. About 30–39% of Americans age 20 and older have an LDL >130mg/dL and 15–28% have an HDL <40 mg/dL.
   B. A 30% reduction in the incidence of coronary heart disease can be attained with a 10% decrease in total cholesterol levels.
   C. Therapeutic Lifestyle Changes (TLC) can lower LDL up to 16%
   D. Plant stanols and plant sterols can lower LDL up to 15%
   E. Weight loss of 5–10% can improve total cholesterol, LDL:HDL and the total cholesterol:HDL. Another study showed a decrease in total cholesterol, TG and VLDL.
   F. Medical Nutrition Therapy (MNT) counseling studies report reduction in LDL cholesterol by 15–25%

II. NUTRITION IMPLICATIONS

A. TLC Diet

<table>
<thead>
<tr>
<th>Saturated fat &amp; trans-fatty acids</th>
<th>Cholesterol</th>
<th>Total fat</th>
<th>Plant stanols</th>
<th>Total fiber</th>
<th>Soluble fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td>7% of total calories</td>
<td>200mg</td>
<td>25-30% of total calories</td>
<td>Soft margarines Plant sterols</td>
<td>25-30g</td>
<td>7-15g Fruits, vegetables and whole grains</td>
</tr>
</tbody>
</table>

B. Weight Management

<table>
<thead>
<tr>
<th>Weight</th>
<th>Waist Circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieve or maintain a healthy weight BMI 19–25</td>
<td>&lt;35″ Female</td>
</tr>
<tr>
<td></td>
<td>&lt;40″ Male</td>
</tr>
</tbody>
</table>

C. Physical Activity
   1. 30 minutes most days if not all days
   2. Can help raise HDL and lower LDL

D. Hypertriglyceridemia
   1. Omega-3 fatty acids from fish or fish oil supplements will reduce TG levels; also may increase HDL

<table>
<thead>
<tr>
<th>Fish (Oily)</th>
<th>Fish Oil Supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eat two 4oz servings a week (without CHD) Salmon, trout, mackerel, sardines, fresh tuna, pilchards, herring kipper, eel &amp; whitebait</td>
<td>EPA + DHA 1g a day (with CHD) 2–4g a day (high TG)</td>
</tr>
</tbody>
</table>
PART 3: DIABETES

I. GENERAL
A. As of 2005, 20.8 million people of all ages have diabetes, 7% of the US population. 14.6 million people were diagnosed, leaving 6.2 million undiagnosed. In the population of <20 years old, 1 of every 400–600 has DM1. DM2 in children and adolescents, though still rare, is being diagnosed more frequently in American Indians, African Americans and Hispanic/Latino Americans. In the adult population >20 years old, 9.6% have diabetes, and in the > 60 years old population, 10.3 million or 20.9% have diabetes. More men, 10.9 million, 10.5% age >20 have diabetes than women, 9.7 million, 8.8%. There were 1.5 million new cases diagnosed in 2005 ages >20

B. Medical Nutrition Therapy (MNT) most beneficial at diagnosis; improves metabolic outcomes, such as blood glucose and HgA 1c (~1–2% in DM2, depending on the duration of diabetes)

C. A moderate weight loss of 5% of body weight decreases insulin resistance and improves measures of glycemia

II. NUTRITION
A. Weight reduction in overweight and obese insulin resistant people, 5–7% of starting weight

B. Medical Nutrition Therapy with registered dietitian or certified diabetes educator

C. Reduction in calories and fat ~30%. Goal BMI 19–25. Very low carbohydrate diets are not recommended

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<th>Calories</th>
<th>Carbohydrates</th>
<th>Protein</th>
<th>Fat</th>
<th>Alcohol</th>
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<tr>
<td>If overweight or obese 500 (1,000) less calories a day = 1 (2) lb weight loss a week</td>
<td>Minimum 130g a day</td>
<td>10–35% of calories</td>
<td>Saturated &lt;7% of calories</td>
<td>Women 1 or less drinks a day</td>
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<tr>
<td>Most women need 165–210 g a day (3–4 carb choices per meal, 1–2 carb choices for snack)</td>
<td>0.8g/kg body weight</td>
<td>Transfats 0–2g a day</td>
<td>Men 2 or less drinks a day</td>
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<td>Most men need 210–255g a day (4–5 carb choices per meal, 1–2 carb choices per snack)*</td>
<td>Transfats 0–2g a day</td>
<td>&lt; 200mg cholesterol</td>
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<td>* 15 grams (g) of total carbohydrate = 1 carbohydrate (carb) choice</td>
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PART 4: OBESITY

I. GENERAL
A. 66% of US adults age 20 or older are either overweight (BMI 25–29.9) or obese (BMI ≥ 30), 2003–2004 data. “Overweight refers to an excess of body weight compared to set standards. The excess weight may come from muscle, bone, fat, and/or body water. Obesity refers specifically to having an abnormally high proportion of body fat.”

B. 17% of children and adolescents 2–19 years old are overweight, (BMI at or above the 95th percentile of sex-specific BMI growth charts)

C. Having a BMI ≥40 increases mortality from all causes, 10–50% compared to healthy weight individuals

D. The estimated annual medical cost of obesity in the US in 2008 was $147 billion

E. Pharmacotherapy: Used in patients with a BMI ≥30 or a BMI ≥27 and have obesity-related medical conditions such as hypertension, type 2 diabetes, or hyperlipidemia

1. Sympathomimetic amines
   a. Act as appetite suppressants
   b. Indicated for short-term use only (up to 12 wks). Many state medical boards have strict guidelines on its use
   c. Contraindicated in hypertension, CVD, hyperthyroidism, glaucoma, history of drug abuse
   d. Major side effects: insomnia, nervousness, dry mouth, constipation, palpitations, elevated blood pressure. Be aware of drug interactions
   e. Drugs in this class include:
128. Nutrition for 4 Entities

**Appendix**

- **Benzphetamine** (C-III): 25–50mg 1–3 × daily
- **Phendimetrazine** (C-III): 35mg 2–3 × daily
- **Diethylpropion** (C-IV): 25mg TID or 75mg ER QD
- **Phentermine** (C-IV): 15–30mg/d

2. **Lorcaserin (Belviq)** CIV
   - Acts as a serotonin 2C receptor agonist to suppress appetite
   - Indicated for chronic weight management
   - Dose: 10mg BID
   - Discontinue therapy if at least 5% of baseline body weight has not been lost by wk 12
   - Side effects: headaches, dizziness, fatigue, nausea, dry mouth, cough, and constipation
   - Drug interactions: serotonin syndrome if coadministration with SSRIs or MAOIs

3. **Qsymia (Phentermine/Topiramate)** CIV
   - A combination product of a sympathomimetic amine anorectic (Phentermine) and an antiepileptic drug (Topiramate)
   - Indicated for chronic weight management
   - Dosing
     - Initial dose: 3.75/23mg tab 1 QD × 14 days, then increase to 7.5/46mg tab once daily
     - Discontinue or escalate dose if 3% weight loss is not achieved after 12 weeks on 7.5/46mg dose
     - To escalate the dose: increase to 11.25mg/69mg tab QD × 14 days, followed by 15/92mg once daily
     - Discontinue therapy if 5% weight loss is not achieved after 12 weeks on maximum daily dose 15/92mg
     - Discontinue 15/90mg gradually by taking a dose every other day × 1 wk
   - FDA mandates a medication safety program, REMS
     - Prescribers are required to counsel women of childbearing potential about the risks of treatment during the first trimester of pregnancy and the need to undergo pregnancy testing before starting therapy and monthly during treatment, and use of effective contraceptive methods during treatment
     - Prescription must be sent to a certified pharmacy
     - Quantity limits: an initial 14-day supply of 3.75/23mg, followed by a 30-day supply of 7.5/46mg. Prescriptions for the maintenance dose may have up to 5 refills
   - Side effects: Constipation, dizziness, dry mouth, dysgeusia, insomnia, and paresthesia
   - Contraindicated in pregnancy (due to potential fetal harm), glaucoma, hyperthyroidism, use within 14 days following administration of MAOIs

4. **Lipase inhibitor**
   - **Orlistat**: as 120mg **Xenical** by prescription and 60mg Alli available OTC
   - Dose: 60–120mg TID with each main meal containing fat. A daily multivitamin at bedtime is recommended
   - Side effects: Oily spotting, flatus with discharge, fecal urgency, oil stools incontinence
   - Contraindications: Pregnancy, chronic malabsorption syndrome, cholestasis
   - Drug interactions: administer Cyclosporine 3 h after **Orlistat**; **Levothyroxine** and **Orlistat** at least 4 h apart

II. NUTRITION & LIFESTYLE MODIFICATIONS: Treatment recommendations are to reduce caloric intake, increase physical activity, and make healthy permanent behavioral lifestyle changes.
A. Treatment Algorithm

1. 
- Treatment

2. 
- Examination

3. 
- Brief reinforcement/educate on weight management

4. 
- Periodic weight check

5. 
- Advise to maintain weight/address other risk factors

6. 
- Clinician and patient devise goals and treatment strategy for weight loss and risk factor control

7. 
- Assess reasons for failure to lose weight

8. 
- Maintenance counseling:
  - Dietary therapy
  - Behavior therapy
  - Physical activity

9. 
- Weight gain

10. 
- BMI measured in past 2 years?

11. 
- Hx BMI ≥ 25?

12. 
- BMI ≥ 25 OR waist circumference > 88 cm (F) > 102 cm (M)

13. 
- ≥ 2 risk factors

14. 
- Does patient want to lose weight?

15. 
- Progress being made/goal achieved?

16. 
- This algorithm applies only to the assessment for overweight and obesity and subsequent decisions based on that assessment. It does not include any initial overall assessment for cardiovascular risk factors or diseases that are indicated.

B. Calorie reduction

1. Deficit of 500 (1,000) calories a day (from usual consumption) = 1 lb (2 lb) weight loss a week. Daily intake goals 55% carbohydrate, ~ 15% protein, 30% fat and 20–30 grams fiber. Initial weight loss goal 10% in 6 months

2. Harris-Benedict Equations (calories/day):
   Male: \((66.5 + 13.8 \times \text{kg wt}) + (5.0 \times \text{cm ht}) - (6.8 \times \text{age})\)
   Female: \((655.1 + 9.6 \times \text{kg wt}) + (1.8 \times \text{cm ht}) - (4.7 \times \text{age})\)


C. Physical activity is an essential component for weight loss and weight maintenance. Aim for 60–90 minutes of daily moderate-intensity physical activity

1. Assess patient’s ability to exercise

2. Ascertain what activity patient would enjoy doing initiate slowly, gradually increasing intensity. Example: walking, start at 10 minutes a day, 3 days a week and increase to 30–45 minutes a day most days of the week

3. Reduce sedentary time

D. Behavioral therapy

1. Make the most of the patient visit time
   a. Consider attitudes, beliefs and histories. Patients know they are overweight or obese; be nonjudgmental, objective and realistic
   b. Build a partnership with the patient. The patient must be an active partner in the consultation, planning and setting goals for behavioral changes
   c. Set achievable goals that are collaborative and a few goals at a time
   d. Cultivate the partnership. Encourage follow-up visits to monitor health and weight status. Frequent contact with the patient is a major determinant of success
   e. Encourage self-monitoring

E. Pharmacotherapy: Commonly used drugs

1. Sibutramine (Meridia): CNS stimulants, schedule IV

2. Orlistat: Lipase inhibitor
   a. Rx: Xenical 120mg TID with each meal
   b. OTC: Alli 60mg TID with each meal

3. Common side effects: Fatty/oily stool, fecal incontinence/urgency, flatus with discharge. Reduce the absorption of fat-soluble vitamins and B-carotene; encourage patients to take a MVI daily

F. Weight Loss Surgery (WLS)

1. Vertical banded gastroplasty

2. Roux-en-Y gastric bypass

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Frequently Used Phone Numbers

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